CHAPTER 18

Infectious Diseases of the Nervous System

ACUTE BACTERIAL MENINGITIS

Purulent meningitis represents inflammatory reaction of pia and arachnoid (leptomeninges), which surround spinal cord and brain. The pathologic response includes congestion of superficial cerebral and pial vessels, thickening of meninges, reduced cerebral blood flow, cerebral edema of vasogenic and cytotoxic type, elevated intracranial pressure, exudate in basal cisterns and cortical subarachnoid spaces, exudate in ventricles (ependymitis, ventriculitis), vascular thrombosis (arteries, veins and dural sinuses), and hydrocephalus. Following treatment of meningitis, neurological outcome correlates with control of intracranial pressure and prevention of herniation and maintenance of reduced cerebral blood flow to prevent cerebral ischemia. Early recognition and treatment of bacterial meningitis are the keys to good neurological outcome!

The most frequent etiologic agents are *streptococcus pneumoniae* (50%) and *Neisseria meningitides* (25%); however, the number of cases in which no organism is isolated from CSF has increased, as more patients receive antibiotics prior to CSF analysis. Etiology is dependent upon patient age. In neonates, *Escheria coli* and *Group B streptococcus* are most common; and in young children Hemophilus influenza is most common, but this is rapidly decreasing due to vaccine development. In immunocompromised patients (diabetics, alcoholics, pregnant women, sepsis, AIDS, medication use including corticosteroid and chemotherapeutic agents), *L. monocytogenes* must be considered potential etiologic agent. Parameningeal infections (ear, sinus, face, eye, head trauma with CSF leak) can cause bacterial infection as a result of *Pseudomonas aeruginosa, Staphylococcus aureus*, or multiple diverse pathogens. In children over 5 year old and adults (including elderly patients), *S. pneumoniae* and *N. meningitides* are the most common; however, *L. monocytogenes, S. aureus, P. aeruginosa* must also be considered.

Clinical features of bacterial meningitis usually develop rapidly over several hours; however, in certain cases they develop more insidiously over several days. Signs and symptoms include headache, fever, nausea, vomiting, photophobia, and stiff neck caused by meningeal irritation. In children younger than 1 year with meningitis, CNS signs can be absent, and only findings may be fever, failure to thrive, irritability, or lethargy. In elderly patients diagnostic clues can be limited - febrile response and headache can be minimal or absent, and meningeal signs may not be convincingly demonstrated. Altered mental state can be the only diagnostic clue to meningitis in elderly patients. In both neonates and elderly patients index of suspicion for meningitis must be high if patient has unexplained febrile illness, and lumbar puncture (LP) should be performed early. In other meningitis patients, clinical findings include nuchal rigidity demonstrated by placing examiner's hand beneath the occiput (back of the head) and passively flexing the head to elicit neck extensor muscle spasm, Brudzinski sign (passive flexion of patient's head causes flexion of thighs and legs) and Kernig sign (with hip and knee flexed, legs cannot be straightened without hamstring spasm and pain). Cranial nerve palsies (especially damage to auditory and facial nerves; hearing loss can be permanent; facial paralysis can develop after improvement in CSF reaction) can result from basal meningeal exudate infiltrating the
cranial nerves or from vascular thrombosis. Disturbances of consciousness result from effects of bacterial toxins, cerebral edema, hydrocephalus, vasculitis, or cerebral ischemia. Seizures, focal neurologic deficit, or papilledema do not usually occur in bacterial meningitis unless there are complicating neuropathological conditions. These include cerebral infarction resulting from inflammatory arteritis or cortical vein thrombosis, focal suppurative cerebritis or brain abscess, subdural or epidural empyema, and hydrocephalus.

LP with cerebrospinal fluid (CSF) examination (Table 18-1) is necessary to establish diagnosis of meningitis and to identify the etiologic agent(s). Untreated bacterial meningitis is usually fatal disorder; delay in initiating therapy can result in irreversible neurologic sequelae. If focal neurologic signs are present, LP should be avoided until CT or MRI is done and shows no lesion which might precipitate cerebral herniation. Risk of transtentorial or tonsillar herniation following LP as result of cerebral edema and intracranial hypertension is low in uncomplicated meningitis. If bacterial meningitis is suspected but delay in diagnostic LP is warranted, initiation of antibiotic therapy (after blood cultures are obtained) should be done. This empirical treatment is warranted if patient's clinical condition is critical and delay in initiating antibiotics could be disastrous. Because bacterial meningitis can progress rapidly, immediate initiation of antibiotics should be considered even when immediate LP is carried out because time required for performance of LP and subsequent CSF analysis can use up precious hours during which neurological deterioration can occur. Remember - the benefit of LP and CSF analysis outweigh the potential risk of neurological worsening subsequent to LP. The neurological worsening post-LP can be due to the pathological process and not the LP. There are patients who neurologically deteriorate post-LP who have bacterial meningitis and subsequently die; however, autopsy shows no cause of neurological deterioration.

In bacterial meningitis, CSF pressure is usually elevated; this finding is of unknown prognostic significance. CSF can appear clear, turbid, or cloudy. Cloudy CSF indicates pleocytosis of at least 200 white blood cells. CSF white cell count can contain as few as 10 or as many as 10,000 cells/mm$^3$ of which 60% to 90% are polymorphonuclear (PMN) leukocytes; however, there are usually more than 1,000 white blood cells. There can be minimal CSF pleocytosis in meningitis; this is particularly true for early meningococcal meningitis or in immunocompromised patients. If meningitis is strongly suspected clinically but there are equivocal CSF findings, a repeat CSF study should be performed 4 to 6 hours later to follow possible evolution of abnormal CSF findings. If the diagnosis is bacterial meningitis, subsequent CSF examination should worsen.

CSF protein content is usually elevated. When increased (excess of 1 g/dl), fluid appears yellow tinged (xanthochromic). Peripheral blood glucose specimen should always be drawn just before LP puncture because stress of LP can elevate blood glucose concentration. If there is peripheral hypoglycemia or hyperglycemia, CSF glucose concentration can be normal, but CSF/blood glucose ratio (normal, 0.5-0.6) can be altered. CSF glucose content is decreased in bacterial meningitis as well as in other conditions (subarachnoid hemorrhage, meningitis caused by Mycobacterium tuberculosis, fungi, sarcoid, syphilis, carcinoma, rarely viral meningitis as a result of mumps or herpes simplex virus). Decreased glucose content can be spurious and result from deterioration of CSF (5 mg decrement per hour) if determination is not performed immediately after obtaining CSF.

Gram stain of CSF suggests the causative organism in two thirds of cases of bacterial meningitis; however, this is often misinterpreted because of observer inexperience or faulty
preparation of smear. The culture should confirm presence of causative microorganism(s); delay in plating the culture can result in false negative results. Because bacterial meningitis is sometimes caused by multiple agents, culture for both aerobic and anaerobic organisms should be considered if Gram stain shows more than one morphotype. If cause of meningitis is not defined by Gram stain and culture, other CSF studies should include acid-fast stain and culture for Mycobacterium tuberculosis, India ink preparation for Cryptococcus neoformans, latex particle agglutination to identify capsular antigens (Cryptococcus neoformans, H. influenzae, N. meningitides), polymerase chain reaction (PCR), counterimmunoelectrophoresis for S. pneumoniae, H. influenzae, and N. meningitides; serologic tests for syphilis; cytologic examination for malignant cells; viral cultures (including acute and convalescent serum samples 7-14 days apart); and fungal cultures.

Patients with subarachnoid hemorrhage, toxic metabolic encephalopathy, and meningismus (clinical features of meningeal irritation, but normal CSF findings) can have clinical findings to simulate meningitis; differentiation is established by CSF findings. In patients whose CSF shows pleocytosis without evidence of infectious cause, other conditions must be considered. If patients with bacterial meningitis are treated with inadequate dosage of antibiotics or inappropriate antibiotics, there can be sufficient reduction in number of microorganisms such that Gram stain and culture are negative but a complete cure has not been achieved (partially treated bacterial meningitis). At this stage of partially treated meningitis CSF formula including cell count and differential (ratio of lymphocytes to PMNs), sugar, and protein content is variable. In cases of partially treated bacterial meningitis, tests for capsular antigens are most useful. Certain patients with neoplastic meningitis have CSF pleocytosis with PMN cell preponderance, elevated protein, and decreased glucose; all studies for infectious causes and malignant cells are negative and diagnosis is established by cytologic examination.

