Intoxications and Infections of the Nervous System (Dr. Merchut)

Intoxications

1. Bacterial toxins

Tetanus is the neurological syndrome produced by the exotoxin of *Clostridium tetani*, tetanospasmin, which is produced anaerobically in soil-contaminated wounds or unsterile IV needles shared by drug abusers. **Tetanospasmin binds to cortical, brain stem, and spinal interneurons, preventing the release of the inhibitory neurotransmitters glycine and γ-aminobutyric acid (GABA)**. Clinical manifestations of motor neuron disinhibition begin days to 2 weeks after exotoxin exposure. Severe, prolonged, **painful muscle spasms** occur. If there is only limited retrograde axonal transport of tetanospasmin near the wound, muscle spasms are confined to that area (localized tetanus). Spread of the exotoxin through the bloodstream produces diffuse muscle spasms and **generalized convulsive seizures** from cortical disinhibition (generalized tetanus). Painful muscle spasms lead to a clenching jaw (trismus or lockjaw), grimacing smile (risus sardonicus), and arching back (opisthotonus). These muscle contractions occur with little to no provocation and may impair swallowing and breathing. The diagnosis of tetanus is made on clinical grounds, coupled with a history of exotoxin exposure. Patients often require ICU care with mechanical ventilation, sedation, pharmacological neuromuscular blockade, and anticonvulsants until the muscle spasms and seizures abate. The administration of human tetanus immune globulin may neutralize any remaining tetanospasmin, whereas antibiotics are given for the wound infection.

Botulism is the neurological syndrome produced by the exotoxin of *Clostridium botulinum*, which is produced anaerobically in **improperly canned or contaminated food**, or in wound infections. Botulinum toxin, the most potent toxin known, is heat-sensitive and can thus be destroyed with sufficient cooking of the contaminated food item. This **exotoxin binds to presynaptic nerve terminals and prevents the release of acetylcholine from lower motor neurons and parasympathetic nerves**. Paralysis of skeletal muscle, bowel, bladder, and salivary glands occurs, the severity of which depends on the amount of exotoxin ingested. Symptoms begin within 12 to 48 hours of ingestion, initially with **ptosis, diplopia, and pupillary paralysis, followed by dysphagia, facial and limb weakness, and possibly respiratory paralysis**.

The diagnosis is straightforward if several patients develop a similar paralytic syndrome after sharing a meal or canned food item. A solitary patient is more of a diagnostic challenge, with the differential diagnosis including myasthenia gravis, a brain stem infarction, or variant of Guillain-Barre syndrome. Brain MRI and electromyography (EMG) may help exclude these other causes of paralysis. In addition, EMG may show some characteristic electrophysiological findings of botulism. Botulinum toxin may be detected by bioassay in contaminated food samples or fecal testing, but this takes days to perform. Most patients with botulism have a good prognosis, but require monitoring in the ICU, where mechanical ventilation can be provided if needed. A specific antitoxin may be given. Guanidine is an oral drug which helps facilitate acetylcholine release from motor nerve endings, and may improve clinical

strength. Gradual, spontaneous recovery after days to weeks is the rule for most patients given good supportive care.

It is curious, then, that these two species of *Clostridium* bacteria produce potent exotoxins with opposite effects, with the disinhibition of motor neurons in tetanus producing muscle spasms and seizures, in contrast to botulism, where the prevention of acetylcholine release leads to paralysis.

2. Environmental toxins

Exposure to particular toxic substances may occur in the workplace, so inquiries as to the patient's occupation are helpful, as well as whether any fellow workers have similar neurological symptoms. An individual patient may have a toxic exposure by means of a hobby or recreational use or abuse of a substance as well.

Lead poisoning tends to occur from workplace inhalation during painting, glazing, and lead battery processing. Affected **adults tend to exhibit peripheral neuropathy**, often with prominent focal neuropathies like **wrist drop**. In substandard housing, **children** may ingest peeling or flaking lead-based paint, and usually **develop encephalopathy and abdominal pain**. Elevated serum lead levels guide treatment with chelating agents. **Organic solvent** exposure in chemical plants may lead to **peripheral neuropathy or encephalopathy** or both. Similar chemicals in glues or adhesives are recreationally "sniffed" and over time may cause a peripheral neuropathy.

