

# Microbiology

## Modified no. 2 Final

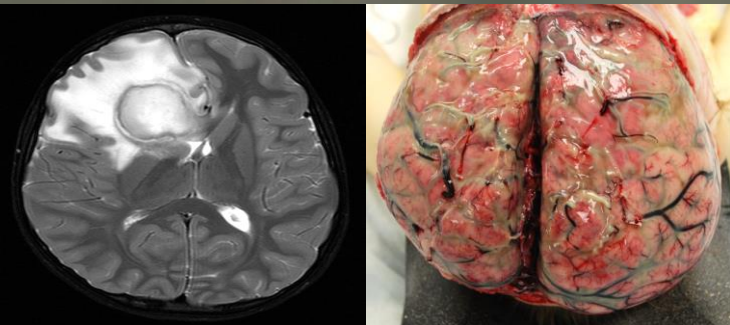
Writer: Mhammad Ali Alnwaihi

### Overview

In this lecture we will discuss the following :

- Encephalitis
- Transmissible spongiform encephalopathies
- **Very easy lecture inshaallah**

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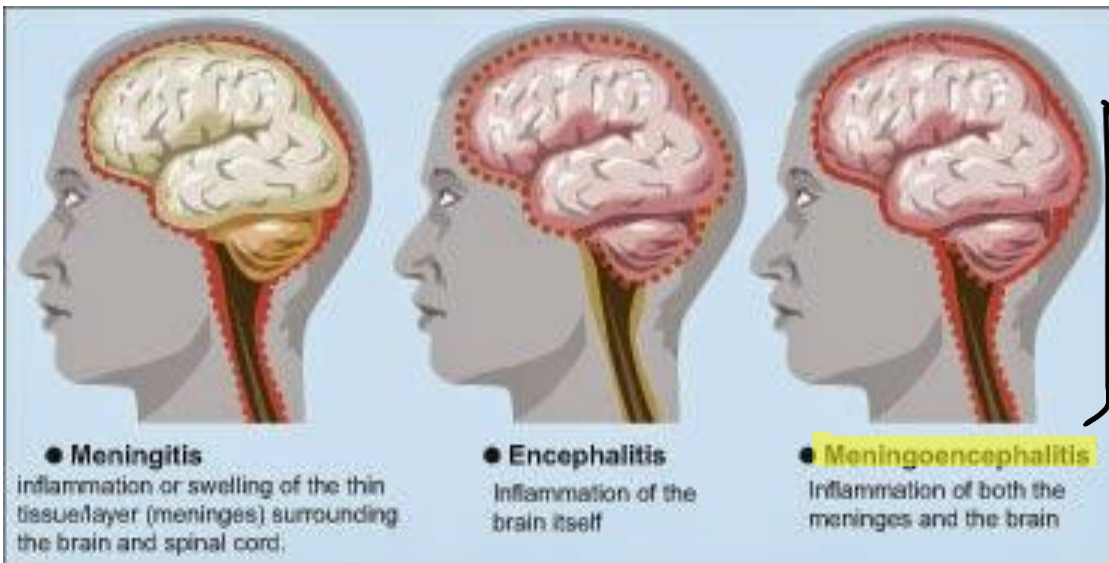


What is encephalitis and how is it different from meningitis?

- **Encephalitis** is an inflammation of the 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**, and the **meninges appear to play a protective role in limiting pathogen spread to the CNS**.

Its not uncommon to see meningitis along with encephalitis (they can occur together)

When we have signs and symptoms of brain dysfunction (such as an altered level of consciousness or suppressed level of consciousness), **so you should suspect that the brain parenchyma is involved.**





Usually viruses that cause encephalitis, herpes simplex virus type 1 and 2 is the most common one **type 1 is more common** although its rare in general.

So, how does the pathogen get to the brain parenchyma ??

Like meningitis, they can spread hematogenous (blood) + direct spread, **But** in case of encephalitis, there are more ways that the pathogen can reach the CNS

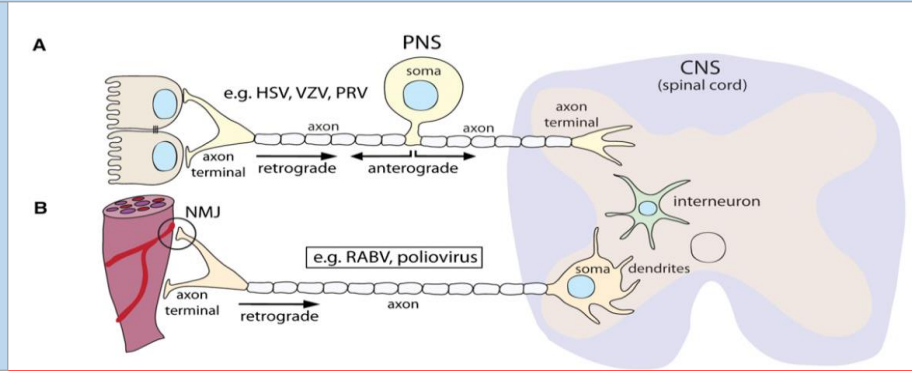
• Invasion of Sensory and motor Nerve Endings.

