CENTRAL NERVOUS SYSTEM INFECTIONS

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Acute meningitis

- Meningitis is an inflammatory process of the leptomeninges and cerebrospinal fluid (CSF) within the subarachnoid space, usually caused by an infection.
- Meningoencephalitis refers to inflammation of the meninges and brain parenchyma
- May be chemical
- Grouped as to:
- Pyogenic
- Aseptic
- Chronic

Acute meningitis

- There are systemic signs of infection
- Clinical evidence of meningeal irritation and neurologic impairment
- May see:
- Headache and photophobia
- Irritability
- Clouding of consciousness
- Neck stiffness

Acute meningitis

- Absence of fever, stiff neck, or altered mental state excludes meningitis in an adult.
- Lack of jolt accentuation of headache excludes meningitis (negative likelihood ratio, 0).
- Safe to perform LP without prior CT if no focal signs.

Acute meningitis

- A spinal tap yields cloudy or frankly purulent cerebrospinal fluid
- Increased pressure
- Large numbers of neutrophils
- Increased protein concentration
- Markedly reduced glucose content
- Normal CSF glucose is 2/3 that of concurrent serum level
- Bacteria may be seen on a smear or may be cultured

Table 28-2 Common Central Nervous System Infections

Type of Infection	Clinical Syndrome	Common Causative Organisms
Bacterial Infections		
Meningitis	Acute pyogenic meningitis	*Escherichia coli* or group B streptococci (infants) *Neisseria meningitidis* (young adults) *Streptococcus. pneumoniae* or *Listeria monocytogenes* (older adults)
	Chronic meningitis	*Mycobacterium tuberculosis*
Localized infections	Abscess Empyema	Streptococci and staphylococci Polymicrobial (staphylococci, anaerobic gram-negative)
Viral Infections		
Meningitis	Acute aseptic meningitis	Enteroviruses Measles (subacute sclerosing panencephalitis) Influenza species Lymphocytic choriomeningitis virus
Encephalitis	Encephalitic syndromes	Herpes simplex (HSV-1, HSV-2) Cytomegalovirus Human immunodeficiency virus JC polyomavirus (progressive multifocal leukoencephalopathy)
	Arthropod-borne encephalitis	West Nile virus Eastern equine encephalitis virus Western equine encephalitis virus St. Louis encephalitis virus La Crosse encephalitis virus Venezuelan equine encephalitis virus Japanese encephalitis virus Tick-borne encephalitis virus
Brainstem and spinal cord syndromes	Rhombencephalitis Spinal poliomyelitis	Rabies Polio West Nile virus
Rickettsia, Spirochetes, and Fungi		
Meningitic syndromes	Rocky Mountain spotted fever	*Rickettsia rickettsii*
	Neurosyphilis	*Treponema pallidum*
	Lyme disease (neuroborreliosis)	*Borrelia. burgdorferi*
	Fungal meningitis	*Cryptococcus neoformans* *Candida albicans*
Protozoa and Metazoa		
Meningitic syndromes	Cerebral malaria	*Plasmodium falciparum*
	Amebic encephalitis	*Naegleria* species
Localized infections	Toxoplasmosis	*Toxoplasma gondii*
	Cysticercosis	*Taenia solium*

Pyogenic meningitis

- Pyogenic meningitis is usually bacterial
- Neonates (0-4 weeks of age):
- Escherichia coli, group B streptococci, Listeria monocytogenes
- Hemophilus influenzae in the unvaccinated infants
- Children (4 weeks-6 years of age):
- Streptococcus pneumoniae, Neisseria meningitidis, Hemophilus influenzae type B, and Enterovirus

Pyogenic meningitis

- Children and adults (>6 years of age):
- Neisseria meningitidis, Enterovirus, Streptococcus pneumoniae, and Herpes Simplex virus
- Older adults:
- Streptococcus pneumoniae and Listeria monocytogenes

Pyogenic meningitis

- In acute meningitis, an exudate is evident within the leptomeninges over the surface of the brain
- The meningeal vessels are engorged and stand out prominently.
- In H. influenzae meningitis the exudate is usually basal
- In pneumococcal meningitis the exudate is often densest over the cerebral convexities near the sagittal sinus.
- Tracts of pus follow along blood vessels on the surface of the brain.
- May produce ventriculitis.

Pyogenic meningitis

- On microscopic examination, neutrophils fill the subarachnoid space in severely affected areas and are found predominantly around the leptomeningeal blood vessels in less severe cases.
- In fulminant meningitis, the inflammatory cells infiltrate the walls of the leptomeningeal veins and may extend focally into the substance of the brain (cerebritis).
- Phlebitis may lead to venous thrombosis and hemorrhagic infarction of the underlying brain.

Pyogenic meningitis

- Leptomeningeal fibrosis may follow pyogenic meningitis and cause hydrocephalus.
- Particularly in pneumococcal meningitis, large quantities of the capsular polysaccharide of the organism produce a gelatinous exudate that promotes arachnoid fibrosis (chronic adhesive arachnoiditis).

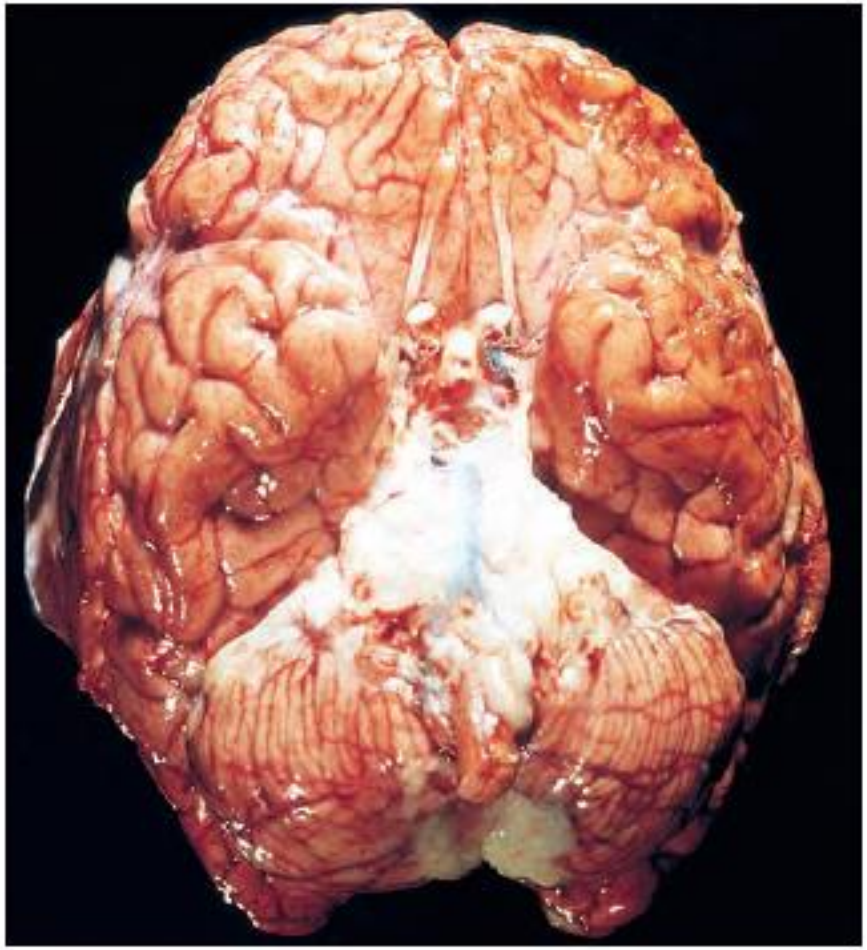


Figure 28-21 Pyogenic meningitis. A thick layer of suppurative exudate covers the brainstem and cerebellum and thickens the leptomeninges. (From Golden JA, Louis DN: Images in clinical medicine: acute bacterial meningitis. N Engl J Med 333:364, 1994.)

