CNS
MICROBIOLOGY

5

Writer: Ahmed Freihat

Science: Mohammad Sallam

Final: Nour Awamleh

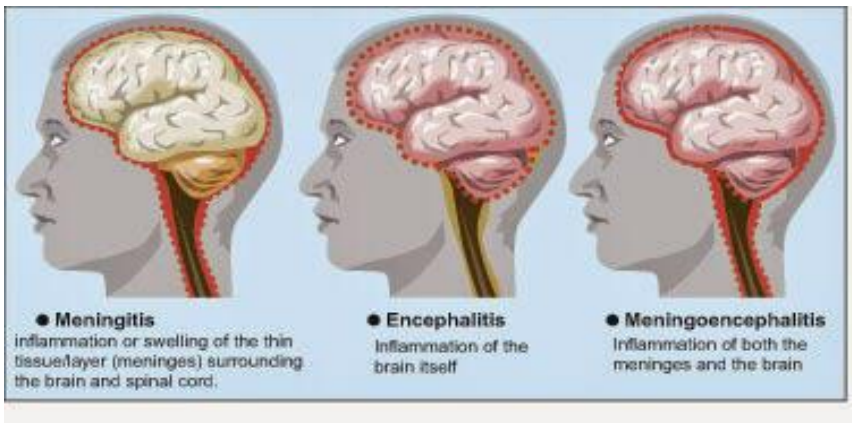
Doctor: Anas Abu-Humaidan

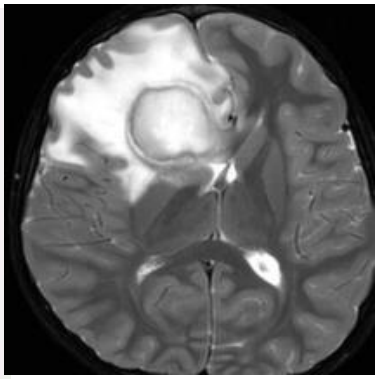
We have previously talked about *meningitis* and *suppurative space occupying infectious lesions in the brain*.

Today we will talk about:

1- Encephalitis.
2- Transmissible spongiform encephalopathy.
3- Infectious myelopathy.

What is encephalitis and how is it different from meningitis?





Meningitis includes inflammation of brain meninges, while in ***encephalitis*** there is involvement of brain parenchyma that arises from **penetration of the blood–brain barrier or overlying meninges.**

• In meningitis, the inflammatory response is limited largely to the meninges.

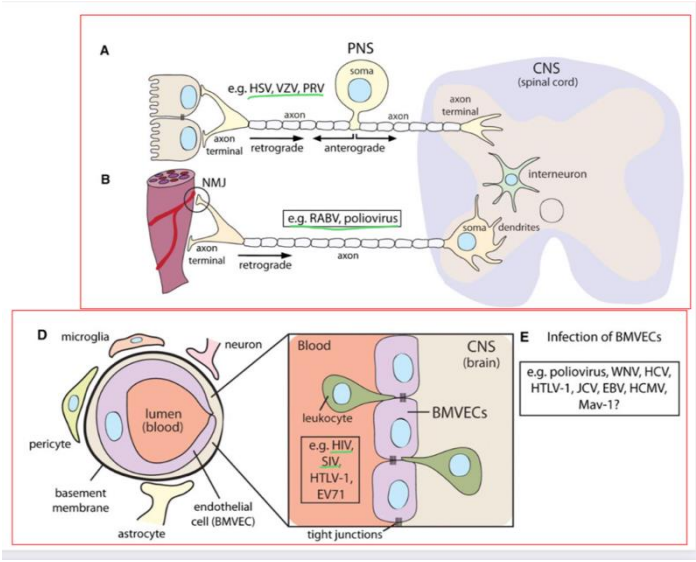
• Meningitis is more common than encephalitis as the meninges appear to play a protective role in limiting pathogen spread to the CNS.

When a patient is admitted with signs of meningitis and loss of consciousness, the doctor should consider the involvement of brain parenchyma (***meningoencephalitis***).

Meningitis is commonly due to bacterial infection, while viral infections (most common cause is HSV1) are more common in encephalitis.