Patients may be accidentally exposed to **carbon monoxide (CO)** from malfunctioning stoves or heaters, or from nonventilated automobile exhaust in a garage. The latter situation sometimes is an intentional means of suicide. A dangerous aspect of CO is its greater affinity, compared to oxygen, for hemoglobin. It is also odorless and detectable only with specialized monitors. Early symptoms of CO toxicity include **headache, vomiting, and blurry vision**, which can progress during continued exposure to **coma, seizures, and cardiopulmonary arrest**. Once the condition is recognized, urgent treatment with inhalation of 100% oxygen is given, or a hyperbaric chamber is used. Survivors may have residual **deficits of memory or cognition**, and after a few weeks some may show signs of **parkinsonism**, from the sensitivity of the basal ganglia to CO.

3. Illicit or recreational drugs

Neurological symptoms are frequent side effects of intoxication with abused drugs or "a high," but also occur during drug withdrawal. During periods of drug-induced euphoria, impaired judgment, altered consciousness, or hallucinations, **head trauma** may occur and cause **intracranial hemorrhage.** Drug-induced **seizures** may occur and cause further injury. A **stroke syndrome in a young, otherwise healthy patient** should raise the suspicion of drug induced vasoconstriction or hypertension leading to ischemic infarction or brain hemorrhage. **Cocaine** is most commonly responsible here, although strokes have been reported from amphetamines, phencyclidine (PCP), and LSD. Uncommonly, ischemic infarction may occur in intravenous drug-abusers having vasculitis, an immune-mediated vascular reaction to the drug or its "filler" material.

4. Alcohol toxicity

Although not an illegal drug, for centuries alcohol has been the source of acute intoxication as well as chronic dependency. **Acute "drunkenness" causes social disinhibition, impairment of consciousness, and cerebellar dysfunction**. The latter consists of dysarthria, dysmetria, nystagmus, and ataxia, which are often the focus of the police roadside examination of a drunk driver. **Head trauma** may secondarily occur as unsteady, groggy, inebriated patients stumble and fall. In most cases, all symptoms resolve as the blood alcohol level falls, although very high levels may lead to coma and death.

When heavy drinking over several days finally ends, an **alcohol withdrawal syndrome** may develop in the next few days. Initially there is a **hypersympathetic stage**, with tremulousness, sweating, tachycardia, and jitteriness. A limited number or **cluster of generalized tonic-clonic seizures** ("rum fits") occurs from 12 hours to 3 days after the last drink. These seizures are primarily generalized in onset from a diffuse, toxic effect on the brain. If any aura or partial seizure occurs here, a focal brain lesion, especially related to head trauma, must be suspected. By about 3-4 days after alcohol cessation, **delirium tremens** ("DTs") may be apparent, with fluctuating motor and autonomic activity, confusion, and hallucinations. Delirium tremens or any associated complications such as infection or head trauma may become fatal if unrecognized and untreated. Patients in significant alcohol withdrawal require hospitalization, hydration and metabolic care, including thiamine supplementation. **Benzodiazepines** provide sedation and seizure control.