Waterhouse-Friderechsen syndrome

- Meningitis-associated septicemia with hemorrhagic infarction of the adrenal glands and cutaneous petechiae
- It occurs most often with pneumococcal meningitis
- Meningococcal disease less likely in a vaccinated population
- Immunosuppressed individuals may be infected with other organisms.

Aseptic meningitis

- Absence of organisms by bacterial culture in patient with acute onset of meningeal irritability and fever
- 80% caused by enteroviruses
- May be bacterial, rickettsial, or autoimmune in origin
- An aseptic meningitis-like picture may also develop subsequent to rupture of an epidermoid cyst into the subarachnoid space or the introduction of a chemical irritant (chemical meningitis).

Brain abscess

- A localized focus of necrosis of brain tissue with accompanying inflammation, usually caused by a bacterial infection.
- May arise by:
- Direct implantation of organisms
- Local extension from adjacent foci
- Mastoiditis, paranasal sinusitis
- Hematogenous spread
- From the heart, lungs, or bones of the extremities, or after tooth extraction

Brain abscess

- The increased intracranial pressure can lead to fatal herniation.
- Other complications include abscess rupture with ventriculitis or meningitis, and venous sinus thrombosis.

Brain abscess

- Infections of bone or air sinuses can spread to the subdural space, producing a subdural empyema.
- Underlying arachnoid and subarachnoid spaces are usually unaffected
- A large subdural empyema may produce a mass effect or a thrombophlebitis of the bridging veins that cross the subdural space
- Extradural abscess, commonly associated with osteomyelitis, often arises from an adjacent focus of infection, such as sinusitis or following a surgical procedure.

Brain abscess

- Abscesses are discrete lesions with central liquefactive necrosis surrounded by brain swelling.
- At the outer margin of the necrotic lesion there is exuberant granulation tissue with neovascularization around the necrosis.
- The newly formed vessels are abnormally permeable, accounting for marked vasogenic edema in the adjacent brain tissue.
- In well-established lesions, a collagenous capsule is produced by fibroblasts derived from the walls of blood vessels.
- Outside the fibrous capsule is a zone of reactive gliosis containing numerous gemistocytic astrocytes.

Chronic meningitis

- May have symptoms of headache, vomiting, mental confusion.
- Moderate pleocytosis in CSF, principally mononuclear cells; protein elevated; glucose near normal.
- Obliterative endarteritis; may see granulomata.

  (Obliterative endarteritis with perivascular infiltrates rich in plasma cells characterizes neurosyphilis.)
- Mycobacterium tuberculosis is the most common cause of a space occupying lesion in the brain in lesser developed countries.

Chronic meningitis

- Mycobacterium tuberculosis
- Usually a silent lung infection
- The most serious complications are arachnoid fibrosis producing hydrocephalus, and obliterative endarteritis producing arterial occlusion and infarction of underlying brain.
- In the spinal cord subarachnoid space, nerve roots may also be affected.
- Tuberculoma may produce a space-occupying lesions (not generally noted in Mycobacterium avium-intercelluare infections I the immunosuppressed)
- More common than brain tumors in an area of high prevalence of TB

Chronic meningitis

- Neurosyphilis is a manifestation of the tertiary stage of syphilis
- 10% of individuals with untreated infection.
- The major patterns of CNS involvement are:
- Meningovascular neurosyphilis
- Chronic meningitis
- Involves the base of the brain
- Obliterative endarteritis (Heubner arteritis)
- Parenchymal gummas

Chronic meningitis

- Taboparetic neurosyphilis
- Cognitive impairment with mood elevations, terminates in dementia
- Frontal lobes
- Lesions are characterized by loss of neurons, proliferation of microglia (rod cells), gliosis, and iron deposits.
- Direct brain invasion by Treponema.
- Tabes dorsalis
- Loss of both axons and myelin in the dorsal roots, with corresponding pallor and atrophy in the dorsal columns of the spinal cord
- Ataxia and sensory loss

Neuroborelliosis

- Lyme disease
- Neurologic symptoms are highly variable and include aseptic meningitis, facial nerve palsies and other polyneuropathies, as well as encephalopathy.
- Focal proliferation of microglial cells in the brain as well as scattered extracellular organisms.

Viral encephalitis

- A parenchymal infection of the brain almost invariably associated with meningeal inflammation (meningoencephalitis) and sometimes with simultaneous involvement of the spinal cord (encephalomyelitis).
- May see perivascular demyelination despite no direct involvement of brain (autoimmune phenomenon)
- Congenital infections (rubella)
- Late onset degenerative disease (influenza)

Viral encephalitis

- Arboviruses important in the Western hemisphere are Eastern and Western equine, West Nile, Venezuelan, St. Louis, and La Crosse
- Elsewhere in the world, Japanese B (Far East), Murray Valley (Australia and New Guinea), and tick-borne (Russia and Eastern Europe).
- All these viruses have animal hosts and insect vectors.
- Clinically, affected individuals develop generalized neurologic deficits, such as seizures, confusion, delirium, and stupor or coma, as well as focal signs.

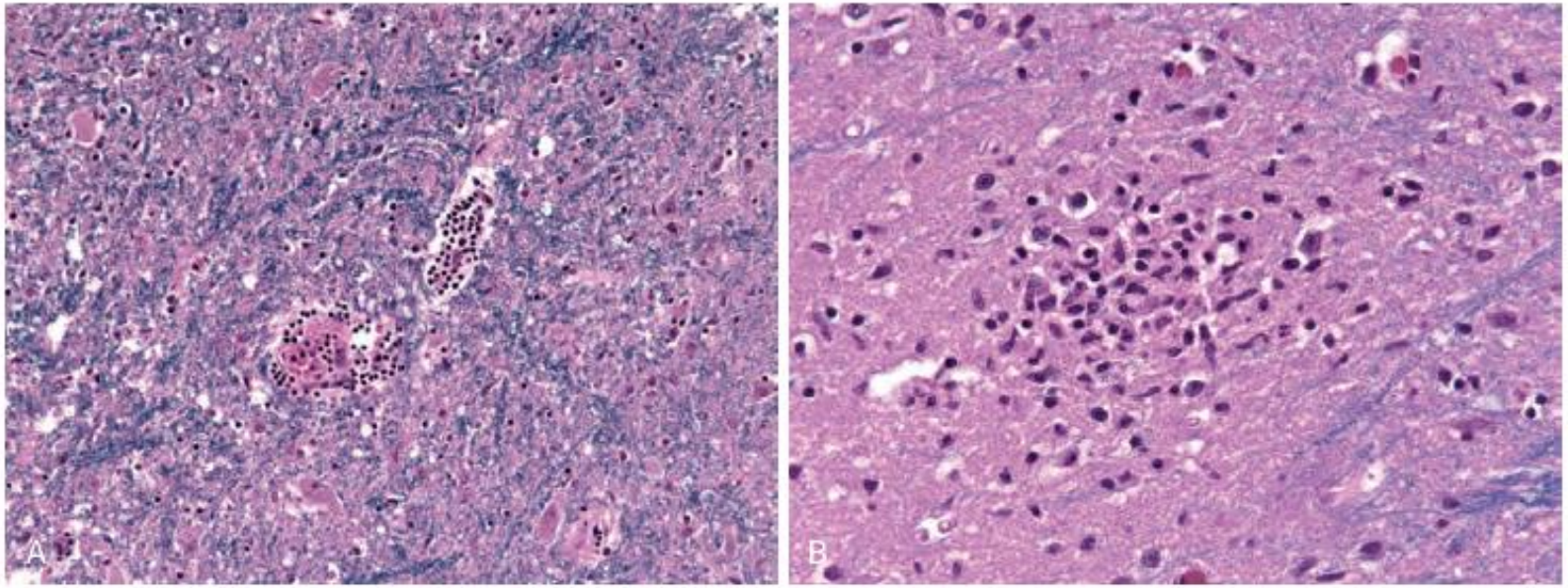


Figure 28-23 Characteristic findings of viral encephalitis include perivascular cuffs of lymphocytes **(A)** and microglial nodules **(B)**.