When we talked about meningitis, we said that the infectious agent can reach the meninges by direct or hematogenous spread. However, in Encephalitis, there are more routes of spread as we will see next.

Viral spread to the CNS



Viruses have many routes to reach brain parenchyma and cause encephalitis:

1- Invasion of sensory nerve endings. It can be seen in the case of HSV1(more common), HSV2 or VZV where they infect the skin first. Then, they reach dorsal root ganglia and become latent. At a different time point, they reactivate and reach the skin or even the ***CNS (retrograde fashion).***
2- Invasion of motor nerve endings. It can be seen in the case of **polio and rabies virus.** (will be demonstrated later)
3- Infection of brain microvascular endothelium (hematogenous). Then, they reach the parenchyma.
4- Some viruses invade the CNS via infected circulating leukocytes that will eventually reach the parenchyma (HIV, Simian immunodeficiency virus).

- Encephalitis, in general, is quite uncommon and even HSV causing it is rare. This is because CNS infections are deadly to the host, which is unbeneficial to the pathogen (as it limits the transmission ability of the pathogen from one host to another).
- In addition to the damage that is caused by the pathogen itself, an immune response (by microglia, astrocytes, neutrophils) plays a major role in the damaging the parenchyma.

How do encephalitis patients present?

In addition to fever, headache, and symptoms of accompanying meningitis (if present), the patient with encephalitis commonly presents with:

• An altered level of consciousness (hallucinations, agitation, personality change, behavioral abnormalities).

• Depressed level of consciousness ranging from mild lethargy (lack of energy) to coma.

• Sometimes the patient has either **focal or diffuse neurologic signs** and symptoms (aphasia, ataxia, upper or lower motor neuron patterns of weakness).

• Focal or generalized **seizures** occur in many patients with encephalitis.

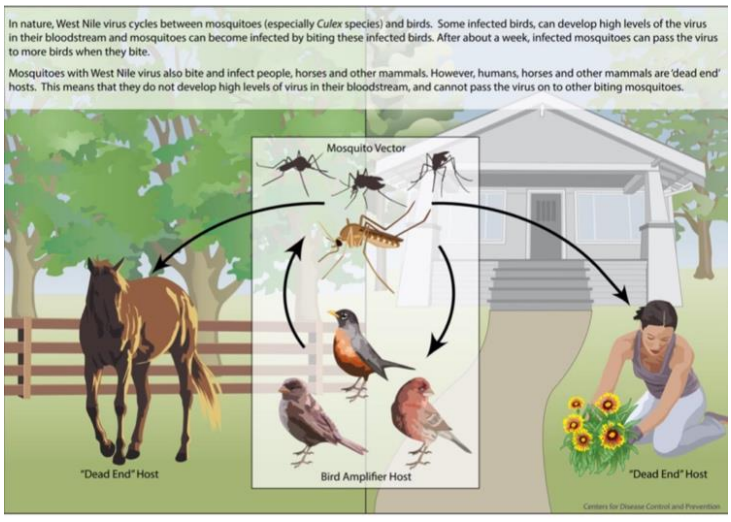
> Some viruses have a tendency to infect a certain area in the brain. For example, HSV tends to infect the temporal lobe, so there will be symptoms related to the area infected, memory loss in this case.

Clinical examination alone cannot distinguish the causative agent, so additional tests should be carried out.

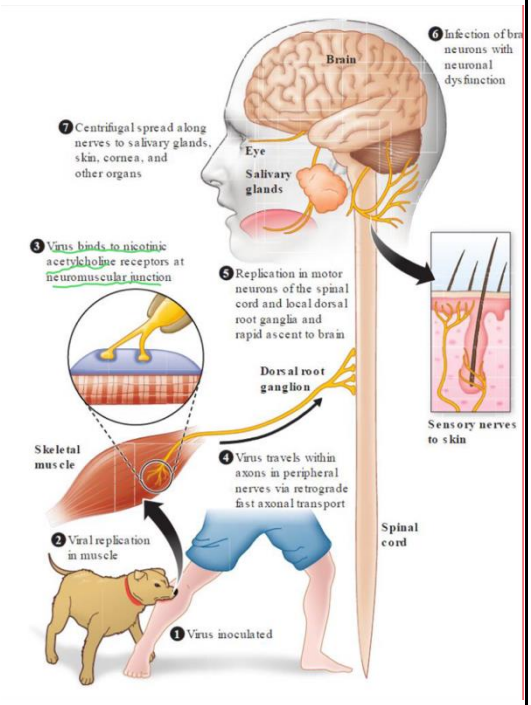
What are the commonly encountered pathogens?