In bacterial meningitis treatment with intravenous antibiotics is usually determined by Gram stain and culture results. If Gram stain of CSF is positive, use this regimen: Gram positive-cocci - Vancomycin plus ceftriaxone; Gram negative-cocci - Penicillin G or ceftriaxone; Gram positive-bacilli - Ampicillin plus aminoglycoside; Gram negative-bacilli - ceftriaxone plus aminoglycoside. Third generation cephalosporins (ceftriaxone, cefotaxime) have been initial therapy, but as H. influenzae and S. pneumoniae have developed penicillin resistance, adding vancomycin may be necessary. If the CSF shows PMN predominance but the initial Gram stain is negative and no identifiable systemic source is defined, the initial empiric treatment depends on patient's age and other epidemiologic data. If Listeria monocytogenes is suspect, utilize ampicillin, as this is resistant to cephalosporins. In meningitis with unknown etiology utilize, third generation cephalosporin and vancomycin. For staphyloccoci, oxacillin is most effective, and treatment course of 2 to 4 weeks is needed. If CSF shows mixed pleocytosis with negative Gram stain and normal sugar content, latex particle agglutination or counterimmunoelectrophoresis can be helpful in detecting capsular bacterial antigens; positive results are consistent with partially treated bacterial meningitis. Latex particle agglutination, if available, can define cause of meningitis more reliably than Gram stain and much more rapidly (within minutes) than culture, which requires 48 hours to complete.

Antibiotics used to treat bacterial meningitis are listed in Table 18-2. Following initiation of therapy, CSF analysis can be repeated 48 hours later; Gram stain and culture should revert to negative if organism causing meningitis is susceptible to antibiotics. Cellular reaction begins to decrease, and shift to lymphocytic predominance occurs. There should be normalization of sugar
content, and this is important prognostic parameter. Reduction of elevated protein content can occur slowly, and unless protein is markedly elevated, this has little prognostic significance. Following 2 weeks of antibiotics, cell count usually normalizes; however, slight pleocytosis can persist for several months. In patients whose initial CSF shows mixed pleocytosis with normal sugar content and negative Gram stain and there is no history of prior antibiotic therapy, antibiotic therapy is usually initiated but is stopped if culture is negative 48 hours later. Recurrent bacterial meningitis (usually caused by *S. pneumoniae*) suggests abnormal communication into subarachnoid spaces (skull fracture) or, less frequently, parameningeal infection focus. Blood culture can be helpful in determining the cause. Bacterial meningitis should be treated with intravenous antibiotics. For *H. influenza* and *N. meningitides*, 7 to 10 days is probably adequate, but as many as 21 days can be needed for neonatal meningitis.

In acute bacterial meningitis, over-hydration should be avoided because cerebral edema and inappropriate secretion of antidiuretic hormone can complicate this condition. Corticosteroid medication is not routinely used unless there is symptomatic intracranial hypertension or herniation syndromes; however, recent studies have reported that dexamethasone (0.15 mg/kg administered intravenously every 6 hours for 4 days) can improve neurologic outcome, especially for children with *H. influenza* meningitis, but also for adults. Dexamethasone should be administered immediately before initial antibiotic dose. Other treatment for symptomatic cerebral edema includes hyperosmolar agents (mannitol, glycerol).

Potential neurologic sequelae of poorly or late treated bacterial meningitis includes blindness, deafness, seizures, cerebellar dysfunction, mental changes, cranial nerve palsies (most commonly third, sixth, seventh), and motor disturbances (hemiparesis, quadriplegia). Symptoms due to hydrocephalus can develop in early or delayed stages of bacterial meningitis, as CSF pathways are blocked in ventricles, basal cisterns or venous sinuses. These occur more commonly in meningitis cases when diagnosis was delayed or organism was drug resistant; however, it can occur unpredictably in other cases of bacterial meningitis. CSF findings that often correlate with poor outcome include number high number of bacteria seen on initial Gram stain, amount of capsular antigen detected (greater the amount, worse the prognosis), and very low CSF sugar content.

**TUBERCULOUS MENINGITIS**

This can develop from dissemination of miliary tuberculosis to disseminate throughout meninges. Nodules are encapsulated by surrounding tissue; these break down, and bacilli are discharged into subarachnoid spaces. Thick white exudate forms in basal cisterns. Pathologic findings include proliferative arachnoiditis with thick proteinaceous exudate in basal cisterns infiltrating cranial nerves, vasculitis with arterial wall inflammation and thrombosis resulting in cerebral ischemia, hydrocephalus caused by inflammatory exudate obstructing cisterns, and tuberculomas (caseating granulomas). Using CT or MRI multiple small parenchymal and basal meningeal focal lesions can be visualized; however, these usually resolve with adequate medical treatment.

Symptomatology of tuberculous meningitis usually develops insidiously. Ask patient for history of any possible tuberculosis contact. Evaluate patients for systemic tuberculosis (positive chest radiogram, urinary tract involvement, abnormal liver function tests). Clinical findings of tuberculous meningitis include fever, headache, stiff neck, focal neurologic deficit, and behavioral or mental changes. There may be no evidence of active systemic tuberculosis: skin
test (intermediate strength purified protein derivative) is usually positive (50% to 75% of patients), or chest roentgenogram can show pulmonary involvement but frequently does not, especially among older adults. CSF cultures for \textit{M. tuberculosis} are positive in 90%, whereas acid-fast stains of CSF showing \textit{M. tuberculosis} are positive in 30%. If initial CSF culture and acid-fast stain are negative, repeat LP three additional times using specimens that contain at least 20 ml of CSF. The larger the volume of CSF, the better the diagnostic yield.

If tuberculous meningitis is suspected, initiate treatment on empiric basis. Treatment regimens vary but include 4 drugs and continue for 18 to 24 months. These are isoniazid (300 mg/day), usually in combination with ethambutol (15 mg/kg/day), rifampin (600 mg/day), and pyrazinamide (25 mg/kg/day). When drug resistance is suspected, for example, on the basis of prior drug treatment, streptomycin (750-1000 mg intramuscularly per day) is used. After initial diagnosis is established, repeat CSF study is performed 1 week after initiating treatment. If patient is clinically improving and CSF formula is normalizing, LP should be performed before hospital discharge and several weeks after completion of therapy to confirm that relapse has not developed. Dexamethasone should be used to reduce cerebral edema, intracranial hypertension, and inflammatory response (prevent hydrocephalus or vasculitis). There is no evidence that dexamethasone delays elimination of tuberculosis if adequate antituberculous treatment is initiated.

Primary antituberculous drugs are potentially toxic:

\begin{itemize}
  \item Streptomycin causes eighth nerve damage with hearing loss and vestibular disturbances which can be irreversible.
  \item Ethambutol causes optic nerve damage with early impairment of color vision, but this usually is not seen if dosage of 15 mg/kg/day is not exceeded.
  \item Isoniazid can cause peripheral neuropathy and rarely encephalopathy; these side effects are dose dependent and preventable if supplemental pyridoxine is administered. Hepatotoxicity occurs in 3% of older patients.
  \item Rifampin has no known neurotoxicity but is potentially hepatotoxic.
  \item Pyrazinamide can cause hyperuricemia and gout.
\end{itemize}

**CRYPTOCOCCAL MENINGITIS**

Cryptococcal meningitis is most common CNS fungal infection. One half of patients are immunologically suppressed (diabetes mellitus, transplant patients, lymphoma, leukemia, AIDS); in the others no predisposing factor is identified. The usual finding is basilar granulomatous meningitis; granulomas or cysts rarely develop intracerebrally. Clinical onset of symptoms is insidious; patients complain of headaches for several weeks to months. CSF findings include lymphocytic pleocytosis (100%), decreased sugar content (50%), elevated protein content (90%), positive India ink preparation (50%), presence of cryptococcal antigen (90%), and positive fungal culture (95%). The initial CSF analysis may show only pleocytosis; it may be necessary to perform several studies or obtain fluid by cisternal or ventricular tap to diagnose cryptococcal meningitis. Removal and culturing of large CSF volumes (15-25 ml) increases success. If serum cryptococcal antigen is negative, it is highly unlikely that patient has cryptococcal meningitis. In AIDS patients, CSF can show minimal lymphocytic pleocytosis as result of systemic
lymphopenia. In these patients, if CSF is acellular with normal protein and sugar content, perform cryptococcal antigen and fungal cultures because of high index of suspicion of this disorder.