Viral encephalitis

- West Nile virus can produce a polio-like syndrome with paralysis
- Histologically, there is a meningoencephalitis marked by the perivascular accumulation of lymphocytes (and sometimes with neutrophils).
- Multiple foci of necrosis of gray and white matter are found; in particular, there is evidence of single-cell neuronal necrosis with phagocytosis of the debris (neuronophagia).
- Microglial cells form small aggregates around foci of necrosis (microglial nodules)

Viral encephalitis

- Commonly in children and young adults
- 90% have no prior infection
- Abnormal TLR3 pattern signalling
- Presents with mood alteration and behavioral difficulties
- 50% of neonates born by vaginal delivery to women with active primary HSV genital infections acquire the infection during passage through the birth canal and develop severe encephalitis.
- HSV-1 most common

Viral encephalitis

- Necrotizing encephalitis that involves the inferior and medial regions of the temporal lobes and the orbital gyri of the frontal lobes .
- Often hemorrhagic in the most severely affected regions.
- Perivascular inflammatory infiltrates are usually present
- Cowdry type A intranuclear viral inclusion bodies may be found in both neurons and glia
- Similar changes noted with HSV-2
- PCR positive in CSF (<25 cycles)

Viral meningitis

- Cytomegalovirus (CMV) infection of the nervous system occurs in fetuses and immunosuppressed individuals.
- The outcome of infection in utero is periventricular necrosis that produces severe brain destruction followed later by microcephaly and periventricular calcification.
- The infection tends to localize in the paraventricular subependymal regions of the brain, where it results in a severe hemorrhagic necrotizing ventriculoencephalitis and a choroid plexitis.

Viral encephalitis

- The virus can also attack the lower spinal cord and roots, producing a painful radiculoneuritis.
- May see viral inclusions.
- Nuclear inclusion surrounded by clear halo.
- PCR positive for CMV in CSF (<25 cycles).
- Lymphocytic meningoencephalitis
- Perivascular accumulation of inflammatory cells. Necrosis in both gray and white matter. Neuronophagia.
- Glucose content generally near normal in CSF.

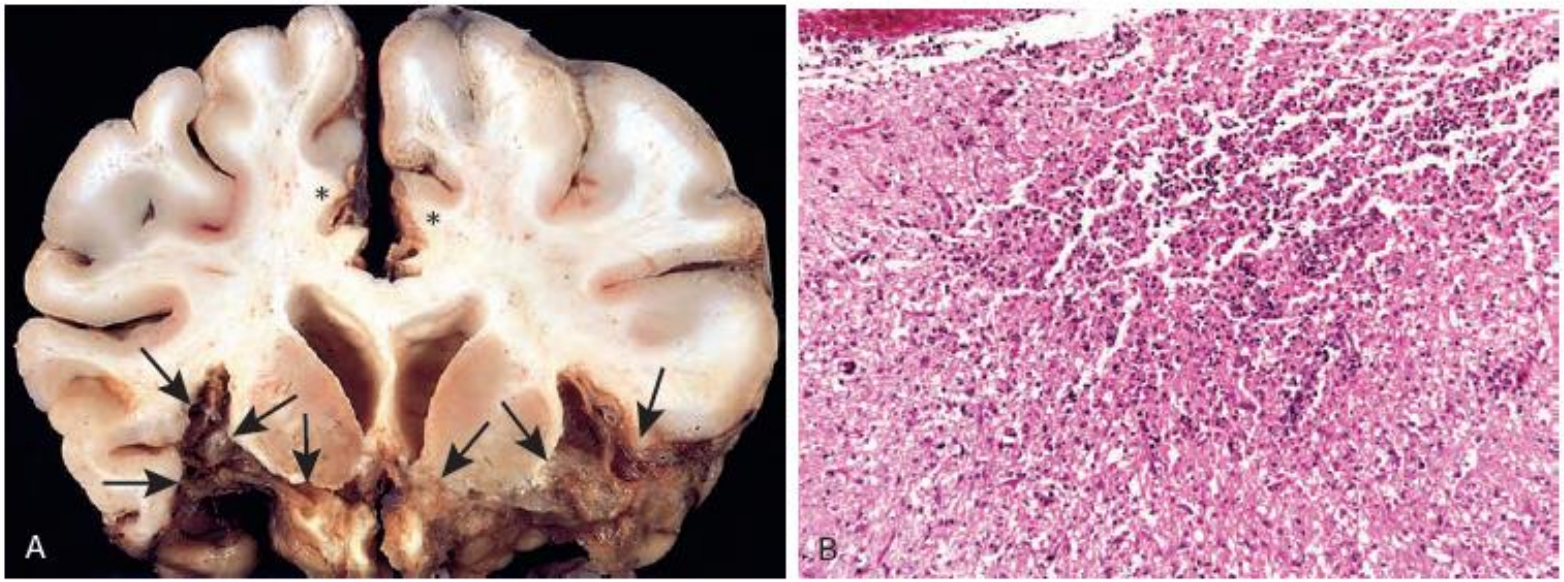


Figure 28-24 **A,** Herpes encephalitis showing extensive destruction of inferior frontal and anterior temporal lobes (*arrows*) and the cingulate gyri (*asterisks*). **B,** Necrotizing inflammatory process characterizes acute herpes encephalitis. (**A,** Courtesy Dr. T. W. Smith, University of Massachusetts Medical School, Worcester, Mass.)

Congenital rubella

- Rubella is believed to invade the upper respiratory tract, with subsequent viremia and dissemination of virus to different sites, including the placenta.
- The fetus is at highest risk of developmental abnormalities when infected during the first 16 weeks of gestation, particularly the first 8 to 10 weeks.
- Early in gestation, the virus is thought to establish a chronic intrauterine infection.
- Its effects include endothelial damage to blood vessels, direct cytolysis of cells, and disruption of cellular mitosis.

Congenital rubella

- Microcephaly
- Cataracts
- Retinopathy
- Patent ductus arteriosus and pulmonic stenosis
- Hearing loss
- May later develop diabetes mellitus

Polio

- Enterovirus
- Presents as a mild gastrointestinal infection
- Acute cases show mononuclear cell perivascular cuffs and neuronophagia of the anterior horn motor neurons of the spinal cord.
- The inflammatory reaction is usually confined to the anterior horns but may extend into the posterior horns, and the damage is occasionally severe enough to produce cavitation.
- Neurogenic muscular atrophy is late finding.
- Because of the destruction of motor neurons, paresis or paralysis follows

Polio

- When the diaphragm and intercostal muscles are affected, severe respiratory compromise and even death may occur.
- A myocarditis sometimes complicates the acute infection.
- Post polio syndrome can develop in patients 25 to 35 years after the resolution of the initial illness.
- It is characterized by progressive weakness associated with decreased muscle mass and pain

Rabies

- The virus enters the central nervous system (CNS) by ascending along the peripheral nerves from the wound site
- The incubation period (usually between 1 and 3 months) depends on the distance between the wound and the brain.
- Paresthesias about the wound in conjunction with malaise, headache, and fever are diagnostic clinically