• Infection of Brain Microvascular Endothelium

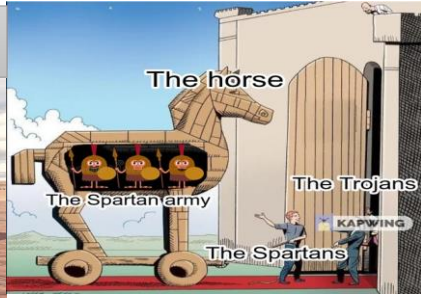
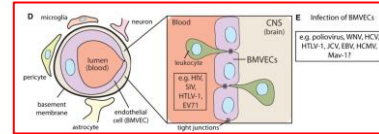
• Invasion by Infected Circulating Leukocytes

A) Herpes simplex (HSV), Varicella zoster (VZV) they infect the epithelial layers of skin (for ex.) and from skin can cause primary infection within CNS then can go to dorsal root ganglia having latent infection in it, And at different time points, they can reactivate and either go again and infect the epithelial cells of the skin or they can go and infect the central nervous system.

B) Some other viruses can hijack motor neurons first by infecting the muscles and then through the axon terminals at the CNS. Rabies virus and polio viruses can take this route.



When the leukocyte migrates into the brain parenchyma, similar to the Trojan horse, the viruses will go also inside with the leukocytes



HIV , Semi-immune deficiency virus are common through this pathway



## Virus Induced Immune-Mediated CNS Pathogenesis

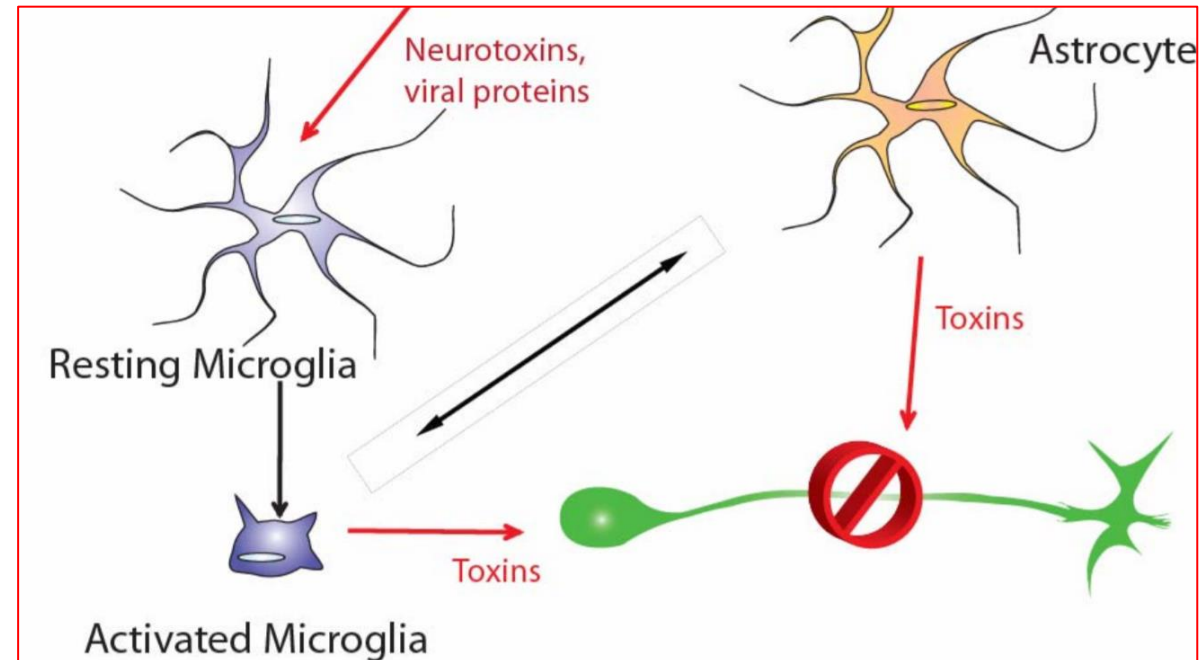
Viruses + also immune response cause damage to CNS