- Despite comprehensive diagnostic efforts, the majority of cases of acute encephalitis of suspected viral etiology remain of **unknown cause.**
- Many viruses can cause encephalitis, but the **most commonly identified** viruses causing **sporadic** cases of acute encephalitis in immunocompetent adults are **herpesviruses** (HSV, VZV, EBV).

- **Epidemics** of encephalitis are caused by **arboviruses** (viruses that are transmitted by arthropod vectors). Since 2002, West Nile virus (**WNV**) has been the cause of the majority of outbreaks.
- WNV can be carried by mosquitoes or ticks. Its life cycle is demonstrated as follows, an arthropod (main host) infects a bird, the bird then transmits it to another arthropod which infects humans (humans are accidental and dead-end hosts).



Rabies virus as a cause of encephalitis:



Rabies (داء الكلب) is a zoonotic infection that occurs in a variety of mammals. It is transmitted to humans through a bat's or dog's bite.

A common scenario is when an infected dog bites a human, viral particles are transmitted through its saliva to replicate inside the muscles. Then, via **motor neurons**, they reach the brain. Onset of symptoms differs between cases as incubation period ranges from days to even months.

Rabies symptoms:

• In addition to encephalitis symptoms, in encephalitic (furious) rabies, episodes of hyperexcitability (strange behavior) are typically followed by periods of complete lucidity that become shorter as the disease progresses.

• In late stage, when there is CNS involvement, brain stem dysfunction progresses rapidly and **coma— followed within days by death**—is the rule unless the course is prolonged by supportive measures.

TABLE 105-1

CLINICAL STAGES OF RABIES

PHASE	TYPICAL DURATION	SYMPTOMS AND SIGNS
Incubation period	20–90 days	None
Prodrome	2–10 days	Fever, malaise, anorexia, nausea, vomiting; paresthesias, pain, or pruritus at the wound site
Acute neurologic disease		
Encephalitic (80%)	2–7 days	Anxiety, agitation, hyperactivity, bizarre behavior, hallucinations, autonomic dysfunction, hydrophobia
Paralytic (20%)	2–10 days	Flaccid paralysis in limb(s) progressing to quadriparesis with facial paralysis
Coma, death[a]	0–14 days	

[a]Recovery is rare.
Source: MAW Hattwick: Rabies virus, in Principles and Practice of Infectious Diseases, GL Mandell et al (eds). New York, Wiley, 1979, pp 1217–1228. Adapted with permission from Elsevier.

Management of Rabies:

• On the basis of exposure (bite of infected dog) and local epidemiologic information, the physician must decide to initiate ***post exposure prophylaxis*** (based on the possibility of getting Rabies).

• Prophylaxis involves wound care and passive immunization with rabies immune globulin. Prophylaxis should be given as soon as possible as death can occur within two weeks of exposure!!

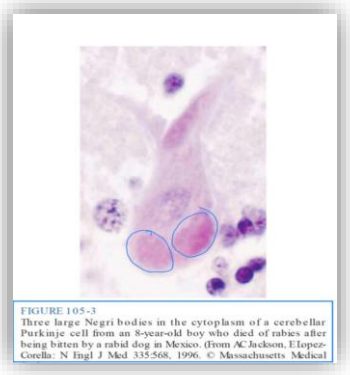


FIGURE 105-3
Three large Negri bodies in the cytoplasm of a cerebellar Purkinje cell from an 8-year-old boy who died of rabies after being bitten by a rabid dog in Mexico. (From AC Jackson, E Lopez-Corella: N Engl J Med 335:568, 1996. © Massachusetts Medical

Histopathology: Negri bodies, which are eosinophilic cytoplasmic inclusions inside neurons, are **pathognomonic** to rabies.

How to diagnose a suspected encephalitis patient?