Initial treatment consists of systemic amphotericin B and flucytosine. Amphotericin B is administered intravenously in dosages of 0.3 to 0.6 mg/kg/day mixed in a 5% dextrose and water solution during a 2- to 3-hour interval. Untoward effects include fever, hypotension, nausea, and vomiting; renal toxicity with impaired tubular function; anemia due to bone marrow depression; phlebitis; and hypokalemia. Treatment is continued for 6 to 10 weeks or until total dose is 2.5 g. Intrathecal amphotericin B is used for patients showing poor response to systemic drug or with impaired renal function. Flucytosine is antifungal agent administered orally in dosage of 150 mg/kg/day divided into six doses and continued for 6 weeks. It is synergistic with amphotericin B. Flucytosine is toxic to bone marrow; thrombocytopenia or leukopenia can also result. In AIDS patients, fluconazole (diflucan) is used in dosage of 200 mg per day for lifelong suppressive treatment. It is not used alone because organisms rapidly become resistant. Repeat course of treatment is necessary if CSF shows increased cell count, decrease in glucose content, or elevation of cryptococcal antigen titer. Intracranial hypertension may complicate cryptococcal meningitis and LP can result in herniation syndrome, even if all precautions are taken.

NEUROSYPHILIS

CNS infection caused by *Treponema pallidum* can cause several clinical patterns: latent (asymptomatic), basilar meningitis, granuloma (gumma), meningovascular, parenchymal (general paresis), and tabes dorsalis. CSF should be analyzed in all patients having positive serum treponemal tests who have not received adequate antibiotic therapy for syphilis or if nontreponemal serum titers are elevated above posttreatment levels.

In latent neurosyphilis the patient is neurologically normal; CSF shows positive syphilis serology. Serodiagnosis of syphilis is established by demonstrating two types of antibodies: nonspecific reagin (VDRL, RPR) and specific treponemal, including *T. pallidum* immobilization test (TPI), fluorescent treponemal antibody-absorption test (FTA-ABS), and microhemagglutination assay for *T. pallidum* (MHA-TP). Reagin antibody tests can have false-negative results; furthermore, these tests lack specificity, and false-positive results can occur in certain conditions including systemic lupus erythematosus, bacterial endocarditis, rheumatoid arthritis, and pregnancy. In active neurosyphilis, serologic titers are elevated; they become low or negative following treatment. Specific reagin antibody tests are "scarlet letter" of syphilis and remain positive even with adequate treatment. Serologic tests for syphilis can become negative spontaneously with late CNS involvement for unknown reasons.

Patients with syphilitic meningitis can have meningeal signs. CSF findings include mononuclear pleocytosis, elevated protein content, decreased glucose content, and positive serology (VDRL test of CSF should be performed) in blood and CSF. In AIDS patients with neurosyphilis, CSF may not show abnormalities, and there must be high index of suspicion of neurosyphilis in these patients. The presence of confusion, seizures, hemiparesis, and cranial nerve palsies suggests parenchymal involvement; stroke can be indication of syphilitic vasculitis. CSF findings in parenchymal and vasculitis neurosyphilis include mononuclear pleocytosis, elevated protein content, reduced sugar content, and positive serology. General paresis usually develops as the most advanced form of neurosyphilis. Clinical findings include dementia, neurobehavioral abnormalities, postural tremor, and seizures. CSF findings include pleocytosis,
elevated protein (with increased gamma-globulin component) content, and positive serology. CT/MRI shows brain atrophy. Pathologically cerebral gyral pattern is atrophic, meninges are thickened, and sulci are widened.

Tabes dorsalis is syphilitic involvement of nerve roots and spinal cord. Clinical findings include recurrent lancinating and paroxysmal lightning-like pains of burning, electrical, or cramping quality involving legs or abdomen; visceral crises consisting of abdominal pain, nausea, vomiting; sensory defects and paresthesias with loss of vibration and position sense in lumbosacral region; neurogenic bladder; sensory ataxia; and neurotrophic joint changes. The finding of small, irregularly shaped miotic pupils nonreactive to light with normal response to accommodation (Argyll Robertson pupil) is pathognomonic of neurosyphilis.

For neurosyphilis, treat with aqueous crystalline penicillin G (2 million units every 4 hours for 14 days). Benzathine penicillin (24 million units administered intramuscularly by weekly injection for 3 consecutive weeks) does not provide adequate CSF levels to treat neurosyphilis. If recurrence is suspected, indications for repeat antibiotic course include clinical progression of neurologic findings, CSF pleocytosis persisting 1 year after initial treatment, fourfold increase in VDRL titer, and initially high titer that fails to decrease fourfold within 1 year. Unfortunately, no good data exist regarding efficacy of alternative forms of therapy for penicillin-allergic patient. Recommendations include tetracycline, 2 g per day for 30 days; doxycycline, 100 mg twice per day for 30 days; or intramuscular ceftriaxone, 1 g per day for 14 days.

LYME DISEASE

Lyme disease is caused by spirochete referred to as *Borrelia burgdorferi* and is carried by specific genus of wood tick (Ixodes). It is endemic in northeastern United States, upper Midwest states including Minnesota and Wisconsin, and wooded Pacific coast areas. Pathologic involvement includes skin, joints, eyes, cardiac system, central, and peripheral nervous system. Lyme disease has several stages: flu-like illness (headache, stiff neck, fever, myalgias) with skin lesion erythema chronicum migratorium (circular-shaped at tick bite with lesions later disseminating), meningitic syndrome with prominent cranial and peripheral radiculoneuropathy, polyarthritis, and symptoms simulating multiple sclerosis or diffuse encephalopathy. Antibodies to this spirochete can be determined by immunofluorescent or enzyme-linked immunosorbent assay. Diagnosis of Lyme infection is established by positive *B. burgdorferi* culture or presence of anti-*B. burgdorferi* antibodies in serum of CSF. CSF abnormalities include mononuclear pleocytosis and presence of anti-*B. burgdorferi* antibodies, but CSF findings can be negative. In some clinically suspected cases, CSF may show no abnormalities. Diagnosis of CNS involvement in Lyme disease can be quite difficult as there can be false-positive and false-negative laboratory findings.

Treatment includes doxycycline 100 mg three times daily for 30 days, amoxicillin 500 mg three times daily for 30 days, or azithromycin 500 mg daily for 7 days. For patient with neurological symptoms use parenteral antibiotics. These include 2-week course of ceftriaxone 2 g intravenously daily, penicillin G 20 million units intravenously daily, and cefotaxime 2 g three times daily intravenously. Following successful treatment, post-Lyme disease syndrome including disabling fatigue, headache, dizziness, impaired memory and concentration, myalgia, sleep disturbances, and arthralgias can occur. These symptoms should be treated symptomatically and do not require further antibiotic treatment unless there are definite
laboratory findings of incomplete treatment or CSF abnormality recurrence. Recently many patients with vague and nonspecific symptoms have been diagnosed as having Lyme disease without definitive clinical or laboratory findings, and they have received long-term and high-dose antibiotics indiscriminately. This practice should be discouraged!

WHIPPLE DISEASE
Whipple's disease is relapsing-remitting multisystem disease (diarrhea, steatorrhea, weight loss, abdominal pain, arthralgias) with CNS manifestations (dementia, ataxia, myoclonus, seizures, supranuclear gaze palsy of vertical type, focal deficit) occurring uncommonly. It is caused by bacilliform bacterium, *Tropheryma Whippelii*. CT/MRI shows multiple enhancing lesions, frequently with at least several located in the brain stem. Neurologic manifestations can occur without evidence of clinically apparent intestinal disease. Diagnosis is established by intestinal biopsy or PCR of infective tissue (small intestine, lymph node, vitreous fluid); this shows periodic acid-Schiff-positive macrophages. Treatment includes tetracycline, penicillin or trimethoprim-sulfamethoxazole.

ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS)
Neurologic disorders affecting central or peripheral nervous system occur in more than 80% of patients. CNS manifestations of patients who are HIV positive occur if there is high viral load and CD-4 lymphocyte count is less than 200. The human immunodeficiency virus (HIV) has neurotrophic features. Patients infected with HIV develop opportunistic infections and unusual CNS neoplasms. Neurologic manifestations of AIDS can be due to direct or indirect effects of HIV. Neurological manifestation in asymptomatic seropositive patients or those who have AIDS-related complex are uncommon; majority of central neurologic complications occur in AIDS patients.