Neutrophils + resident microglia (when they are activated)  
+ activated astrocytes (releasing cytokines)

## Synchronous Neutrophil Extravasation During VSV Encephalitis

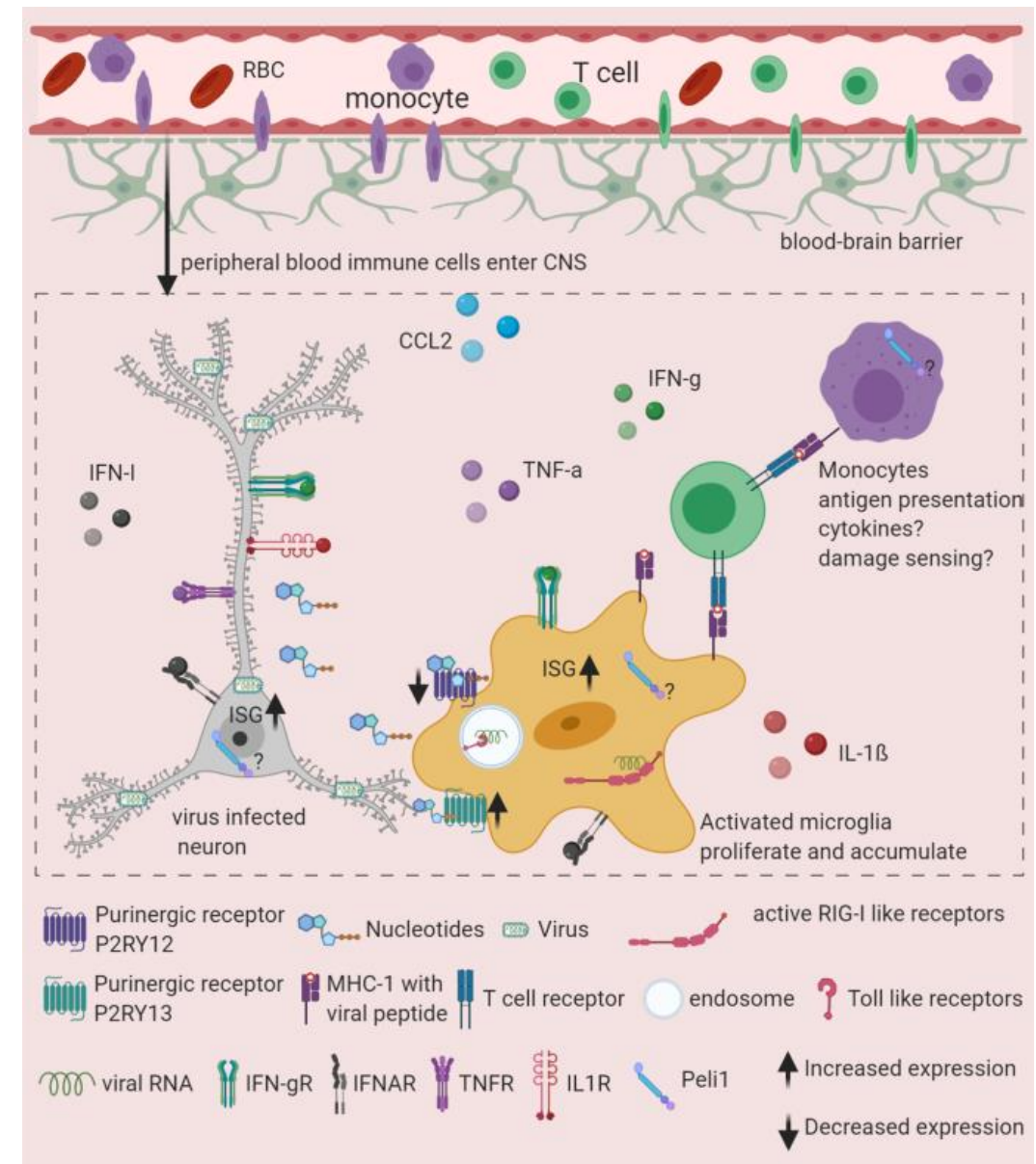
You can see these two videos in the pptx file

## Microglia Activated by a CNS Viral Infection



## Virus Induced Immune-Mediated CNS Pathogenesis

- Microglia, the innate immune cells that reside in the CNS parenchyma, deploy innate immune mechanisms to control virus spread shortly after CNS infection.
- Microglia are nonredundant antigen-presenting cells in the CNS that regulate adaptive immune responses after infection.
- Microglia are involved in CNS damage following the acute phase of viral encephalitis, which does not stop after virus elimination from the CNS.