Several syndromes have been associated with the chronic use of alcohol. In many cases, it is difficult to tell whether symptoms are due to a direct, toxic effect of alcohol on the nervous system, or from any contaminants in the alcoholic beverage used. Malnutrition and vitamin deficiencies as well as repeated head injuries often occur in chronic alcoholics and may likewise cause neurological problems. Common examples include traumatic acute or chronic subdural hematomas and polyneuropathy. Whether or not alcoholism causes a dementia is controversial. The **Wernicke-Korsakoff syndrome** occurs from the deficiency of thiamine (vitamin B1) in patients with malnutrition or malabsorption from a variety of causes, but is most often described in alcoholics. **Wernicke's encephalopathy is the acute phase of the syndrome, consisting of nystagmus, ophthalmoplegia, gait ataxia, and confusion, which may resolve within hours to days of thiamine administration**. Persistent, severe or recurrent thiamine deficiency may lead to **Korsakoff's psychosis**, where a chronic memory deficit or **amnestic syndrome is prominent, with frequent confabulation** ("story telling") as if to "fill in" memory gaps. Pathologically, tiny petechial hemorrhages and gliosis occur in the vicinity of the third and fourth ventricles and connecting aqueduct, involving the mammilary bodies, fornix, and dorsomedial thalamus. **Alcoholic cerebellar degeneration** involves the anterior-superior vermis, causing an ataxic gait and dysmetria of the lower limbs. Although not specifically related to alcohol, **central pontine myelinolysis** occurs in alcoholics and other patients who undergo an overly rapid correction of severe hyponatremia. Demyelination of the corticospinal and corticobulbar tracts in the pons occurs.

Infections

1. Meningitis

Inflammation of the meninges or "meningitis" may occur from blood, foreign material, or an infection within the subarachnoid space. Most often meningitis refers to an infectious process, which is discussed here. Meningitis may **directly spread** from an infection in an area near or adjacent to the subarachnoid space, such as an otitis or sinusitis, or it may arise from infectious organisms **spread through the bloodstream** from a remote or distant infection, such as a pneumonia.

Acute meningitis evolves over hours to days with symptoms that may be severe, including **fever, headache, stiff neck, malaise, lethargy, nausea, and vomiting**. This situation is a medical emergency since **acute bacterial meningitis may be fatal** if untreated or not treated quickly enough with appropriate antibiotics. Acute viral meningitis usually has milder symptoms and is not treatable, but resolves spontaneously without neurological sequelae. On examination, the level of consciousness may range from lethargy to coma, and may rapidly worsen. Neck stiffness or **nuchal rigidity** is present from meningeal irritation and inflammation and may also cause the signs of Kernig or Brudzinski (see Neurological Examination). The patient must also be closely examined for any primary source of infection outside the nervous system. A petechial rash, from tiny skin hemorrhages, is highly suggestive of meningococcal (*Neisseria meningitidis)* meningitis. Cultures of blood, cerebrospinal fluid (CSF), or other infected material are sent to the laboratory to later identify the causative organism, but broader spectrum antibiotics must be started immediately based on the bacteria most likely involved. The commonest bacterial "suspects" for meningitis vary according to patient age (Table 1) and other health factors. **Initial antibiotic coverage** typically consists of a newer generation cephalosporin such as **ceftriaxone plus vancomycin** for any pneumococci (*Streptococcus pneumoniae)* resistant to penicillin. Ampicillin would be added to cover the possibility of *Listeria* species in elderly patients or neonates. Once the bacterium is identified by culture in a few days, specific antibiotic therapy can thereafter be given to the patient. In adults with bacterial (especially pneumococcal) meningitis, **intravenous dexamethasone** (0.15 mg/kg) given just before or with the initial antibiotics reduces neurological complications, such as deafness and cognitive deficits, and lowers mortality. When a substantial amount of purulent exudate or pus develops from bacterial meningitis, it may cause **hydrocephalus** by obstructing CSF pathways. Pus accumulating over the cortical subarachnoid space may lead to inflammation and edema of the cortex itself (**meningoencephalitis**), or cause an **infarction** of the underlying brain or spinal cord when local superficial blood vessels become inflamed and thrombose. Young children recovering from meningitis must be observed for any subsequent **deafness** which may impede their ability to learn to talk.