• **Lumber puncture**: CSF profile is **indistinguishable** from that of viral meningitis. Also, it typically consists of a lymphocytic pleocytosis, a mildly elevated protein concentration, and a normal glucose concentration.

• **CSF PCR** has become the primary diagnostic test for viral CNS infections.

• **Serology**: We look for Abs of the suspected virus. In the case of epidemics, we should suspect WNV. WNV IgM antibodies in the CSF are diagnostic for WNV encephalitis

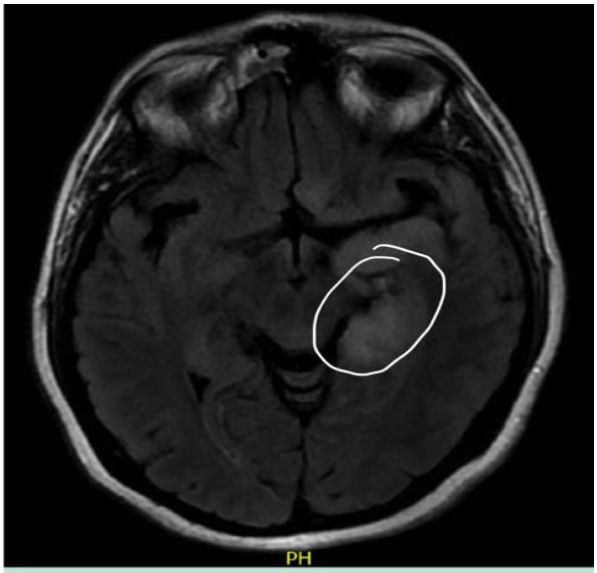


Figure 1 Herpes simplex virus (HSV) encephalitis. Brain magnetic resonance image of a patient who presented with memory impairment, headaches, and fevers. Axial T2 fluid-attenuated inversion recovery (FLAIR) imaging shows left hemispheric hyperintensity in the anterior and medial temporal lobe and mass effect approaching the midbrain. HSV DNA was detected in the cerebrospinal fluid by polymerase chain reaction.

• **Neuroimaging** can help identify or exclude alternative diagnoses and assist in the differentiation between focal, as oppose to a diffuse, encephalitic process.

If all previous examinations failed to detect the pathogen, **brain biopsy** should be performed.

Management and sequelae of encephalitis:

• In the initial stages of encephalitis, many patients will require care in an intensive care unit (ICU). Basic management and supportive therapy should include careful monitoring of **vital signs** and **ICP**.

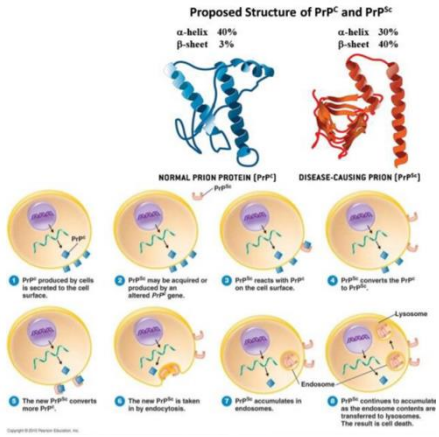
• **Acyclovir** is of benefit in the treatment of HSV (and VSV and EBV severe infections) and should be started empirically in patients with suspected viral encephalitis, while awaiting viral diagnostic studies.

• There is considerable variation in the incidence and severity of sequelae in patients surviving viral encephalitis. Many patients with WNV infection have sequelae, including **cognitive impairment**, **weakness**, and hyper- or hypokinetic movement disorders (including tremor, myoclonus, and parkinsonism).

"Symptoms related to damaged parenchyma are not reversed for sure".

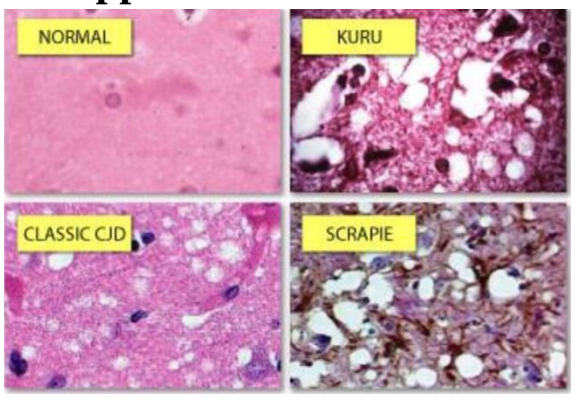
Prions

- Prions are abnormal, misfolded, and pathogenic agents that are transmissible and able to induce abnormal folding of specific normal cellular proteins. (No DNA or RNA, only proteins!)
- They are called prion proteins (PrP) and found most abundantly in the brain.
- Prions composed of the prion protein (PrP) are hypothesized as the cause of **Transmissible spongiform encephalopathies (TSEs)**.