Rabies

- As the infection advances, CNS excitability is extraordinary
- The slightest touch is painful and may produce violent motor responses or convulsions
- Contracture of the pharyngeal musculature on swallowing produces foaming at the mouth, which may create an aversion to swallowing even water (hydrophobia).
- There are signs of meningeal irritation
- As the disease progresses, flaccid paralysis.
- Alternating periods of mania and stupor progress to coma and eventually death from respiratory failure

Rabies

- External examination of the brain shows intense edema and vascular congestion.
- Microscopically, there is widespread neuronal degeneration and an inflammatory reaction that is most severe in the brainstem.
- The basal ganglia, spinal cord, and dorsal root ganglia may also be involved.
- Negri bodies are cytoplasmic, round to oval, eosinophilic inclusions that can be found in pyramidal neurons of the hippocampus and Purkinje cells of the cerebellum, sites usually devoid of inflammation.
- Negri bodies are pathognomonic

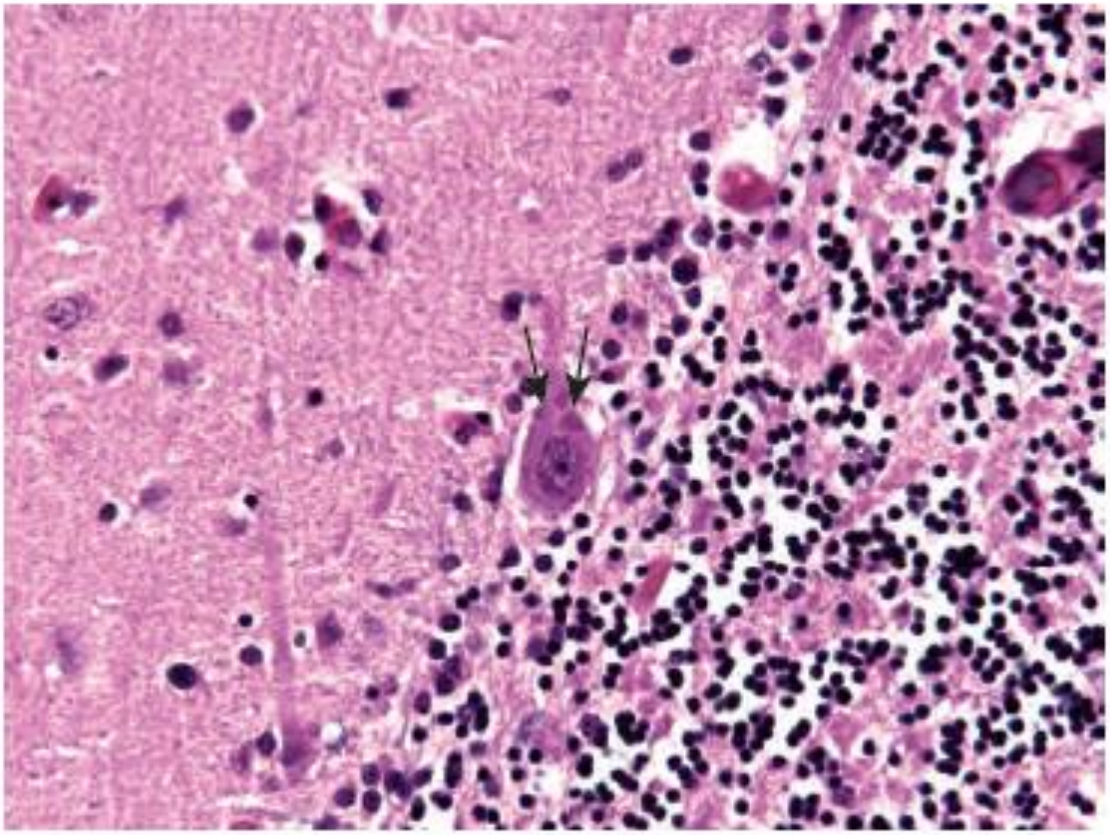


Figure 28-25 The diagnostic histologic finding in rabies is the eosinophilic Negri body, as seen here in a Purkinje cell *(arrows)*.

HIV

- HIV aseptic meningitis occurs within 1 to 2 weeks of seroconversion in about 10% of patients
- Histologically, there is mild lymphocytic meningitis, perivascular inflammation, and some myelin loss.
- Only microglia express both the CD4 co-receptor and the chemokine receptors (CCR5 or CXCR4) that are required in combination for efficient infection by HIV.
- During the chronic phase, HIV encephalitis is commonly found.

HIV

- HIV-associated dementia is thought to be related to effects of inflammatory cytokines produced by microglial cells.
- Histologically, noted are widely distributed microglial nodules, often containing macrophage-derived multinucleated giant cells;
- Foci of tissue necrosis and reactive gliosis are sometimes seen together with these lesions.
- Some of the microglial nodules are found near small blood vessels, which show abnormally prominent endothelial cells and perivascular foamy or pigment-laden macrophages.

HIV

- These changes are especially prominent in the subcortical white matter, diencephalon, and brainstem.
- Multifocal or diffuse areas of myelin pallor, axonal swelling and gliosis may also be found.
- HIV can be detected in CD4+ mononuclear and multinucleated macrophages and microglia.

Progressive multifocal leukoencephalopathy

- An encephalitis caused by the JC polyomavirus
- Most people have serologic evidence of exposure to JC virus by the age of 14 years
- Primary infection is asymptomatic.
- PML results from the reactivation of virus in the setting of immunosuppression.
- Preferentially infects oligodendrocytes
- Demyelination is its principal pathologic effect.
- Clinical signs dependent upon brain area affected

Progressive multifocal leukoencephalopathy

- Lesions restricted to the subcortical white matter.
- Low intensity T1, hyperintense on T2 weighted MRI. Do not enhance.
- PCR positive for JCV In CSF (<25 cycles).