Patient age	Common bacterial organism	Gram stain of CSF
Neonate (0-4 wk old)	Group B streptococci	Gram + cocci in chains
	Escherichia coli (gram – bacilli)	Gram – rods
Children (<15 yr)	*Neisseria meningitidis*	Gram – diplococci
	Streptococcus pneumoniae	Gram + diplococci
Adult (>15 yr)	*S. pneumoniae*	Gram + diplococci
	N. meningitidis	Gram – diplococci
	E. coli (gram – bacilli)	Gram – rods

Table 1. Age-Related Causes of Acute Bacterial Meningitis

Lumbar puncture (LP) is a critical procedure in the management of meningitis, and needs to be performed as soon as possible so CSF can be cultured and empirical antibiotics begun. An LP must be delayed if the patient has thrombocytopenia or deficient clotting factors, or if an infection is present along the skin of the back. An LP must be postponed, or CSF obtained in another way, if the patient appears to have elevated intracranial pressure (unconscious state, papilledema on ophthalmological examination) or an intracranial mass with edema (new onset seizure, focal neurological deficit, history of stroke, cerebral mass lesion or infection, or immunocompromised state). In addition to culture of the CSF, the laboratory also reports the CSF protein level, glucose level, and cell count (number of RBCs and WBCs). Various types of meningitis, encephalitis, cancer, and other inflammatory processes may all cause nonspecific elevation of the CSF protein and increased numbers of CSF lymphocytic WBCs (pleocytosis). **Predominantly polymorphonuclear WBCs and low CSF glucose** (less than 50% of serum glucose) **is the most typical profile for bacterial meningitis** (Table 2). The gram stain test of CSF can be done rapidly in the laboratory and provides early clues as to the bacteria involved (Table 1) before the culture is completed.

Cause	White blood cell count	Protein	Glucose	Specific test
Bacteria	>500-1000 (mostly polymorphonuclears)	High	Low	Grain stain, culture
Virus	<500 (mostly lymphocytes)	Normal to high	Normal	Special culture or polymerase chain reaction (PCR)
Tuberculosis	<500 (mostly lymphocytes)	High	Low	Special culture or PCR
Fungus	<500 (mostly lymphocytes)	High	Low	Special culture
Syphilis	<500 (mostly lymphocytes)	High	Normal to low	Venereal Disease Research Laboratory titer
Normal CSF	No cells	<45 mg/dl	>50% blood glucose	

Table 2. Typical Cerebrospinal Fluid Findings in Meningitis

Chronic meningitis produces more subtle symptoms over weeks or months time, due to various unusual organisms such as tuberculosis, fungus, syphilis, and some parasites. These organisms do not typically infect healthy patients, but those who are elderly, malnourished, or immunocompromised. Confusion, low grade fever, or mild headache may be present without obvious nuchal rigidity. The diagnosis is easily overlooked in chronic meningitis, and CSF testing with various culture methods or polymerase chain reaction (PCR) techniques is critical before any specific treatment can be started (Table 2).

2. Encephalitis

The brain, not the subarachnoid space, is the primary site of infection and inflammation in encephalitis, usually caused by one of a variety of **viruses**. Symptoms evolve over hours to days and involve **fever and headache**, similar to meningitis, but also signs and symptoms indicative of brain involvement itself, such as **seizures, focal neurological deficits, behavioral changes, and impairment of consciousness**. The causative virus may be spread by arthropods (ticks, mosquitoes) during seasonal epidemics. Other modes of viral infection involve ingestion (polio virus), inoculation (rabies from animal bites), and inhalation or reactivation (*Herpes simplex).* Pathologically, viral encephalitis causes patchy demyelination, edema, and tiny, petechial hemorrhages in parts of the brain. Microscopically there is neuronal destruction by proliferating microglia, perivascular lymphocytes, and viral inclusions within neurons or glia.

The diagnosis is made from the clinical signs and symptoms, CSF abnormalities, and brain MRI findings. The CSF looks similar to that in viral meningitis, with a lymphocytic pleocytosis and normal or slightly decreased CSF glucose. Antibody titers to suspected viruses are checked in CSF and serum. It is often important to check for *Herpes simplex virus 1* (HSV-1) with PCR testing to indicate where empirical treatment with the antiviral drug acyclovir should be continued. In general, antiviral drugs are effective only against types of *Herpes* viruses. Encephalitis patients are often hospitalized in the ICU, where significantly **raised intracranial pressure** can be treated and **anticonvulsants and sedatives** given as required. The prognosis varies from full recovery to survival with residual deficits to death.