Direct Effect of HIV on Nervous System

AIDS-Dementia Complex
The earliest signs of the AIDS-dementia complex are usually neurobehavioral (impaired memory, difficulty concentrating, psychomotor retardation, apathy, depression). Motor signs include impaired coordination and ataxia. CSF findings are lymphocytic pleocytosis with elevated protein content; studies for opportunistic infections are negative. CT and MRI are usually negative in early stages; later generalized cerebral atrophic pattern with hypodense lesions in periventricular white matter, subcortical nuclear regions (basal ganglia, thalamus), and brain stem regions can be seen. The clinical course is characterized by rapid progression with development of dementia, myoclonus, seizures, motor impairment, and incontinence. Occurrence of AIDS-dementia complex is less common since introduction of highly active antiretroviral therapy including protease inhibitors and other combination therapies. In AIDS-dementia patients, autopsy findings include necrotic and vacuolated brain lesions containing multinucleated macrophages. The lesions are located predominantly in white matter and brain stem, with the cerebral cortex relatively spared.
Myelitis-Myelopathy
The spinal cord can also show vacuolar necrotizing lesions, believed due to HIV. Spinal MRI is necessary to exclude spinal cord lesions caused by opportunistic infection or neoplasm. CSF analysis should be performed to exclude herpes zoster and cytomegalovirus infection, which can cause myelitis, and to exclude neurosyphilis.

Radiculopathy
Involvement of lumbar and sacral roots by HIV can cause leg weakness and paresthesias with autonomic (bladder, bowel) dysfunction. Radiculopathy is frequently caused by cytomegalovirus (CMV). There is usually also evidence of retinitis. CSF can show polymorphonuclear pleocytosis with positive CSF culture for CMV. Ganciclovir is used to treat CMV.

Muscle Disease
Severe inflammatory myositis in which muscles show profound necrosis with lymphocytic infiltrates can develop in AIDS patients. Viral conditions and toxoplasmosis can precipitate polymyositis. AZT can cause mitochondrial myopathy. Differentiation of HIV-induced or toxoplasmosis myopathy from AZT-induced myopathy can be established by muscle biopsy findings in which drug-related muscle damage shows marked mitochondrial abnormalities.

Neuropathy
Acute inflammatory demyelinating polyneuropathy (similar to Guillain-Barré syndrome) can cause ascending or descending motor weakness. The initial features of demyelinating neuropathy can be bilateral facial paresis. This can occur in early stages of HIV infection. CSF can show pleocytosis, but protein content is usually elevated. EMG-NCV shows evidence of demyelinating neuropathy. This disorder responds to plasmapheresis or intravenous immunoglobulin (IVIG). In AIDS patients, painful sensorimotor neuropathy of axonal type can develop. This can be due to direct HIV effects, complications of antiviral medication (mostly nucleoside antiretrovirals (didanosine, zalcitabine, stavudine, and lamivudine) or complicating metabolic-toxic disorder e.g., alcohol. Sensory symptoms are more prominent than motor weakness in AIDS neuropathy; treatment with amitriptyline or sodium channel blocking, antiepileptic medication administered at bedtime or use of pain medication can be effective in controlling neuropathic pain.

Indirect Effects of HIV on Nervous System
The indirect effects of HIV result from immunodysfunction. It is not uncommon for patients to have multiple infections.

Opportunistic Infections
Toxoplasmosis. This is an intracellular protozoan (Toxoplasma gondii) that is transmitted by human secretions or through transfusions. Pathologically, multiple diffuse necrotizing intracranial lesions with minimal cellular inflammatory response develop. CSF can show lymphocytic pleocytosis. CT/MRI shows multiple ring-enhancing intracranial lesions; however, these findings are not specific enough to establish the diagnosis of toxoplasmosis. Serological
test is positive in almost all people; therefore negative toxoplasmosis serology excludes this diagnosis. Because this is the most common CNS lesion in AIDS patients, empiric antitoxoplasmosis therapy is initiated if CT/MRI shows intracranial lesion(s). Treatment includes sulfadiazine and pyrimethamine. If the patient is allergic to sulfa, substitute clindamycin. If there is improvement evident clinically and with CT/MRI, this supports the presumptive diagnosis; however, if the condition progresses with empiric treatment, brain biopsy is needed. Life-long suppressive treatment for toxoplasmosis is necessary. Corticosteroids are used to supplement antibiotics in acute stage only if edema and mass effect occur as the lymphopenic effect of corticosteroids can be effective in treating lymphoma which is second most common brain lesion in AIDS patients.

**Fungal Disease.** Cryptococcosis is the most common. (see page 18-5)

**Neurosyphilis.** (see page 18-6)

**Mycobacteria.** (see page 18-4)

**Viral infections.** "Subacute meningitis" is most common neurologic disorder affecting patients with AIDS. CSF shows lymphocytic pleocytosis and elevated protein and gamma globulin content. Meningitis can be initial response to HIV and can be seen in 33% of neurologically asymptomatic seropositive patients even in the early stages of the illness. The rule is that CNS infection with CSF lymphocytic pleocytosis occurs early but CNS dysfunction occurs later in the disorder. It is not uncommon for patients with HIV infection to have nonspecific symptoms e.g., dizziness, fatigue, depression, and the physician performs LP and CSF shows lymphocytic pleocytosis. CSF analysis must be performed to search for serious etiologies. All HIV positive patients with new onset headache and seizures must be evaluated for infectious-inflammatory, neoplastic or vascular disorders.

**Progressive Multifocal Leukoencephalopathy.** (see page18- 17)

**Central Nervous System Neoplasms.** Primary CNS lymphomas may be present with dementia, seizures, motor disturbances, and cranial nerve dysfunction. These tumors are located in basal ganglia, thalamus, cerebellum, and periventricular white matter. Diagnosis is established by CT/MRI which shows enhancing periventricular lesions. Patients usually have positive Epstein-Barr virus in CSF as detected by PCR. Brain lymphomas are highly radiosensitive and also respond to corticosteroids but they frequently recur. Kaposi's sarcoma also occurs in AIDS patients and can metastasize to the brain and undergo hemorrhagic degeneration. These lesions are radiosensitive but also rapidly recur.

**INFECTIVE ENDOCARDITIS**

Thirty-percent of patients with infective endocarditis develop neurological complications. Most commonly there is septic embolic stroke with vegetations (consisting of microorganisms with platelet-fibrin material) embolizing to cerebral vessels. If embolus contains microorganisms, these can infect arterial wall. There is necrosis and weakening of arterial wall leading to mycotic aneurysm formation. Mycotic aneurysm forms at distal arterial branch (as contrasted with proximal site of berry aneurysm). This mycotic aneurysm can rupture to cause intracranial hemorrhage. If microorganism migrate into brain parenchyma, cerebritis or abscess may develop. Mycotic aneurysm can be single or multiple. These are detected by angiography. Antibiotics treat endocarditis, and mycotic aneurysm can heal with medical (antibiotic) therapy. Those not resolving with antibiotics can require surgery to avoid the risk of hemorrhage.
Heparin should not be used to prevent embolic stroke in patients with endocarditis; however, some of the emboli are nonseptic and embolization can be prevented by anticoagulation. The risk-benefit ratio of anticoagulation in these situations must be considered carefully.

**SUBDURAL EMPYEMA (SDE)**

SDE can develop from infected contiguous source (paranasal sinusitis, orbital cellulitis, mastoiditis, skull osteomyelitis, meningitis). SDE is defined as pus collection between dura and arachnoid. The most common location is over frontal convexities or in interhemispheric fissure. Cortical vein and dural sinus thrombosis or brain abscess can complicate SDE. Clinical features of SDE include headache, fever, and stiff neck; however, altered mentation, focal neurologic deficit, and papilledema occur later. Rapid neurologic deterioration can occur; lumbar puncture is potentially hazardous procedure with SDE, sometimes precipitating transtentorial herniation. CSF findings are nondiagnostic and include elevated intracranial pressure, sterile pleocytosis, elevated protein, normal sugar, and negative culture. Diagnosis is established by CT/MRI showing lenticular-shaped extracerebral lesions. Choice of initial antibiotics depends on SDE source. Following head trauma, *S. aureus* is common; with ear infections, *Proteus mirabilis, Pseudomonas aeruginosa*, or anaerobic streptococci; with sinus infection, bacteroids, gram negative aerobes and sometimes mixed infections. SDE patients are frequently very ill, and the CT/MRI should be immediately performed. Early initiation of empiric antibiotics and surgical drainage should be carried out. Subsequent antibiotic therapy is continued by 4-6 weeks; choice of subsequent antibiotics is determined by results of bacterial Gram stain and culture obtained from surgery.