The roles of microglia in viral encephalitis: from sense to therapeutic targeting <https://www.nature.com/articles/s41423-020-00620-5#Sec9>

How do encephalitis patients present?

In addition to **fever** and **headache**, and symptoms of accompanying meningitis (if present), we should expect meningeal signs such as : neck stiffness, a positive Kernig's Sign Brudzinski's sign  
Other than that :

- An altered level of consciousness (**hallucinations**, agitation, personality change, **behavioural abnormalities**), or a
- Depressed level of consciousness ranging from mild **lethargy** to complete **coma**,
- An evidence of either **focal** or **diffuse neurologic signs** and symptoms (aphasia, ataxia, upper or lower motor neuron patterns weakness).
- Focal or generalized **seizures** occur in many patients with encephalitis.

Neurotropic viruses typically cause pathologic injury in distinct regions of the CNS such as HSV likes to infect temporal lobes. But cannot be distinguished only by clinical examination.



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.

probably because we have many viruses that can cause encephalitis.

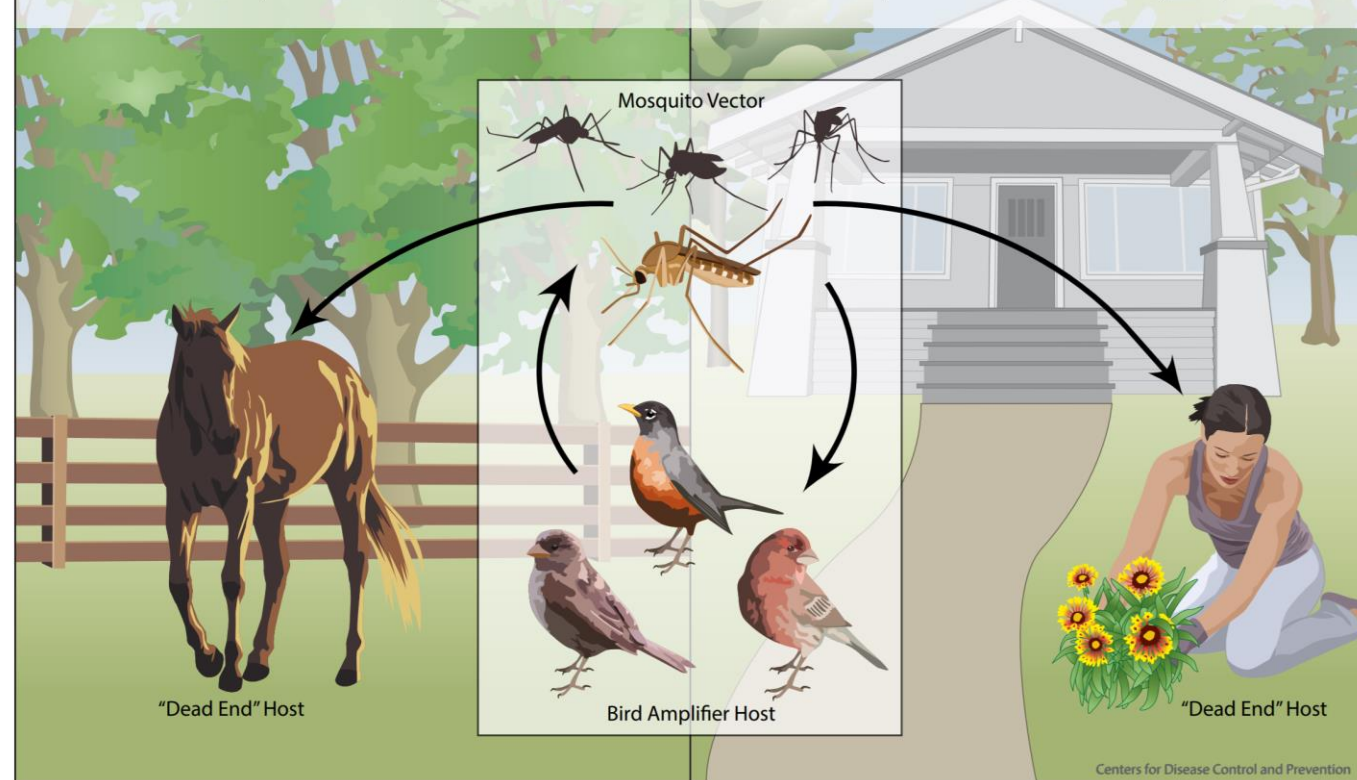
Many viruses can cause encephalitis, but the most commonly identified viruses causing sporadic cases of acute encephalitis in immunocompetent adults are herpesviruses (HSV, VZV, EBV).