***Herpes simplex* encephalitis (HSE)** is important to recognize since it is nonepidemic, nonseasonal, and carries a high mortality rate when not treated. HSE is caused by *Herpes simplex virus 1* (HSV-1), which is responsible for oral herpes. (HSV-2 causes genital herpes.) HSE has a predilection for involving the **inferior frontal and medial temporal lobes**, often bilaterally and asymmetrically (Fig. 1). Signs and symptoms highly suggestive of HSE thus include **aphasia, behavioral changes, and memory deficits**. Intravenous **acyclovir should be started if clinical suspicion of HSE is high**, and later continued if the diagnosis is supported by a positive CSF PCR for HSV-1. Acyclovir treatment has dropped the mortality of HSE from 40-70% down to 20%.

In recent summers, the **West Nile virus** (WNV) primarily infected birds with subsequent mosquito transmission to people. In addition to fever, headache, and rash,

WNV encephalitis may also uniquely cause significant weakness by affecting peripheral nerves (similar to Guillain-Barre syndrome) or anterior horn cells (similar to polio).

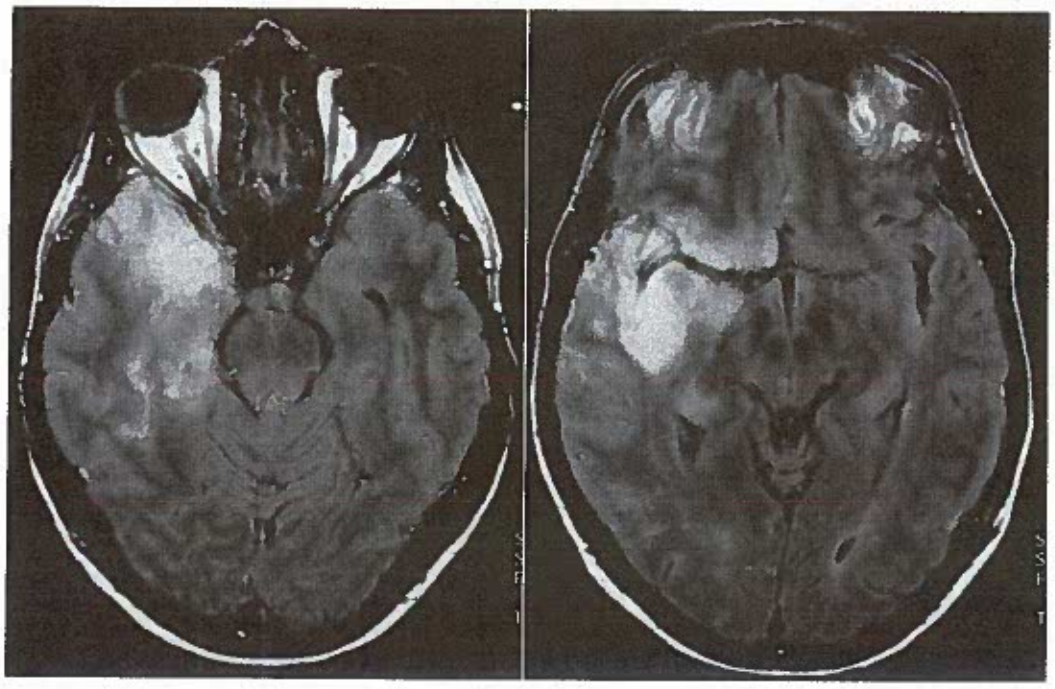

Fig. 1
Brain MRI scan (without contrast) in *Herpes simplex* encephalitis. Note edema and abnormal high signal intensity in the right frontal and anteromedial temporal lobes.