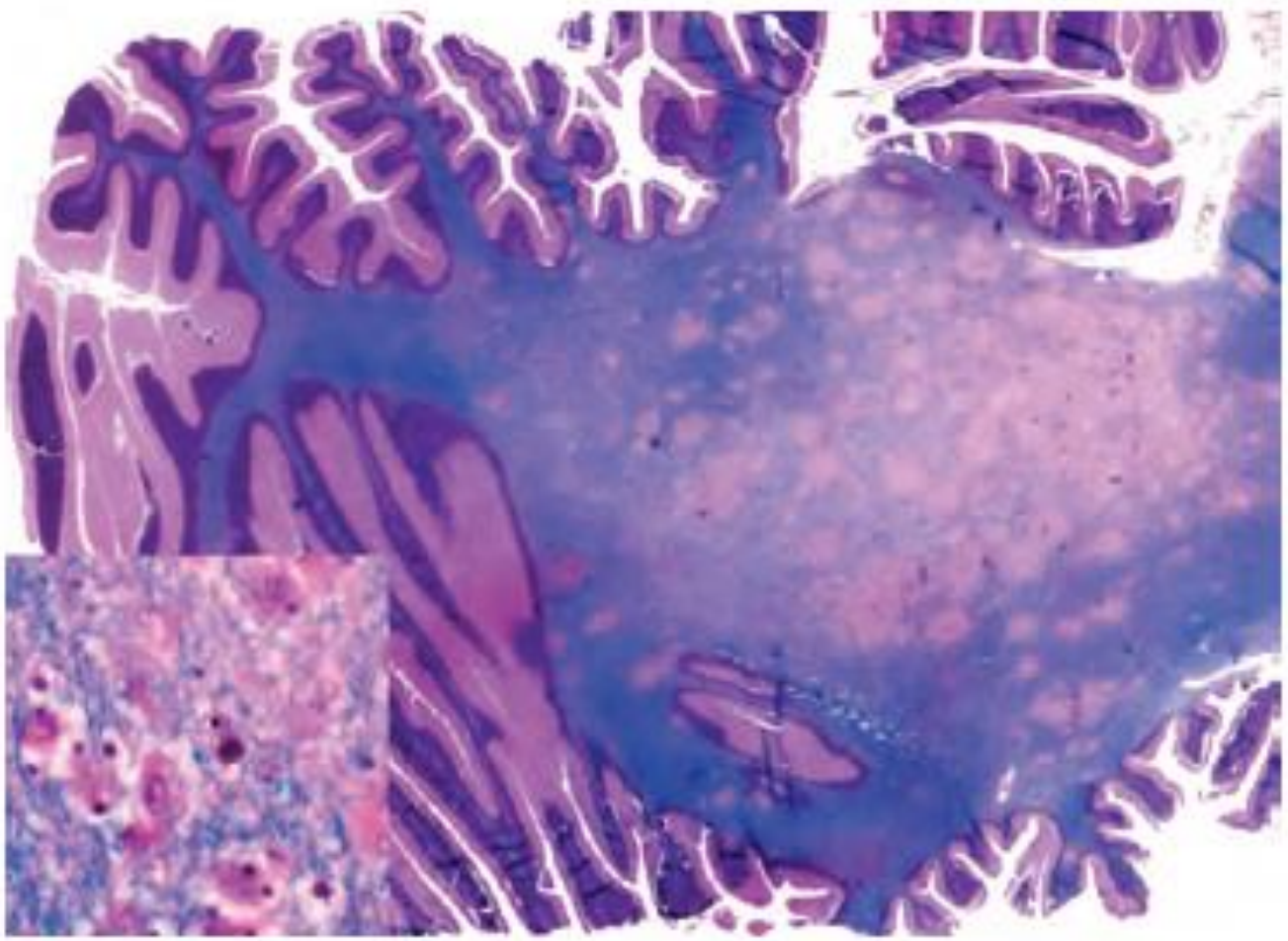


Figure 28-27 Progressive multifocal leukoencephalopathy. Section stained for myelin showing irregular, poorly defined areas of demyelination, which become confluent in places. *Inset*, Enlarged oligodendrocyte nucleus represents the effect of viral infection.

Progressive multifocal leukoencephalopathy

- The lesions consist of patches of irregular, ill-defined white matter injury
- Confluent involvement of large regions of the brain.
- Histologically, individual lesions show an area of demyelination, most often in a subcortical location, in the center of which are scattered lipid-laden macrophages and a reduced number of axons.

Progressive multifocal leukoencephalopathy

- Particularly at the edge of the lesion are greatly enlarged oligodendrocyte nuclei containing glassy amphophilic viral inclusions.
- Giant astrocytes may be found.
- Granular cell neurons in the cerebellum may be involved.

Subacute sclerosing panencephalitis

- SSPE is characterized by cognitive decline, spasticity of limbs, and seizures.
- It occurs in children or young adults, months or years after an initial, early-age acute infection with measles
- Characterized by:
- Widespread gliosis and myelin degeneration
- Viral inclusions, largely within the nuclei of oligodendrocytes and neurons
- Variable inflammation of white and gray matter
- Neurofibrillary tangles

Guillan-Barré syndromes

- Acute inflammatory demyelinating neuropathy
- Most common form in Europe, Australia, the US and Canada.
- Ascending polyneuropathy.
- Perivenous lymphocytic infiltrates. Demyelination.
- IgM and IgG antibodies to GM_1.
- Acute motor-sensory axonal neuropathy
- Common in China (north), Japan, Mexico.
- Pronounced paralysis. Muscular atrophy. Axonal degeneration.
- IgG antibodies to GM_1.

Guillan-Barré syndromes

- Acute motor axonal neuropathy
- Common in China (north), Japan, Mexico.
- Pure motor neuropathy with axonal degeneration.
- IgG antibodies to GM_1, GD_{1a}, GD_{1b}.
- Miller Fisher syndrome
- External ophthalmoplegia (diplopia), ataxia, areflexia.
- IgG antibodies to GQ_{1b} correlate with course of the disease.

Guillan-Barré syndromes

- Campylobacter jejuni, Epstein Barr virus, cytomegalovirus, hepatititis viruses, varicella-zoster virus, and Mycoplasma pneumoniae as pathogenic triggers.
- Group B streptococcus is the most common cause of acute motor paralysis in children.

Autism

- Autism is a neurodevelopmental condition that has a strong genetic component with genesis before one year of age, when MMR vaccine is typically administered.
- No association with MMR vaccination in several large population studies.

Fungal meningoencephalitis

- Immunocompromised
- Follows widespread hematogenous dissemination
- Usual organisms:
- Candida albicans, Mucor species, Aspergillus fumigatus, and Cryptococcus neoformans.
- Histoplasma capsulatum, Coccidioides immitis, and Blastomyces dermatiditis may follow pulmonic infection
- Mucor species are locally invasive

Fungal meningoencephalitis

- Vasculitis is most frequently seen with Mucormycosis and Aspergillosis
- Both directly invade blood vessel walls
- May occur with candidiasis.
- The resultant vascular thrombosis produces infarction that is often strikingly hemorrhagic and that subsequently becomes septic from ingrowth of the causative fungus.

Fungal meningoencephalitis

- Parenchymal infection can occur with most of the fungi and often coexists with meningitis
- Usually in the form of granulomas or abscesses
- The most commonly encountered fungi that invade the brain are Candida and Cryptococcus.
- Candidiasis usually produces multiple microabscesses, with or without granuloma formation.

Fungal meningoencephalitis

- Chronic meningitis affecting the basal leptomeninges
- Opaque and thickened by reactive connective tissue that may obstruct the outflow of cerebrospinal fluid from the foramina of Luschka and Magendie, giving rise to hydrocephalus.
- Cryptococcus neoformans
- Opportunistic infection
- May be indolent or fulminant

Fungal meningoencephalitis

- Histologically, the brain disclose a gelatinous material within the subarachnoid space and small cysts within the parenchyma (“soap bubbles”)
- Prominent in the basal ganglia in the distribution of the lenticulostriate arteries
- Parenchymal lesions consist of aggregates of organisms within expanded perivascular (Virchow-Robin) spaces associated with minimal or absent inflammation or gliosis