**CRANIAL EPIDURAL EMPYEMA (CEE)**

This is localized pus collection in preformed space between skull and dura. CEE occurs in setting similar to that of SDE. Expansion of CEE occurs as dura is torn away from inner skull table, forming well-circumscribed pus collection; this contrasts with diffuse extracerebral pattern of SDE. Clinically there can be tenderness over skull, ear or sinus with specific tenderness over CEE site. These patients develop cranial nerve paresis as CEE extends into foramen of cranial nerves through which they exit dura and bone. For example, with temporal bone involvement trigeminal and abducens paresis can develop with tenderness over temporal bone, and there can be facial pain and paresthesias. Diagnosis is established by CT or MRI showing localized extracerebral collection, frequently with evidence of bone or sinus involvement. Treatment includes bone and dural surgical debridement and antibiotic therapy.

**FOCAL SUPPURATIVE CEREBRITIS AND BRAIN ABSCESS**

Suppurative brain reaction can result from local contiguous extension or hematogenous dissemination of systemic infection (endocarditis, bronchiectasis) or sepsis. Hematogenous dissemination frequently results in multiple noncontiguous lesions, usually in areas supplied by middle cerebral artery; whereas direct local extension always causes solitary or directly contiguous multiple lesions(s). In focal suppurative cerebritis, initial pathologic reaction includes edema, tissue necrosis, PMN cellular infiltration, and multiple petechial brain hemorrhages. Brain abscess is defined as sharply demarcated focus of suppuration within brain tissue with surrounding capsule. In region surrounding necrotic core there is fibroblastic response with granulation tissue developing within the capsule. Because vascular supply is
better formed in superficial cortex, this portion of capsule is thicker than capsule on ventricular surface. If abscess rupture occurs, it is usually through thinner ventricular portion rather than into subarachnoid spaces due to protective effect of thicker capsule on cortical (superficial) surface.

In early stage of focal suppurative cerebritis, patients show meningeal signs and altered mentation; focal neurologic deficit and papilledema are uncommon. EEG shows slow wave focus; CSF shows sterile pleocytosis with normal sugar content. CT/MRI findings are usually positive. CT shows hypodense lesion with significant mass effect, and post-contrast study shows incomplete ring enhancement (Figure 18-1). MRI can show central necrotic core, surrounding edema, and mass effect; postgadolinium MRI can show ring enhancement. Both CT and MRI have high degree of sensitivity but low specificity for cerebritis-abscess diagnosis as other inflammatory and neoplastic conditions can have similar CT/MRI appearances. It is important to differentiate cerebritis (in which there is an absent or poorly formed capsule) from abscess as treatment options are different. This is usually possible with CT/MRI if clinical history indicates infectious condition. From treatment perspective, antibiotics can penetrate cerebritis or thin-wall abscess, and surgical treatment can be avoided; whereas thick-walled abscess will require surgical drainage.

Treatment of focal suppurative cerebritis includes intravenous antibiotics; this can be supplemented by corticosteroids to reduce cerebral edema. Many cases of brain abscess are caused by multiple microorganisms. Initial antibiotics include penicillin plus metronidazole. Metronidazole penetrates blood-CSF and blood-brain barrier and exhibits bactericidal activity against anaerobic bacteria. Adequate coverage against anaerobic bacteria is necessary because these are present in 90% of nontraumatic focal brain infections and can be sole causal organism in 50% to 66%. If cerebritis-abscess has resulted from open head trauma or develops following neurosurgical procedure, coverage for Staphylococcus aureus and aerobic gram-negative bacilli is necessary and this includes Vancomycin. Intravenous antibiotics should be continued for 6 to 8 weeks and this should be followed by oral antibiotics for 3 months. Following antibiotic treatment clinical recovery is expected with normalization of CT/MRI findings. In certain cases the area of suppuration becomes encapsulated. In these cases clinical and CT resolution do not occur, and the CT/MRI shows dense ring enhancement consistent with firm nonpenetrable capsule; surgical drainage is necessary at this stage.

If encapsulated abscess forms, clinical findings include altered mentation, focal neurological deficit, and papilledema. Symptoms and signs associated with brain abscess are nonspecific, and an infectious condition may not be initially considered because fever is absent (30% to 50%), and peripheral white cell count is normal (40%). Headache (64%) is the most common complaint. The most characteristic clinical picture consists of a headache, recent seizure, altered consciousness, low-grade fever, papilledema, and focal neurological deficit.

CT and MRI are the safest, most sensitive, and most specific procedures to detect brain abscess (Figure 18-1), being positive in 95%. This shows ring-enhancing lesion representing encapsulation. The abscess capsule is sometimes thick enough that it is relatively impermeable to antibiotics; however, in other cases capsule is completely formed but remains thin and can be permeable to antibiotics.

The outcome for suppurative cerebritis and brain abscess was associated with 25% to 30% mortality before CT/MRI despite antibiotic treatment. With CT/MRI it is possible to determine three crucial features: (1) presence of single or multiple lesions; (2) stage of capsule
development, for example, cerebritis, early abscess with thin wall, or late abscess with thick wall; and (3) degree of mass effect. With CT/MRI, mortality has decreased to less than 5%, probably because of earlier diagnosis, better localization, earlier and more precise determination of need for medical or surgical management. If multiple abscesses are present, medical therapy is indicated. The primary therapy for certain single (solitary) brain abscess consists of antibiotics and surgical drainage, especially if CT/MRI shows thick-walled abscess. In certain single or multiple abscess(es), antibiotics and corticosteroids cause resolution of abscess without surgery, especially if abscess wall appears thin. This represents a major advance because before CT/MRI all patients would have required surgery. Corticosteroids are used to decrease cerebral edema, but their effect on pathologic process (immunologic suppression and fibroblastic proliferation) is not known. The initial antibiotic therapy for abscess(es) includes intravenous penicillin and vancomycin. The choice of empiric therapy is based on the most likely bacterial source. If there is septicemia or endocarditis, antibiotics are selected based on the results of the blood culture. Brain abscess developing as a result of head trauma can require coverage for \textit{S. aureus} using oxacillin and vancomycin. Treatment is usually continued for 6 to 8 weeks after the surgical drainage of a brain abscess. Serial CT/MRI is helpful in monitoring response to therapy. The pathological process as visualized by CT/MRI can take several additional months to resolve after antibiotics have been discontinued.

\textbf{VIRAL MENINGOENCEPHALITIS}

Acute viral infections can present in three forms: (1) meningitis which is usually self-limited disorder manifested by headache, neck stiffness and photophobia; (2) encephalitis characterized by altered mental status, seizures and focal neurological deficit; (3) myelitis with involvement of spinal cord with motor, sensory and autonomic (bladder and bowel incontinence), or with only involvement of anterior horn cells (poliomyelitis). There is hematogenous infection; the virus enters CNS across endothelial cell. Certain viruses infect meninges and ependyma (meningitis), others infect neurons and glial cells (encephalitis), and some viruses infect both meninges and brain to cause meningoencephalitis. Initial symptoms of meningoencephalitis are headache, nausea, vomiting, and change in behavior. Findings include altered mentation, seizures, focal and neurologic deficit. CSF findings are pleocytosis (lymphocytic predominance), normal sugar content, and elevated protein content. The causal virus is isolated in only 25% of cases of viral meningoencephalitis. The viruses most likely to cause encephalitis are arbovirus and herpes simplex virus type 1. Recently, West Nile has become a new disorder causing encephalitis or myelitis. The course of viral CNS infection is monophasic; improvement begins within 2 to 3 weeks; however, in some cases significant residual neurologic deficit can persist. Most viral encephalitis appear as diffuse encephalitic condition; however, herpes simplex type 1 appears as focal temporal-frontal cerebritis.