Epidemics of encephalitis are caused by arboviruses (viruses that are transmitted by arthropod vectors like ticks and mosquitoes). Since 2002 West nile virus (WNV) has been the cause of majority of outbreaks.

## West Nile Virus Transmission Cycle

In nature, West Nile virus cycles between mosquitoes (especially *Culex* species) and birds. Some infected birds, can develop high levels of the virus in their bloodstream and mosquitoes can become infected by biting these infected birds. After about a week, infected mosquitoes can pass the virus to more birds when they bite.

Mosquitoes with West Nile virus also bite and infect people, horses and other mammals. However, humans, horses and other mammals are 'dead end' hosts. This means that they do not develop high levels of virus in their bloodstream, and cannot pass the virus on to other biting mosquitoes.



**West nile virus (WNV) :**  
**Birds: virus reservoir**  
**Mosquito: main host**  
**Human: accidental host**

## Rabies virus as a cause of encephalitis

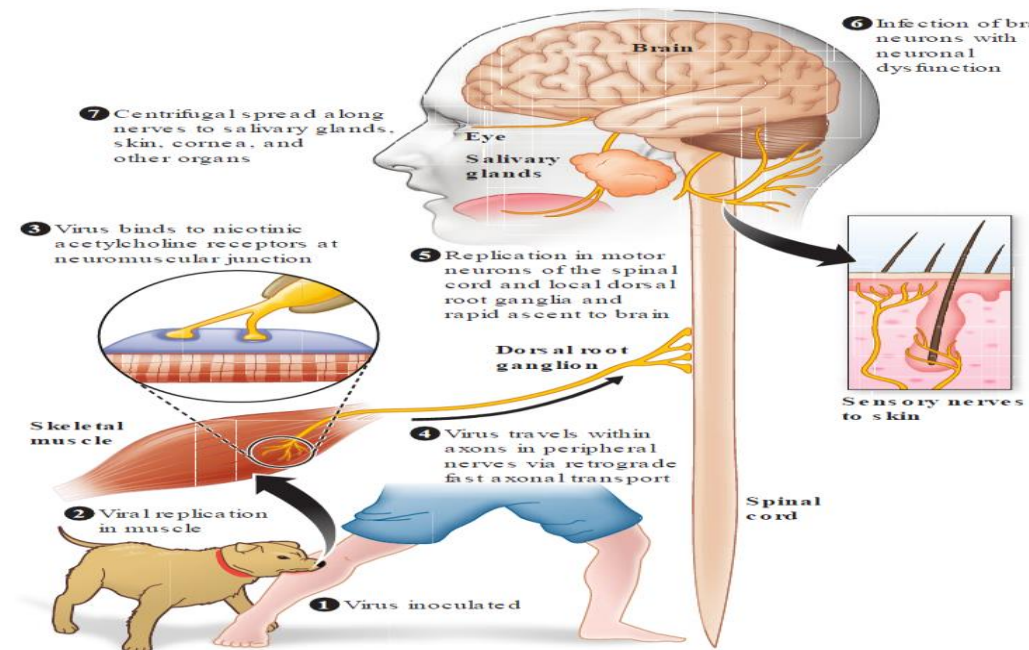
We also have a disease called rabies that is caused by the rabies virus and rabies also have encephalitis as part of the syndrome.

Rabies is a **zoonotic infection** that occurs in a variety of Mammals, transmitted to humans through **bites**.

canine bite (dog bite) or bats

- Incubation period ranges from days to less than a year.
- In addition to encephalitis symptoms, in encephalitic (furious) rabies, episodes of hyperexcitability (as strange behavior) are typically followed by periods of complete lucidity that become shorter as the disease progresses
- Brainstem dysfunction progresses rapidly, and coma— followed within days by death—is the rule unless the course is prolonged by supportive measures.

The virus will replicate within skeletal muscles and through the neuromuscular junction the virus goes into the axons of peripheral nerves and then replicates in motor neurons and can go up into the brain.





- On the basis of exposure and local epidemiologic information, the physician must decide whether initiation of **post exposure prophylaxis** is warranted  
 post-exposure prophylaxis, if we think that the animal that bite the person is infected
- Prophylaxis involves **wound care** > cleaning the wound is important to limit the spread and passive immunization with rabies immune globulin.