Cerebral toxoplasmosis

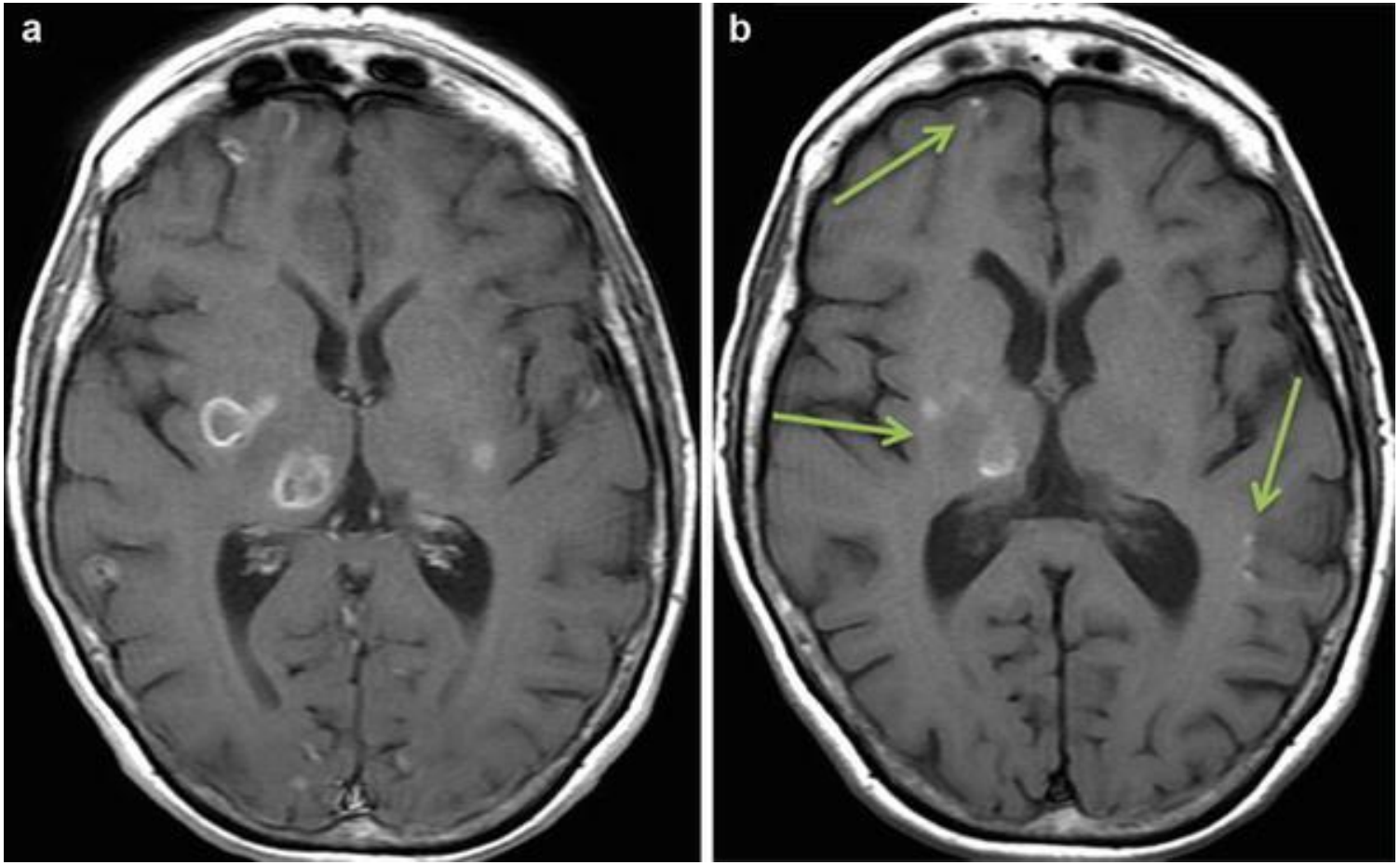
- An opportunistic infection commonly found in the setting of HIV-associated immunosuppression.
- Often frontal (bilateral)
- May also be noted in pregnant women (and fetal transmission)
- Leads to multifocal necrotizing lesions that may calcify
- The clinical symptoms of infection of the brain by Toxoplasma gondii are subacute, evolving during a 1- or 2-week period, and may be both focal or diffuse.
- CT and MRI studies may show multiple ring enhancing lesions with mass effect and edema

Cerebral toxoplasmosis

- Involve the cerebral cortex (near the gray-white junction) and deep gray nuclei, less often in the cerebellum and brainstem, and rarely in the spinal cord
- Acute lesions exhibit central necrosis, petechial hemorrhages surrounded by acute and chronic inflammation, macrophage infiltration, and vascular proliferation.
- Both free tachyzoites and encysted bradyzoites may be found at the periphery of the necrotic foci.

Cerebral toxoplasmosis

- Meningismus is not a common finding.
- Cerebrospinal fluid may not show a particular abnormality.
- PCR is specific but not sensitive (<25 cycles)
- Diagnosis is unlikely in someone negative for antibodies to Toxoplasma.
- Blood vessels near these lesions may show marked intimal proliferation or even frank vasculitis with fibrinoid necrosis and thrombosis.
- Chronic lesions consist of small cystic spaces containing scattered lipid- and hemosiderin-laden macrophages that are surrounded by gliotic brain.



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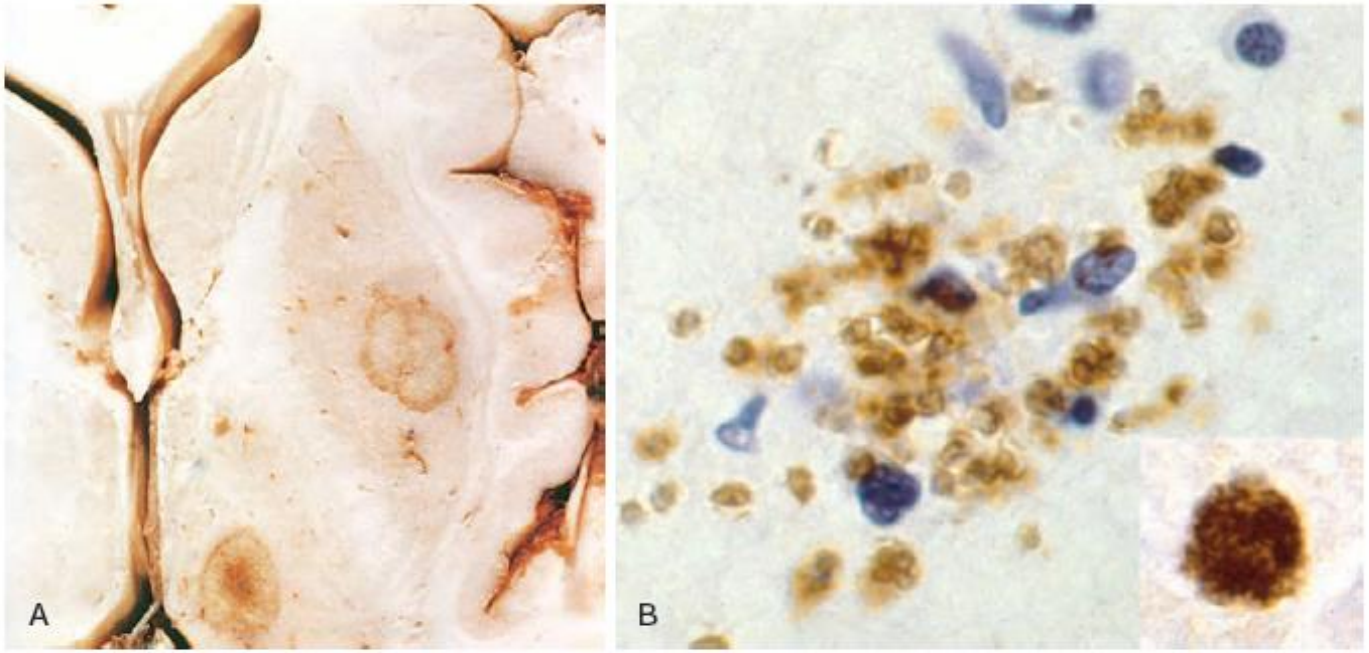

Figure 28-29 **A,** *Toxoplasma* abscesses in the putamen and thalamus. **B,** Free tachyzoites demonstrated by immunostaining; *inset*: *Toxoplasma* pseudocyst with bradyzoites highlighted by immunostaining.

Cerebral amebiasis

- A rapidly fatal necrotizing encephalitis results from infection with Naegleria species
- A chronic granulomatous meningoencephalitis has been associated with infection with Acanthamoeba.
- Methenamine silver or PAS stains are helpful in visualizing the organisms.