3. Other viral infections

The **polio** virus infected many children in the 1940s and 1950s until effective vaccines were developed to prevent it. Poliomyelitis consisted of an acute febrile illness, with a preferential **viral invasion and destruction of anterior horn cells and brain stem motor nuclei,** varying in extent and severity. Lower motor neuron signs were often asymmetrical so many polio survivors used braces or crutches to compensate for a weak, atrophic lower limb. The chronic joint or back pain, fatigue, and imbalance from such deficits became the "postpolio syndrome." Decades later, some patients slowly noted weakness in adjacent muscles or in the stronger, contralateral limb due to **postpolio muscular atrophy** (PMA). PMA was attributed to the gradual metabolic failure or "burn out" of those lower motor neurons which collaterally sprouted to control the denervated muscle fibers in polio-weakened muscles.

The varicella-zoster virus, another type of *Herpes* virus, remains latent for years in dorsal root ganglia after a childhood outbreak of chickenpox. Years later in adult life, perhaps as immune system function partly wanes, this virus is reactivated**. Zoster or shingles consists of eruption of a vesicular rash with severe neuralgic pain along one or two adjacent dermatomes** on the torso or limb. Acyclovir or a similar antiviral should be administered as soon as possible. Some unfortunate patients have persistent

neuralgic pain long after the infection subsides (post-herpetic neuralgia). For this reason a shingles vaccine is recommended for adults older than 60 years of age. In immunocompromised patients, the varicella-zoster infection may be more extensive, as an encephalitis or myelitis.

Human immunodeficiency virus (HIV-1) is especially important regarding its neurological involvement and is discussed in detail below.

4. Acquired immunodeficiency syndrome (AIDS)

AIDS has led to substantial morbidity and mortality in the past few decades, affecting millions of people worldwide. It is caused by the **human immunodeficiency virus (HIV-1)** which **destroys T4 helper lymphocytes**, creating inadequate immune responses and constitutional symptoms. The initial infection may be asymptomatic, followed months to years later by fatigue, weight loss, fever, and diarrhea. AIDS is spread through infected body fluids via sexual intercourse, drug abusers sharing intravenous needles, maternal-fetal transmission, and transfusion of contaminated blood or blood products. The AIDS epidemic is primarily responsible for the current practice of "universal precautions" whereby healthcare providers routinely use disposable gloves and other barrier protection from the body fluids of all patients. With the availability of effective anti-retroviral medications, AIDS patients now survive much longer and with fewer complications. A curative therapy still does not exist for HIV.

Nervous system syndromes in AIDS tend to develop at different stages of the disease (Fig. 2). Early on, an acute, aseptic (negative or normal CSF culture) meningitis may occur, as well as a myopathy or inflammatory polyneuropathy very similar to that of Guillain-Barre syndrome. Later in AIDS, a more **chronic, painful sensory neuropathy** predominates, along with **cognitive changes, HIV dementia** and a myelopathy similar to subacute combined degeneration from vitamin B-12 deficiency. HIV affects the nervous system by direct viral invasion, indirect damage from cell lysis and inflammation, or complications related to the immunodeficient state. **Primary cerebral lymphoma**, a rare immune system tumor arising within the brain, most often occurs in AIDS patients.

Immunocompromised patients include those on immunosuppressive therapy for cancer, autoimmune diseases or organ transplantation as well as those infected with HIV. They are all at risk for opportunistic infections with unusual organisms which do not occur in normal hosts. **Common opportunistic infections in AIDS include cerebral toxoplasmosis** (a protozoal parasite), **cryptococcal meningitis** (fungal), **and cytomegalovirus (CMV) retinitis or encephalitis**. Most cases of **progressive multifocal leukoencephalopathy (PML)** currently occur in AIDS patients. PML involves the reactivation of the latent polyomavirus (or JC virus), which goes on to infect oligodendrocytes in immunodeficient patients. **Patchy or spotty demyelination of CNS white matter occurs from destruction of the oligodendrocytes**, creating focal neurological deficits related to the areas involved, and progressive disability. The clinical diagnosis is confirmed with a positive PCR assay for JC virus in the CSF or typical brain biopsy findings. A curative antiviral treatment of PML is still lacking.