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 quadriplegia with facial paralysis
Coma, death <sup>a</sup>	0–14 days	

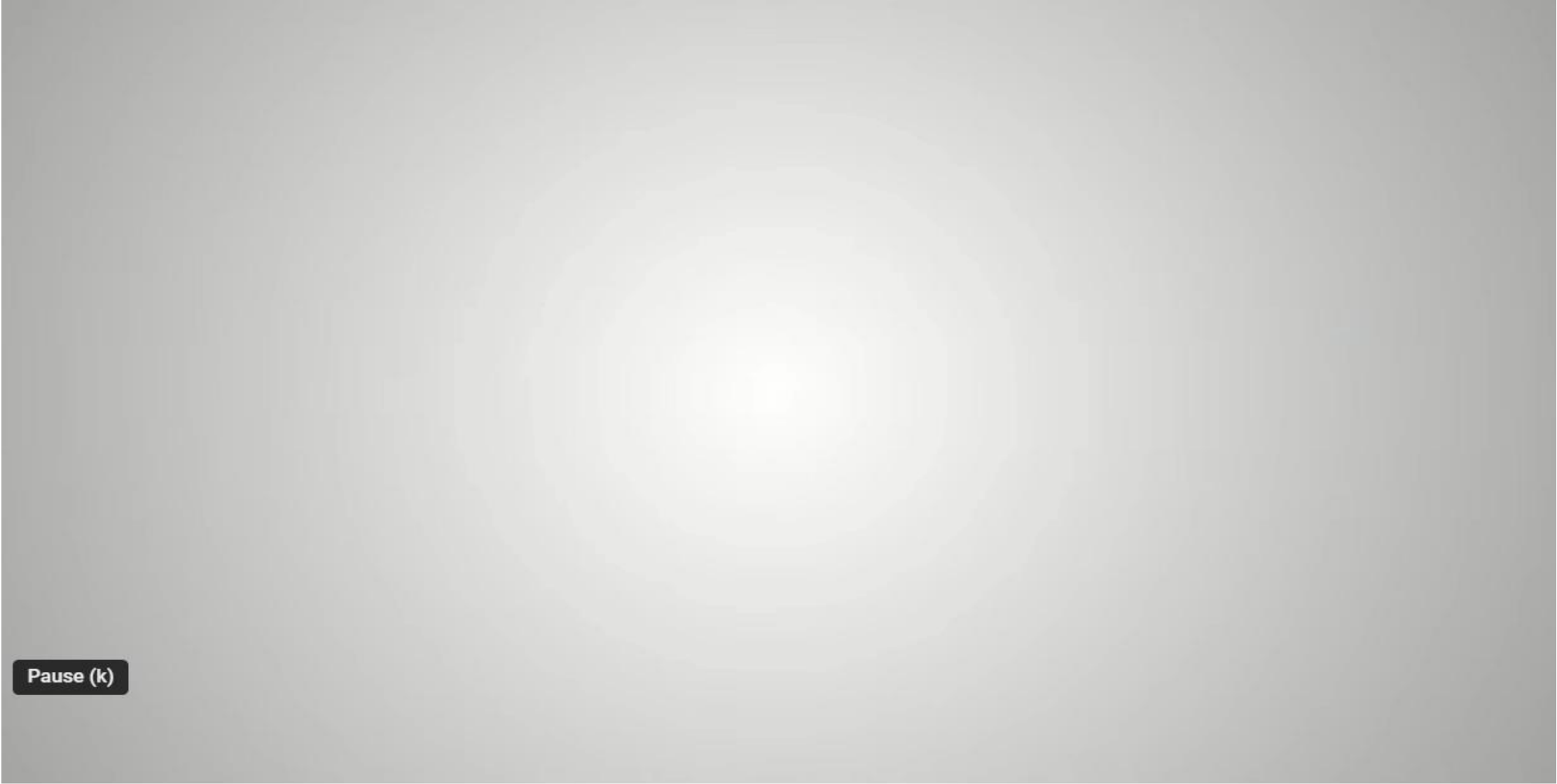
<sup>a</sup>Recovery is rare.  
 Source: MAW Hattwick: Rabies virus, in Principles and Practice of Infectious Diseases, GLMandell et al (eds). New York, Wiley, 1979, pp 1217–1228. Adapted with permission from Elsevier.

we have a pathognomonic sign, **histological sign** of rabies where we see those eosinophilic cytoplasmic bodies within the neurons of brain which are called **nigri bodies**



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 Society.)