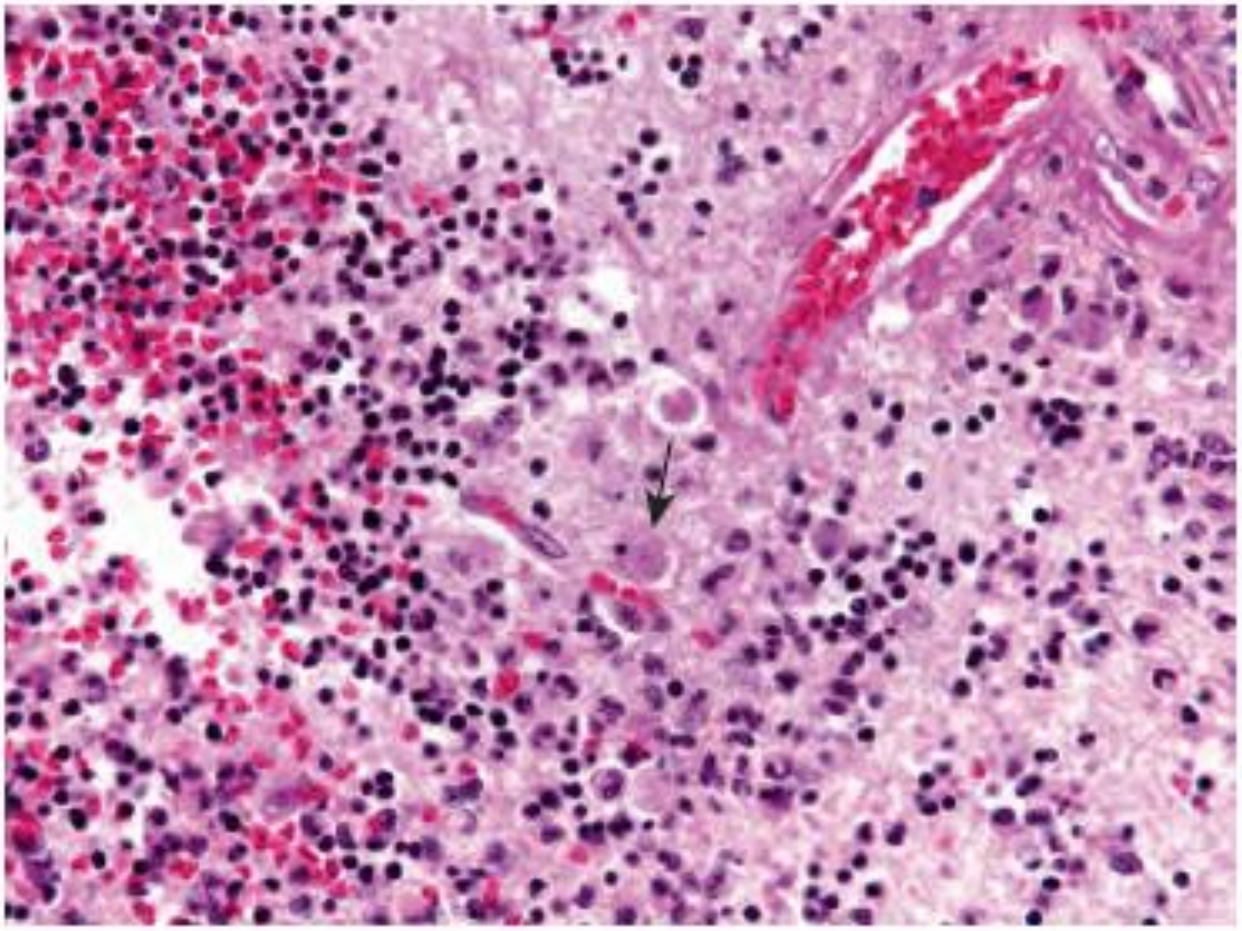

Figure 28-30 Necrotizing amebic meningoencephalitis involving the cerebellum (organism highlighted by *arrow*).

Cerebral malaria

- Plasmodium falciparum
- Most likely the result of vascular dysfunction.
- Cerebral involvement is accompanied by reduced cerebral blood flow and results in ataxia, seizures, and coma in the acute phase.
- Those who survive may have long-term cognitive deficits.
- Up to 20% of children after cerebral malaria

Other CNS infections

- Trypanosomiasis
- Typhus and Rocky Mountain spotted fever
- Cysticercosis and echinococcosis (mass lesions)

Prions

- Abnormal forms of a cellular protein that cause rapidly progressive neurodegenerative disorders
- Includes Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker syndrome, fatal familial insomnia, and kuru.
- Prion protein (PrP).
- They are all characterized morphologically by “spongiform change” caused by intracellular vacuoles in neurons and glia, and clinically by a rapidly progressive dementia.

Prions

- Disease occurs when PrP undergoes a conformational change from its normal α-helix-containing isoform (PrPc) to an abnormal β-pleated sheet isoform (PrPsc).
- Acquires resistance to protease digestion.
- PrPsc, independent of the means by which it originates, then facilitates, in a cooperative fashion, the conversion of other PrPc molecules to PrPsc molecules.
- It is this propagation of PrPsc that accounts for the transmissible nature of prion diseases.

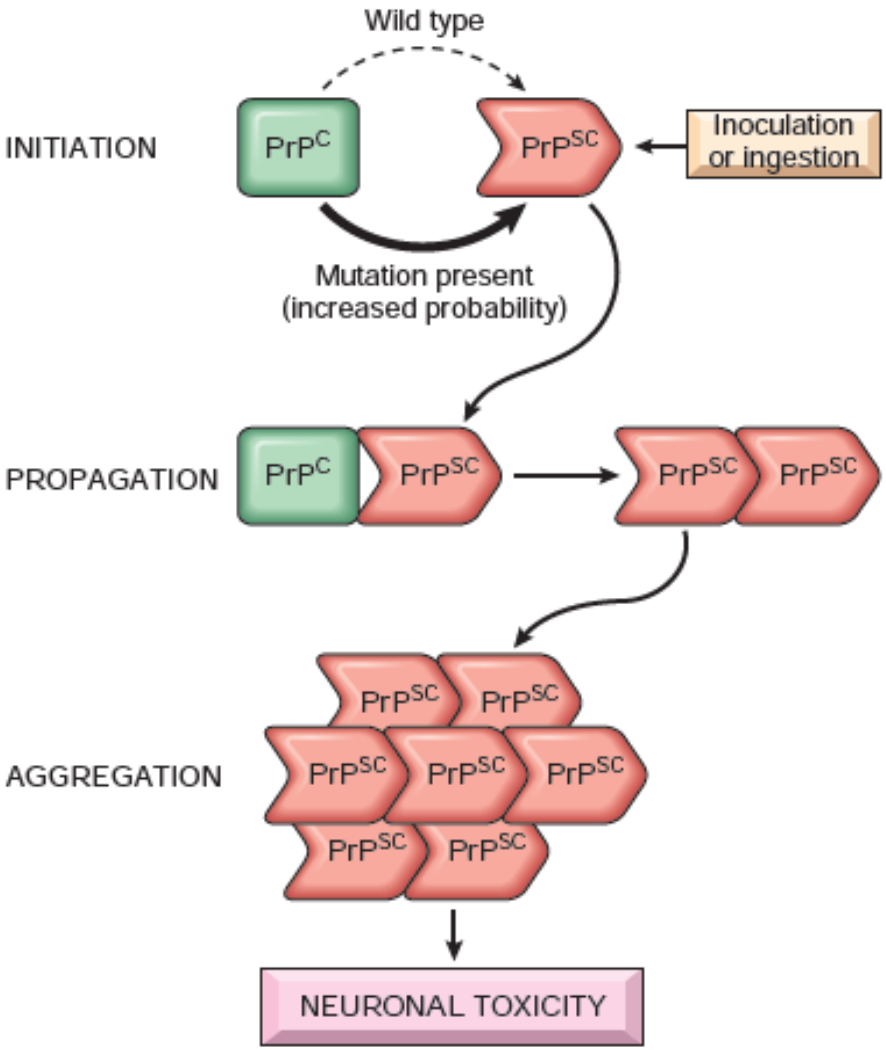

Figure 28-31 Pathogenesis of prion disease. α-helical PrP^{c} may spontaneously shift to the β-sheet PrP^{sc} conformation, an event that occurs at a much higher rate in familial disease associated with germ line PrP mutations. PrP^{sc} may also be acquired from exogenous sources, such as contaminated food, medical instrumentation, or medicines. Once present, PrP^{sc} converts additional molecules of PrP^{c} into PrP^{sc} through physical interaction, eventually leading to the formation of pathogenic PrP^{sc} aggregates.