Transmissible spongiform encephalopathies (TSEs):

• Are a group of diseases that affect the brain and nervous system of humans and animals. The diseases are characterized by a degeneration of cerebral cortex & cerebellum tissue giving it a **sponge-like appearance**.



***TSEs** in humans include:*

1- **Creutzfeldt–Jakob disease** "*discussed later"* (4 forms):

- Sporadic (sCJD).

- Hereditary/familiar (fCJD).

- Iatrogenic (iCJD).

- Variant form (vCJD).

2- **Kuru**, uncommon nowadays, was found in a tribe that practiced ritualistic cannibalism (eating brains of their dead relatives).

3- **Fatal familial insomnia** (FFI).


Kuru

***TSEs** in animals include*:

1- **Scrapie** in sheep and goats.

2- **Bovine spongiform encephalopathy (BSE)** in cows. Also called **Madcow disease.**

These two diseases are caused by the food given to the affected animal.


Scrapie

Now let us talk about ***Forms of* Creutzfeldt–Jakob disease**:

1- Sporadic (sCJD)

• The infectious prions are believed to be made by an error of the cell machinery that makes proteins and controls their quality.

• **These errors are more likely to occur with aging,** which explains the general advanced age at onset of CJD and other prion diseases.

2- Familial (fCJD)

• If the prion protein gene is altered in a person's sperm or egg cells, the mutation can be **transmitted to the person's offspring.**

• The particular mutation found in each family affects how frequently the disease appears and what symptoms are most noticeable.

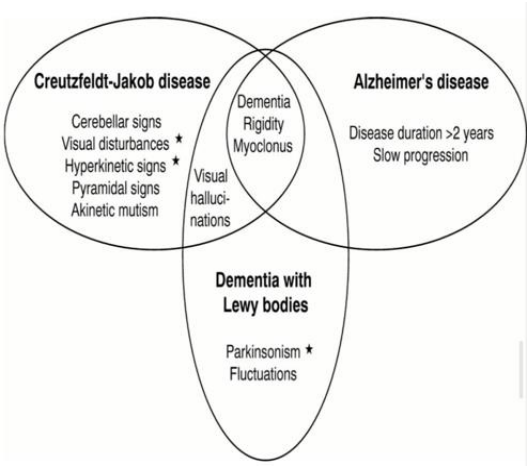
3- Acquired (iCJD)/(vCJD)

Either **iatrogenic** or **variant**.

• **Iatrogenic**: Accidental transmission of **CJD** to humans appears to have occurred with **corneal transplantation, contaminated (EEG) electrode implantation, and surgical procedures**.

• **Variant**: Acquired by **eating meat from cattle affected by** "**Mad Cow**" disease.

Signs & Symptoms of CJD:



Symptoms reflect the degeneration that takes place in the brain, hence there is common signs with other neurodegenerative diseases (Alzheimer's and dementia).

- Rapidly progressive dementia (confusion, disorientation, and problems with memory, thinking, planning and judgment).
- Rigidity.
- Agitation, apathy, and mood swings.
- Myoclonus.

• As the condition worsens, physical manifestations appear, such as:

Ataxia, speech impairment, and changes in gait.

Myoclonus

(refer to the lecture at minute 27:10 to see a demonstrative video of myoclonus)

• Definition: It is a **brief, involuntary twitching of a muscle or a group of muscles** caused by sudden muscle contractions (positive myoclonus) OR brief lapses of contraction (negative myoclonus).

• Most patients (90%) with CJD exhibit myoclonus that appears at various times throughout the illness.

• Myoclonus persists during sleep, unlike other involuntary movements.