Doctor skipped this slide



Pause (k)


Rabies 3/3





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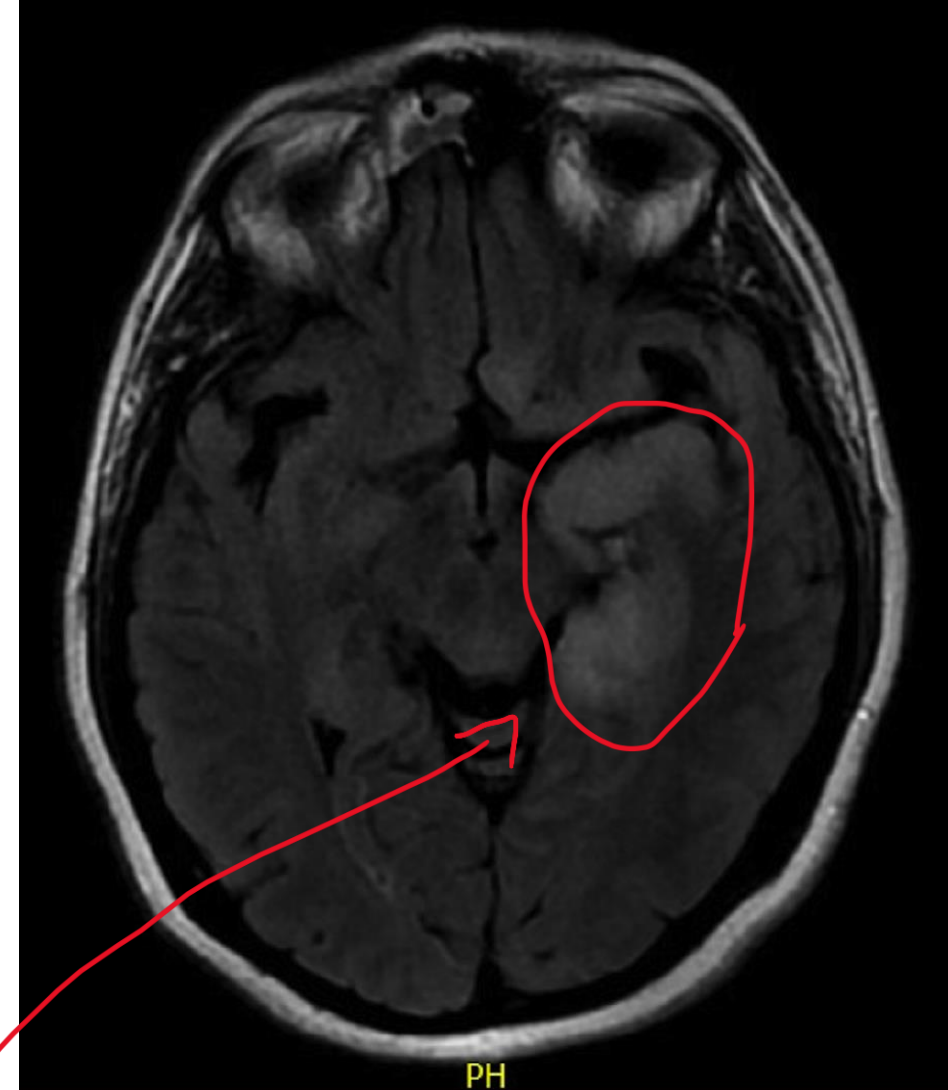
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How to diagnose a suspected encephalitis patient ?

- **Lumber puncture:** and look at CSF profile is indistinguishable from that of viral meningitis and typically consists of a **lymphocytic pleocytosis** (increase in the number of lymphocytes), a **mildly elevated protein** concentration, and a **normal glucose** concentration. Similar to the findings of meningitis. so this indicate either viral meningitis or viral encephalitis. Continue
- **CSF PCR** has become the primary diagnostic test for viral CNS infections. Looking for viral DNA and RNA
- **Serology:** Anti WNV IgM antibodies (on case of epidemics) in the CSF are diagnostic for WNV encephalitis.
- **Neuroimaging:** can help identify or exclude alternative diagnoses and assist in the differentiation between focal, as oppose to a diffuse, encephalitic process.
- **Brain biopsy** (if all the above fails identifying the cause)