\textbf{Arthropod-Borne (Arbovirus)}

Arboviruses include the alphaviruses, and these are part of the togavirus group, and the other part of togavirus is the rubivirus (rubella virus). Equine encephalitis is caused by the alphavirus (Group A arbovirus) and St. Louis encephalitis is caused by flavivirus (Group B arbovirus). Most cases of arbovirus encephalitis occur during summer and fall and are transmitted to humans by mosquitoes. Mosquitoes are responsible for St. Louis encephalitis (SLE), Western equine encephalitis (WEE), Eastern equine encephalitis (EEE), and West Nile encephalitis.
(WNE). WEE is usually mild viral encephalitis with minimal neurologic sequelae; mortality is 10%. EEE is more severe disease characterized by high fever, altered mentation, convulsions, and permanent neurological impairment (dementia, retardation, psychoses, motor deficit, seizures). It has mortality of 70%. Patients with SLE have confusional states, head tremor, prominent primitive reflexes; neurologic residua persists in 10%. The overall case-fatality of arbovirus encephalitis is 10%; however, in elderly patients this can reach 30%. The diagnosis is established by fourfold rise in acute and convalescent blood antibody titer or by viral isolation from CNS tissue (almost never from CSF culture). There is no specific therapy for arbovirus encephalitis, but supportive therapy is important. In West Nile encephalitis, there may be initial myelitis or anterior horn cell presentation similar to poliomyelitis. Diagnosis is established by: (1) West Nile virus IgM in CSF; (2) West Nile virus RNA detected in CSF; (3) 4-fold increase in IgG in acute and convalescent sera; (4) isolation of virus from brain or spinal cord. MRI may show diffuse meningeal enhancement or hyperintense basal ganglia and thalamic lesions. CSF shows lymphocytic pleocytosis with elevated protein and normal sugar.

Herpes Simplex Virus

Herpes simplex virus type 1 attacks skin, mucous membrane, and CNS. It is thought to enter CNS through olfactory or trigeminal nerve(s). Patients have fever, headaches, meningeal signs, altered mentation, papilledema, and focal neurologic deficit with prominent temporal lobe dysfunction (aphasia, visual field defect, amnesia). CSF findings include pleocytosis with lymphocyte predominance, red blood cells (500 to 1,000 mm$^3$), elevated protein, and normal sugar (rarely CSF glucose is decreased and positive PCR for herpes simplex). Because serum antibodies to herpes simplex are present in 40% to 60% of normal subjects, elevated titer is not helpful in establishing diagnosis of CNS infection. This is established only by brain biopsy with analysis for immunofluorescent antibody staining for herpes simplex, intranuclear inclusion bodies, and isolation of herpes virus. In patients with clinical signs of temporal lobe dysfunction and systemic signs of infectious illness who have CT/MRI and EEG evidence of temporal abnormalities, presumptive diagnosis includes herpes simplex encephalitis (Figure 18-2). Pathologic findings include hemorrhagic necrosis localized to inferior medial temporal lobe. Acyclovir (Zovirax) has been proven effective in treating herpes simplex encephalitis and has minimal toxicity. In patients with suspected herpes simplex encephalitis, initiate empiric antiherp es simplex treatment with acyclovir in dose of 10 mg per kgm intravenously for 10 days. Treatment should be initiated immediately to minimize brain inflammatory reaction. If clinical deterioration occurs with acyclovir or CT/MRI shows evidence of worsening despite treatment, brain biopsy should be carried out to exclude alternative etiologies of temporal lobe lesions, for example, neoplasm or other infectious-inflammatory disorders. If diagnosis is initially uncertain because of atypical features, initiate acyclovir therapy, then perform brain biopsy.

Cytomegalovirus Infection (CMV)

Cytomegalic inclusion body virus is member of herpes virus group. This may cause infection in utero by transplacental course or in adults with AIDS. In neonates, it may cause developmental defects (hydrocephalus, microcephaly), and in adults, encephalitis, ventriculitis or radiculitis. CSF culture is negative but PCR amplification is most sensitive diagnostic test. Treatment with ganciclovir, cidofovir and foscarnet may be effective.
Essentials of Clinical Neurology: Infectious Diseases of the Nervous System
LA Weisberg, C Garcia, R Strub
www.psychneuro.tulane.edu/neurolect/

Myxovirus

CNS disorders can be part of mumps infections. Mumps meningoencephalitis can rarely occur in patients without clinical parotitis. The diagnosis is established by mumps virus CSF isolation and fourfold increase of antihemagglutinin antibody titer in acute and convalescent stages. CSF can display lymphocytic pleocytosis, elevated protein, and sometimes low sugar content (hypoglycorrhachia).

Rabies

Rabies is neurotropic myxovirus that can be present in saliva of infected animal (dog, wolf, bat) and is usually but not always transmitted through the bite. The incubation period is 1 to 4 weeks. Initial symptoms are paresthesias and pain at bite site and then ascending motor neuropathy may develop. Within 7 to 14 days features of rabies include irritability, agitation, inability to swallow, hydrophobia, painful spasms, and coma. Diagnosis is established by finding fluorescent antibodies in the brain at necropsy of infected animal or human; presence of Negri bodies is relatively specific finding. Prophylactic treatment must include both rabies immune globulin (passive immunity) and human diploid cell rabies vaccine (active immunity). Use of human diploid cell rabies rather than duck vaccine has decreased neurotoxicity of treatment. Rabies immunoglobulin should be given with initial vaccine dose. After being bitten by potentially rabid animal, meticulous wound cleansing with soap and water followed by 70% ethanol is necessary.

Enterovirus (Picornavirus)

Enterovirus group includes polio, Coxsackie and echo viruses. These are spread by fecal-oral route. Clinical pattern is usually mild meningitis symptoms; CSF shows sterile lymphocytic pleocytosis. Diagnosis is established in following manner: virus is isolated from CSF, throat, or stool to determine subtype involved, then, if this test is positive, acute and convalescent blood titers for neutralization and complement fixation antibodies are performed. Treatment is symptomatic.

Poliomyelitis is caused by enterovirus. The virus enters through pharynx and viremia then develops. Initially, these patients have febrile illness with myalgias; they subsequently fully recover. CSF shows lymphocytic pleocytosis. Virus attacks large spinal and cranial bulbar motor neurons nerves; this causes rapid onset of weakness in limbs and bulbar muscles. There is sudden onset of asymmetrical (frequently unilateral) lower motor neuron type weakness with no sensory disturbances or incontinence. Certain patients progress to quadriplegia with respiratory failure and do not recover; others have mild motor weakness and fully recover. It is presumed that in these patients who recover fully, anterior horn cells were only partially injured and were capable of recovery. Recently, postpoliomyelitis syndrome has been described. This can develop 20 to 30 years after initial acute poliomyelitis. It is characterized by limb pain and increased weakness (in limbs that were initially affected). It is not known if this represents normal aging process or is due to immunologic condition characterized by further attack on motor neurons. Since development of Salk and Sabin immunizations, this paralytic disease due to poliovirus is almost never seen.

Varicella Zoster

Rarely encephalitis can rarely follow chicken pox. This usually develops one week after rash
Encephalitis can involve cerebellum to cause acute ataxia, dysarthria, and incoordination. This cerebellar ataxia usually resolves completely. In other cases, encephalitis causes impaired consciousness, seizures, and motor weakness. In postvaricella encephalitis, recovery is less complete.

**Measles**

Following measles there can be postinfectious disorder characterized by fever recurrence, altered consciousness, seizures, motor deficit, and myoclonus. There is white matter demyelination; this occurs as the rash fades. This is an uncommon measles complication, but neurologic morbidity is high. CT/MRI can show multiple focal white matter lesions which can be confused with white matter demyelinating disorders such as multiple sclerosis.

**Herpes Zoster**

Varicella (chickenpox) zoster virus causes inflammatory lesions in dorsal (sensory) root ganglia and cranial nerve (ophthalmic branch of trigeminal and geniculate) ganglia. Initial symptoms of zoster infection are vesicular skin lesions occurring in distribution of involved ganglia. The patient can later develop dysesthetic pain. These lesions and the resultant pain syndrome most commonly involve thoracic region. In certain cases there can be ophthalmic involvement; this can result in corneal scarring. In otic zoster infection there is involvement of geniculate ganglion. Vesicles can be seen on eardrum, and unilateral facial paralysis can develop. In rare cases bandlike thoracic pain caused by herpes zoster can occur in the absence of vesicles. Acyclovir is used in both immunologically competent and incompetent patients. It is most effective in immunocompromised patients with disseminated herpes zoster. Use acyclovir, 5 mg/kg intravenously three times per day for 5 to 7 days, for these patients. In immunologically intact patients, use acyclovir 800 mg five times per day orally for 7 days. Valacyclovir and famciclovir have been utilized to reduce viral dissemination. Postherpetic pain is characterized by spontaneous burning pain, developing at the site of previously visualized vesicles. Postherpetic pain may respond to amitriptyline, phenytoin, carbamazepine, gabapentin.