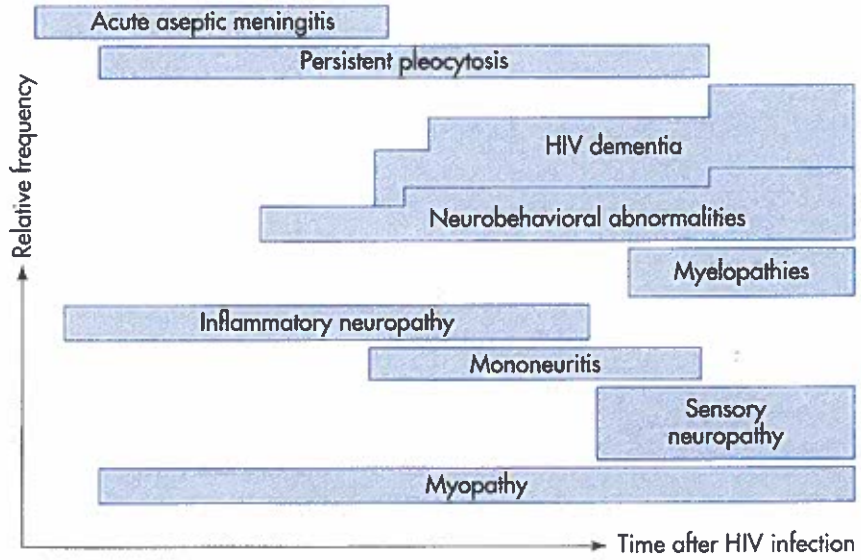

Fig. 2
HIV-related neurological diseases. Neurological syndromes begin early (toward left) or late (toward right) in AIDS. (From AAN AIDS Task Force, *Neurology* 39:119-122, 1989.)

5. Abscesses

An abscess is a **localized, encapsulated infection within or outside** (epidural or subdural) **the brain or spinal cord**. The infection is **usually bacterial, but may be fungal or parasitic** in immunocompromised patients. Like meningitis, an abscess may develop from an adjacent infection or through the bloodstream from a distant infection. Abscesses may be solitary or multiple in number. The patient often has a **fever and headache** and may be severely ill from a serious systemic infection. A cerebral abscess may cause **seizures and focal neurological signs dependent on its location**. It may create **brain edema with mass effect** and increased intracranial pressure. An abscess may rupture into the ventricular system or subarachnoid space and produce meningitis. A CT or MRI brain scan with and without contrast confirms the clinical diagnosis, while a surgical excision of the abscess may be needed to identify the causative organism if cultures of blood and CSF are unremarkable. Positive cultures are needed to guide specific antimicrobial treatment.

6. Prion disease

Prions are "infectious proteins" which can cause transmissible spongiform encephalopathies in humans and animals. They are the exception to the rule that all

infecting organisms contain nucleic acid. Prions have been transmitted by human tissue grafts or neurosurgical instruments. Some prion diseases are hereditary, while many are sporadic in nature. Transmission or pathological genetic production of a prion, existing in a misfolded state or configuration, induces other proteins to convert into the same misfolded state, propagating or "snowballing" this process on and on. The cumulative, progressive aggregation of prions in neurons destroys them in the absence of any inflammatory response.

Creutzfeldt-Jakob dementia (CJD) is the most common of these rare prion diseases, and is most often sporadic rather than transmitted. It is **a very rapidly progressive dementia with cerebellar, corticospinal, lower motor neuron, or extrapyramidal signs and symptoms. Myoclonus** is usually present. It progresses to death within weeks to months and has no cure. A diagnostic brain biopsy shows spongiform changes, which are cytoplasmic vacuoles, in neurons and astrocytes, and neuronal loss without inflammation. Periodic sharp wave discharges are often detected on an electroencephalogram (EEG).

Bovine spongiform encephalopathy is an epidemic prion disease in cattle, also known as "mad cow disease." When transmitted to humans consuming contaminated beef, it produces variant CJD, which is slower in progression and has more psychiatric and behavioral symptoms.