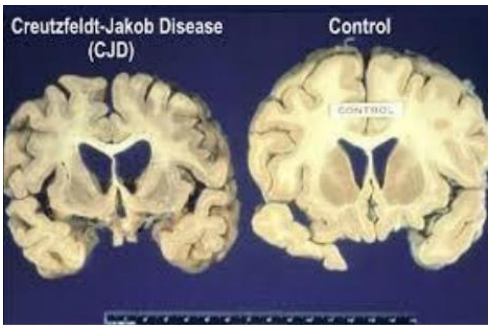
How is CJD diagnosed?

• **Electroencephalography (EEG)**: can be particularly valuable because it shows a specific type of abnormality in major, but not all, types of CJD.

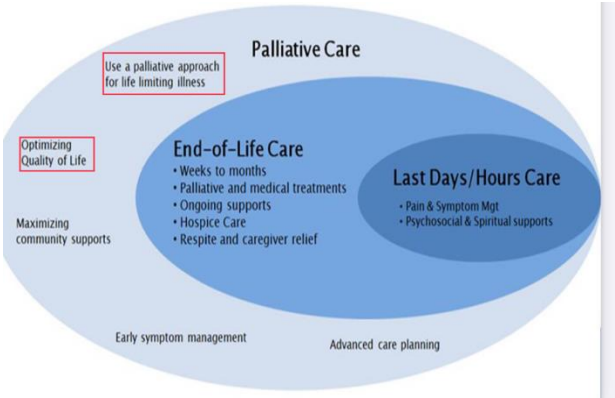
• **Magnetic resonance imaging (MRI):** has recently been found to be accurate in about 90 percent of cases.

• ***The only way to confirm a diagnosis of CJD is by brain biopsy or autopsy***. In a brain biopsy, a neurosurgeon removes a small piece of tissue from the person's brain so that it can be examined by a neuropathologist (it looks spongy).

Treatment of CJD



- **There is no known cure or effective treatment for CJD**. However, *medications can be used to treat some of the mental changes and personality abnormalities that occur*.
- Treatment is usually focused on **optimizing quality of life** and to help patients function safely in their environment (palliative).
- **Opiate drugs** can also help relieve pain if it occurs, and the drugs **clonazepam** and **sodium valproate** may help relieve myoclonus.



The spinal cord can also be involved in infections ***(infectious myelopathies or myelitis).***

- ***Myelitis*** arises from intrinsic infection and inflammation of the spinal cord.
- Clinical manifestations depend on the exact level and location within the cord.

Causes:

1. The **herpesviruses** and **enteroviruses** account for a substantial number of viral myelitis cases.
2. Myelopathies can also be caused by Treponema pallidum, as a late stage of **syphilis** (secondary or tertiary syphilis). However, it is very rare nowadays as syphilis gets treated at an early stage.
3. Also, we can have bacterial space occupying lesions (staph aureus). In this picture, the patient has an epidural abscess (between dura matter and vertebrae), which causes spinal cord compression. The patient requires immediate recognition because permanent neurologic deficits may develop within 36 hours of symptom onset.

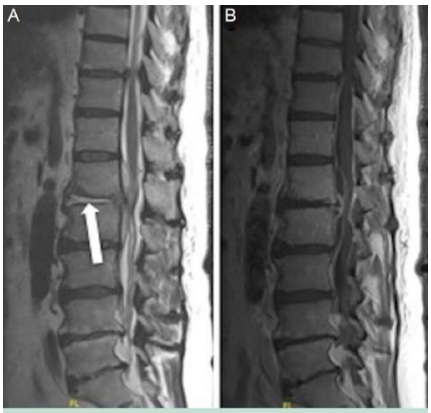


Figure 2 Discitis with associated ventral epidural abscess. Lumbosacral magnetic resonance image of a patient with diabetes mellitus who presented with acute on chronic low back pain, fevers, and weight loss. Sagittal T2 fluid-attenuated inversion recovery (FLAIR) imaging (**A**) and T1 postcontrast imaging (**B**) show high T2 signal within the L1-L2 intervertebral disc (arrow) and an associated ventral epidural fluid collection with peripheral enhancement. Blood cultures grew methicillin-sensitive *Staphylococcus aureus*.

Good Luck