Creutzfeld-Jacob disease

- Prion disorder.
- PrP^{C} is the normal protein found on neuron membranes. It is an α-helix isoform.
- PrP^{SC} has the same amino acid sequence, but is a β-pleated sheet. Its aggregates resist degradation.
- The presence of PrP^{SC} leads to conversion of PrP^{C} to PrP^{SC} .
- Injured neurons shrivel and are hyperchromatic.
- PRNP mutation in familial disorder. Peak incidence in the seventh decade of life.
- Progressive dementia with myoclonus. Ataxia present in a minority of patients.

Creutzfeldt-Jakob disease

- Subtle changes in memory and behavior followed by a rapidly progressive dementia, often associated with myoclonus
- Rapidly fatal
- Pathologically, variant CJD (vCJD) is characterized by the presence of extensive cortical plaques surrounded by a “halo” of spongiform change.
- Younger age
- Slower course

Creutzfeldt-Jakob disease

- The pathognomonic finding is a spongiform transformation of the cerebral cortex and, often, deep gray matter structures (caudate, putamen)
- This multifocal process results in the uneven formation of small, apparently empty, microscopic vacuoles of varying sizes within the neuropil and sometimes in the perikaryon of neurons.
- In advanced cases there is severe neuronal loss, reactive gliosis, and sometimes expansion of the vacuolated areas into cyst-like spaces (“status spongiosus”).
- Inflammation is notably absent

Crutzfeldt-Jakob disease

- In kuru, as well as variant Creutzfeldt-Jakob disease, florid plaques are found in the brain
- A petal fashion about an PrP^{Sc} amyloid core.
- Congo red- and PAS-positive
- Usually occur in the cerebellum
- Are abundant in the cerebral cortex in cases of vCJD

Creutzfeldt-Jakob disease

- Virtually all PRNP polymorphisms are methionine or valine substitutions at codon 129.
- There is no PRNP gene alteration in variant disease.
- These substitutions may influence incubation period.
- Heterozygosity is protective.

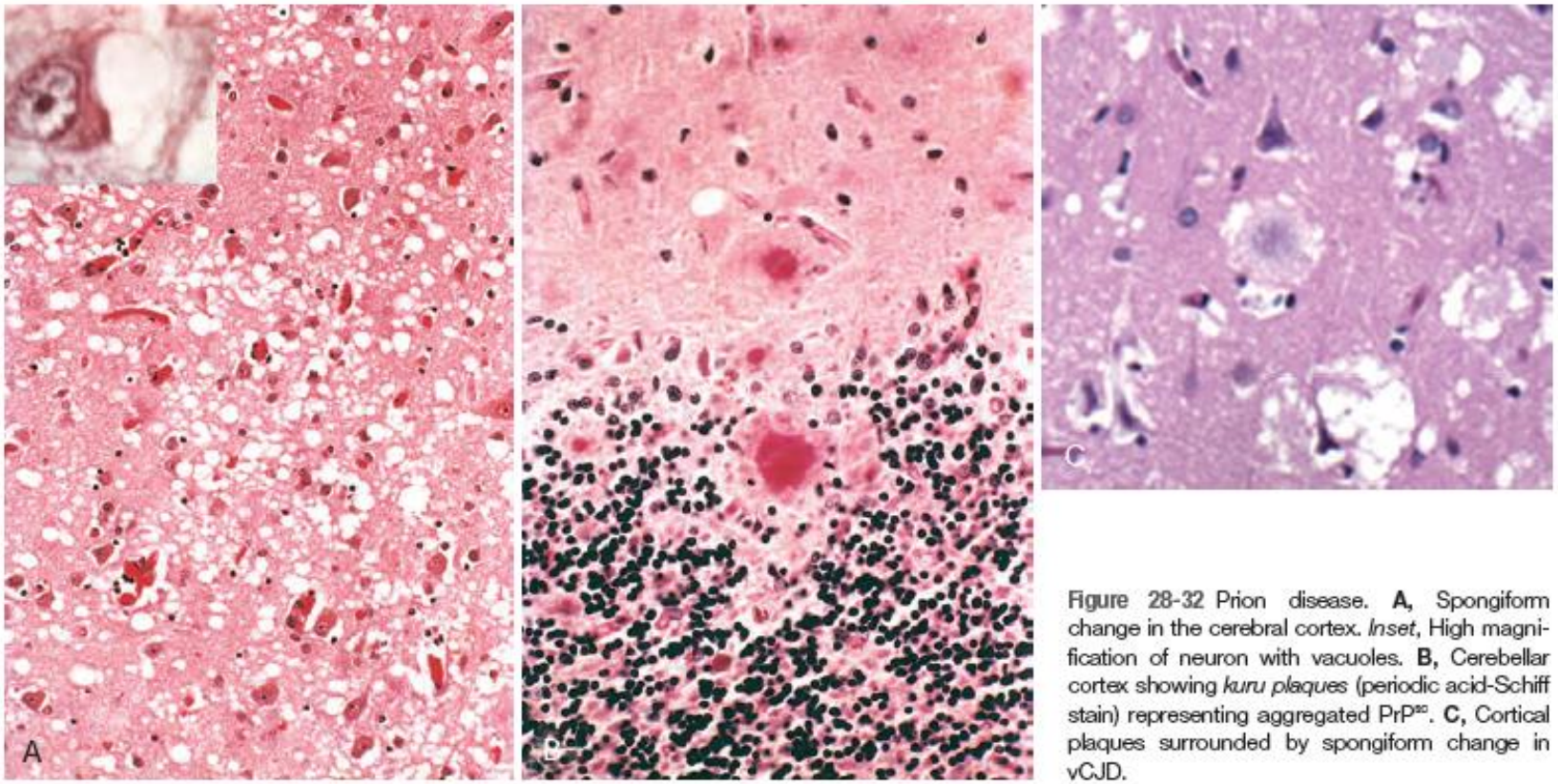

Figure 28-32 Prion disease. **A,** Spongiform change in the cerebral cortex. *Inset*, High magnification of neuron with vacuoles. **B,** Cerebellar cortex showing *kuru plaques* (periodic acid-Schiff stain) representing aggregated PrP^{sc}. **C,** Cortical plaques surrounded by spongiform change in vCJD.

Fatal familial insomnia

- Typically lasts fewer than 3 years
- Affected individuals develop other neurologic signs, such as ataxia, autonomic disturbances, stupor, and finally coma.
- PRNP mutation which leads to an aspartate substitution for asparagine at residue 178 of PrPc, results in FFI when it occurs in a *PRNP* allele encoding methionine at codon 129
- But causes CJD when present in tandem with a valine at this site

Fatal familial insomnia

- Does not show spongiform pathology.
- The most striking alteration is neuronal loss and reactive gliosis in the anterior ventral and dorsomedial nuclei of the thalamus
- Neuronal loss is also prominent in the inferior olivary nuclei.