**PRION DISEASES**

**Creutzfeldt-Jakob Disease (CJD)**

These are transmissible agents which contain no DNA or RNA and are resistant to heat, ultraviolet light and ionizing radiation, but is sensitive to agents which denature protein (phenol). The characteristic pathological brain change is vacuolation and spongiform change with neuronal loss. Prion diseases in humans include Jakob-Creutzfeldt, Kuru, fatal familial insomnia, and in animals - scrapie, chronic wasting disease of deer, bovine spongiform encephalopathy (“mad cow” disease).

CJD is characterized by rapidly progressing dementia and myoclonus. As disease progresses there can be motor signs, for example, ataxia and increased limb tone. CSF shows no abnormal cellular response, but protein can be elevated. The presence of 14-3-3 protein in CSF helps confirm diagnosis of CJD. EEG shows periodic (0.5 to 2.0 seconds) high-voltage spikes or slow wave patterns. CT/MRI shows enlarged ventricles and subarachnoid spaces. Pathologic findings are vacuolated spongiform neurons and astrocytes in cerebral cortex and basal ganglia; however, despite that this is due to transmissible agent, there is no brain inflammatory change.
The agent causing CJD is different from usual viruses and is believed to be a proteinaceous infectious particle not containing nucleic acids; this has been referred to as "prion". Disorders caused by "prions" are not contagious. The exact mechanism of transmission of the disease is not known, but tissue transmission (corneal transplants, human pituitary growth hormone, inadequately sterilized brain surgery equipment, for example, electrodes, stereotactict equipment) has occurred. The transmissible agent is resistant to physical and chemical treatment (heat, ionizing and ultraviolet radiation which affects DNA); therefore, autoclaving or bleach is necessary which denature protein. There is no effective treatment to the neurological disorder. Patients rapidly progress to coma and die.

Kuru
Kuru occurs in natives of New Guinea highlands. Cannibalism is major transmission mode. Clinical symptoms include ataxia followed by mental deterioration. There is progression to coma and death in less than 2 years. Pathologic changes include neuronal and astrocytic spongiform degeneration.

CHRONIC VIRAL INFECTIONS

Progressive Multifocal Leukoencephalopathy (PML)
PML is demyelinating disease caused by papovavirus. It is most common in patients with impaired cellular immunity, e.g., AIDS, transplant patients. Clinical symptoms include rapidly progressive dementia, visual impairment and hallucinations, ataxia, weakness, and cranial nerve dysfunction. This disorder rapidly worsens, and these patients die. CSF and EEG show no abnormalities. The CT/MRI can show symmetrical bilateral subcortical posterior hemispheric white matter lesions. These demyelinated lesions can initially occur in occipital-parietal region; they subsequently enlarge and spread anteriorly. Pathologic findings are multifocal demyelinated areas, loss of oligodendrocytes, and eosinophilic intranuclear inclusion bodies. Viral particles consistent with papovavirus have been recovered from these patients. Treatment with antiviral agents (cytosine, arabinoside, interferon, acyclovir) has not been successful.

Subacute Sclerosing Panencephalitis (SSPE)
SSPE is caused by rubeola (measles) virus; it occurs in children. The initial clinical symptoms include slowly progressive dementia, ataxia, and myoclonus. The disease usually progresses to coma with quadriplegia, dystonia, and seizures; however, rarely patient's condition stabilizes. CSF shows no pleocytosis or elevated protein content, but there is elevated gamma-globulin content. EEG shows periodic high-voltage slow waves followed by an isoelectric (burst suppression) pattern. Measles antibodies are elevated in serum and CSF. Pathologic findings include perivascular cerebral and white matter infiltration with mononuclear cells. There is demyelination in white matter. Intranuclear and intracytoplasmic inclusion bodies are found in neurons and astrocytes; measles virus can be isolated from brain tissue.
PARASITIC INFECTIONS

Toxoplasmosis
Toxoplasmosis is discussed on page 18-9.

Cerebral Malaria
Cerebral malaria occurs rarely in patients affected by *Plasmodium falciparum*. Diagnosis is established by demonstration of organism on thick and thin blood smears. Neurologic symptoms include acute encephalopathy (altered consciousness, seizures) and are due to capillary occlusion by parasites and infected red blood cells. CSF is usually normal. Treatment includes chloroquine and quinine.

Primary Amebic Meningoencephalitis
Primary amebic meningoencephalitis is caused by free-living ameba (including *Naegleria* and *Acanthamoeba* species). These parasites are usually found in freshwater lakes and pools. They enter nasal mucosa and travel along cribriform plate and olfactory nerves to undersurface of frontal lobes. Clinical features include fever, meningeal signs, and frontal headache. CSF findings include polymorphonuclear pleocytosis. Motile amebae can be identified by wet-mount CSF preparations; stained amebae can be demonstrated by Wright's or Giemsa stain. Ameba will not be demonstrated by routine bacterial stains because heat fixation degenerates these organisms. Treatment includes amphotericin B, ketoconazole, or metronidazole.

Trichinosis
Trichinosis is caused by roundworm *Trichinella spiralis*. Infection occurs in humans if raw or poorly cooked pork is ingested. The parasite is contained in striated muscles of pigs. Trichinosis can cause acute febrile illness, rash, conjunctivitis, eyelid edema, gastrointestinal symptoms, and myalgias. Subcutaneous and muscular nodules can be palpated. There can be muscle tenderness and weakness; muscle biopsy can show encysted *Trichinella* organisms. This organism can spread to the brain to cause encephalitis. The diagnosis is established by history of pork ingestion, presence of eosinophilia in blood count, and muscle biopsy findings showing parasite. Treatment includes thiabendazole.

Cysticercosis
Cysticercosis is caused by encystment of larvae of *Taenia solium* (pork tapeworm) in human tissues. Humans ingest ova of *Taenia solium* from contaminated food or water, as well as being infected by fecal-oral transmission of ova derived from intestinal parasite. Ova are digested in the stomach and release oncospheres that extend through gastrointestinal wall to reach CNS and muscle by hematogenous dissemination. When cysticercosis dies there can be an active inflammation in brain, meninges, or ventricles. After active inflammatory response has terminated, intracranial gliosis, calcification, and cyst formation occur. Larval forms develop in skeletal muscle and brain. Cysticercosis can enlarge in meninges, ventricles, or brain parenchyma to form multiloculated cysts. Symptoms depend on cyst location: meningeal with
obstruction of basal cisterns cause intracranial hypertension and meningitic reaction, intraventricular, form mass lesions within lateral ventricles and obstructive hydrocephalus, and parenchymal cause mass lesions or seizures as result of cortical cysts. Intracranial calcification is commonly due to cysticercosis occurring in inactive stage. Diagnosis can be made by biopsy of subcutaneous nodule if any are present. In certain cases CSF shows PMN or eosinophilic pleocytosis. Serologic CSF tests can demonstrate antigens or antibodies for cysticercosis, but these are not diagnostic. CT/MRI can show hydrocephalus, parenchymal lesions, or calcifications (these probably represent dead organisms). Therapy includes shunting for hydrocephalus and corticosteroids to reduce edema associated with inflammatory reaction. Praziquantel, an anthelmintic, is effective to kill live larva. It is used at dosage of 50 mg kg daily for 14 days. This can exacerbate the inflammatory response and worsen clinical symptoms transiently.

**TETANUS**

Tetanus is caused by toxin of anaerobic bacterium. *Clostridium tetani*. This organism is frequently found in soil, and it can contaminate wounds. Toxin spreads along neural sheath or by hematogenous dissemination to invade spinal cord and brain stem. Tetanus toxin blocks interneurons. The earliest symptoms of tetanus include muscle spasms in thoracic and lumbar paraspinal muscles, which can gradually spread to involve jaw (lockjaw), face (risus sardonicus), pharynx (dysphagia), or larynx (respiratory stridor). Initial mild intermittent muscle spasms can progress to persistent muscle rigidity and tetanic spasms. Treatment includes identification and adequate debridement of wound; passive immunization with 12,000 units of tetanus-immune globulin; active immunization with tetanus toxoid; tracheostomy to provide adequate ventilation support for the prolonged 6- to 12-week course of intense generalized muscle spasms; central venous line for hyperalimentation; cardiac monitoring to prevent arrhythmias caused by sympathetic over-discharge; curare to suppress severe tetanic contraction, which if not controlled lead to muscle breakdown with myoglobinuria; and skin care to prevent decubitus ulcers. Mortality from generalized tetanus can be 60% despite adequate supportive care. If complications are prevented, toxin is released from interneurons after several weeks, and the patient gradually recovers.

**SUMMARY**

CNS infection can be caused by bacteria, virus, fungi, tuberculosis, spirochetal organisms, or parasites. The pathological process can be diffuse (meningitis, encephalitis) or focal (cerebritis, abscess, subdural, or epidural empyema). Diagnosis of meningitis and encephalitis is established by performing lumbar puncture with CSF analysis; diagnosis of focal CNS infection is best established by CT or MRI, and LP can be dangerous if focal CNS infectious-inflammatory lesion is present. CNS infection results in damage to blood-brain barrier, and this loss of integrity of the barrier permits antibiotics to penetrate into CNS. Treatment with appropriate antibiotics must be parenteral route and in high dose to treat CNS infection completely. Early diagnosis of CNS infection is mandatory to prevent irreversible brain injury. In patients with HIV infection CNS infectious-inflammatory and neoplastic disorders occur as a result of immunosuppression of patients' natural defense mechanisms.
FIGURES & TABLES

Figure 18-1. A & B
Irregular marginated nonenhancing hypodense left temporal lesion; suppurative cerebritis was evident at autopsy.

Figure 18-1. C
Sharpenly marginated hypodense left cerebellar lesion that effaces the fourth ventricle and is causing obstructive hydrocephalus.

Figure 18-1. D
Following contract infusion there is a thin peripheral enhancing rim. An encapsulated brain abscess was identified at surgery.
Figure 18-2. A
Irregular marginated extensive hypodense in left frontal temporal lesion causing mass effect.

Figure 18-2. B
Following contrast infusion, there is irregular or diffuse enhancement. Herpes simplex encephalitis was diagnosed at surgery.
TABLE 18-1
Differential Diagnosis of Abnormal CSF Using Cell Count, Cell Type, and Sugar Concentration

<table>
<thead>
<tr>
<th>Group</th>
<th>Predominant Cell Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>Thousands of cells, decreased sugar</strong> *</td>
</tr>
<tr>
<td></td>
<td>Bacterial meningitis</td>
</tr>
<tr>
<td></td>
<td>Ruptured brain abscess</td>
</tr>
<tr>
<td></td>
<td>Partially treated bacterial meningitis</td>
</tr>
<tr>
<td></td>
<td>Naeglerial (amebic) meningitis</td>
</tr>
<tr>
<td>2</td>
<td><strong>Thousands of cells, normal sugar ñ</strong></td>
</tr>
<tr>
<td></td>
<td>Early or partially treated bacterial meningitis</td>
</tr>
<tr>
<td></td>
<td>&quot;Chemical meningitis&quot;</td>
</tr>
<tr>
<td>3</td>
<td><strong>Hundreds of cells, decreased sugar</strong></td>
</tr>
<tr>
<td></td>
<td>Bacterial meningitis</td>
</tr>
<tr>
<td></td>
<td>Granulomatous meningitis</td>
</tr>
<tr>
<td></td>
<td>Meningovascular syphilis</td>
</tr>
<tr>
<td></td>
<td>Sarcoïdosis</td>
</tr>
<tr>
<td></td>
<td>Neoplastic meningitis</td>
</tr>
<tr>
<td></td>
<td>Spontaneous subarachnoid hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Rare association with viral meningitis (mumps, and lymphocytic choriomeningitis)</td>
</tr>
<tr>
<td></td>
<td>Rare associated with <em>Herpes hominis</em> type 1 encephalitis</td>
</tr>
<tr>
<td>4</td>
<td><strong>Hundreds of cells, normal sugar</strong></td>
</tr>
<tr>
<td></td>
<td>Early bacterial meningitis</td>
</tr>
<tr>
<td></td>
<td>Partially treated bacterial meningitis</td>
</tr>
<tr>
<td></td>
<td>Early granulomatous meningitis</td>
</tr>
<tr>
<td></td>
<td>Parameningeal infections</td>
</tr>
<tr>
<td></td>
<td>Meningovascular syphilis</td>
</tr>
<tr>
<td></td>
<td>Aseptic &quot;viral&quot; meningitis-encephalitis</td>
</tr>
<tr>
<td></td>
<td>Lead Poisoning (children)</td>
</tr>
<tr>
<td></td>
<td>Bacterial endocarditis</td>
</tr>
</tbody>
</table>

* A CSF cell count > 10/mm³ or more then 1 PMN/mm³ is considered abnormal.  
A decreased sugar concentration is less than 40% of a simultaneous blood sugar concentration.  
Ñ Least common category.  
_Tuberculous, fungal, brucella, listeria, and parasitic._
### TABLE 18-2
Antibiotic Therapy in Bacterial Meningitis

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ROUTE</th>
<th>CHILD’S DAILY DOSE</th>
<th>ADULT’S DAILY DOSE</th>
<th>FREQUENCY</th>
<th>INDICATION</th>
</tr>
</thead>
</table>
| Ampicillin | IV    | 75-100 mg/Kg       | 12 g               | Every 6 hours | *N. meningitides*  
|            |       |                    |                    |           | *S. pneumoniae*  
|            |       |                    |                    |           | *Hemophilus influenzae*  
|            |       |                    |                    |           | *S. agalactiae*  
|            |       |                    |                    |           | *L. monocytogenes* |
| Penicillin G| IV    | 50,000 U/kg        | 20-24 million U    | Every 4 hours | *S. pneumoniae*  
|            |       |                    |                    |           | *N. meningitides*  
|            |       |                    |                    |           | *S. agalactiae*  |
| Nafcillin  | IV    | 50-75 mg/kg        | 12 g               | Every 4 to 6 hours | *Staphylococcus aureus* |
| Chloramphenicol | IV | 25-50 mg/kg       | 6 g                | Every 6 hours | *Hemophilus influenzae*  
|            |       |                    |                    |           | *Escherichia coli*  
|            |       |                    |                    |           | Anaerobes |
| Carbenicillin | IV | 400-500 mg/kg      | 30-40 g            | Every 4 hours | *Pseudomonas* |
| Ticarcillin | IV    | 200-300 mg/kg      | 18-24 g            | Every 4 hours | *Proteus*  
|            |       |                    |                    |           | *Escherichia coli* |
| Metronidazole | PO or IV | Not FDA approved for children | 15 mg/kg loading dose, then 7.5 mg/kg | Every 6 hours | Anaerobes |
| Gentamicin  | IV    | 5 mg/kg            | 5 mg/kg            | Every 6 hours | *Pseudomonas*  
|            |       |                    |                    |           | and other Aerobic gram-negative bacilli |
| Tobramycin  | IV    | 5 mg/kg            | 5 mg/kg            |            |                                   |
| Amikacin    | IV    | 15 mg/kg           | 15 mg/kg           |            |                                   |
| Cefotaxime  | IV    | 50 mg/kg           | 2-3 g              | Every 6 hours | *H. influenzae*  
|            |       |                    |                    |           | *S. pneumoniae*  
|            |       |                    |                    |           | *Enterobacteriaceae*  
|            |       |                    |                    |           | *P. aeruginosa*  |
| Ceftriaxone | IV    | 50 mg/kg           | 2-3 g              | Every 12 hours in children; one daily in adults  
|            |       |                    |                    |           | *H. influenzae*  
|            |       |                    |                    |           | *S. pneumoniae*  
|            |       |                    |                    |           | *Enterobacteriaceae*  
|            |       |                    |                    |           | *P. aeruginosa*  |
| Ceftizoxime | IV    | 50 mg/kg           | 12 g               | Every 6 hours in children; every 8 hours in adults  
|            |       |                    |                    |           | *H. influenzae*  
|            |       |                    |                    |           | *S. pneumoniae*  
|            |       |                    |                    |           | *Enterobacteriaceae*  
|            |       |                    |                    |           | *P. aeruginosa*  |
| Vancomycin  | IV    | 10 mg/kg           | 2 g                | Every 6 hours | *S. aureus* |
| Oxacillin   | IV    | 300 mg/kg          | 12 g               | Every 4 hours | *S. aureus* |
SUGGESTED READINGS

Acute Bacterial Meningitis

Tuberculous Meningitis

Cryptococcal Meningitis

Neurosyphilis

Lyme Disease

**Focal Suppurative Brain Infection**


**Viral Meningoencephalitis**


**Prion Diseases**


**Parasitic Infections**


**HIV Infection**

Whipple Disease

Chronic Viral Infections

Infective Endocarditis