**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.



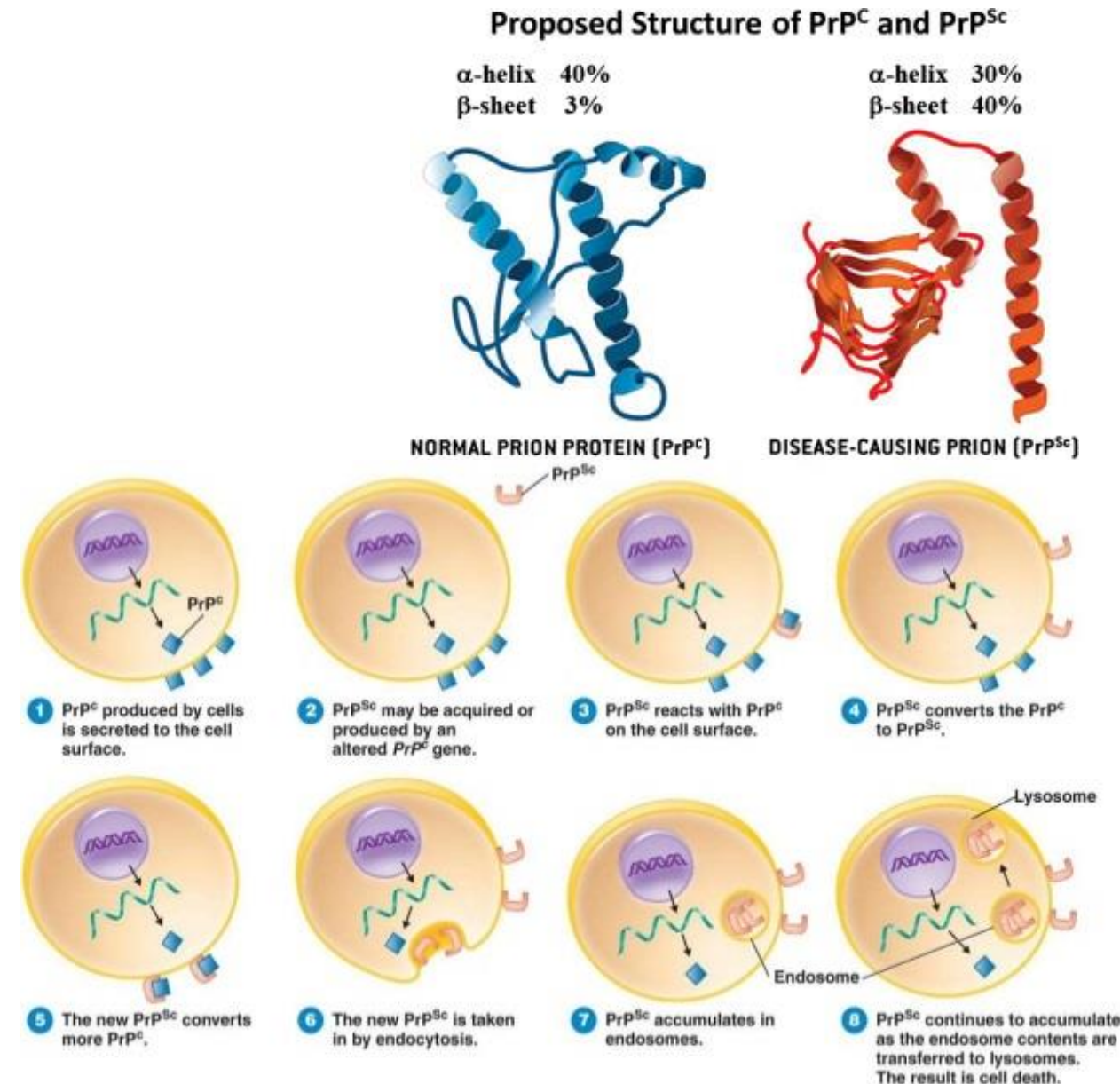
- In the initial stages of encephalitis, many patients will require care in an **intensive care unit**. Basic management and supportive therapy should include **careful monitoring of vital signs and ICP**.
- **Acyclovir** is of benefit in the treatment of HSV (and VSV and EBV severe infections) and should 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. **cuz the neurons are destroyed**

Another disease :

# Prions

**Prions** are abnormal, pathogenic agents that are transmissible and are able to induce **abnormal folding** of specific normal cellular proteins called **prion proteins (PrP)** that are found most abundantly in the brain. And finally, the misfolded proteins accumulate causing cell death.

**Prions** composed of the prion protein (PrP) are hypothesized as the cause of **transmissible spongiform encephalopathies (TSEs)**.



# transmissible spongiform encephalopathies (TSEs).

Include group of diseases

- **Transmissible Spongiform Encephalopathies (TSEs)** are a group of diseases that affect the brain and nervous system of humans and animals. The diseases are characterised by a degeneration of cerebral cortex & cerebellum tissue giving it a sponge-like appearance.

- **TSEs in humans include:**

1- **Creutzfeldt–Jakob disease (4 forms):** most common one  
the sporadic (sCJD) - the hereditary/familial (fCJD)  
- the iatrogenic (iCJD) - the variant form (vCJD).

2- **Kuru.** Not common nowadays

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

- **TSEs in animals include:**

1- **Scrapie** in **sheep and goats.** Prions were first discovered in the sheep

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



Kuru



Scrapie

the two diseases were related to the food that the animals were given.



# Forms of CJD

## 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.

## Familial (fCJD)

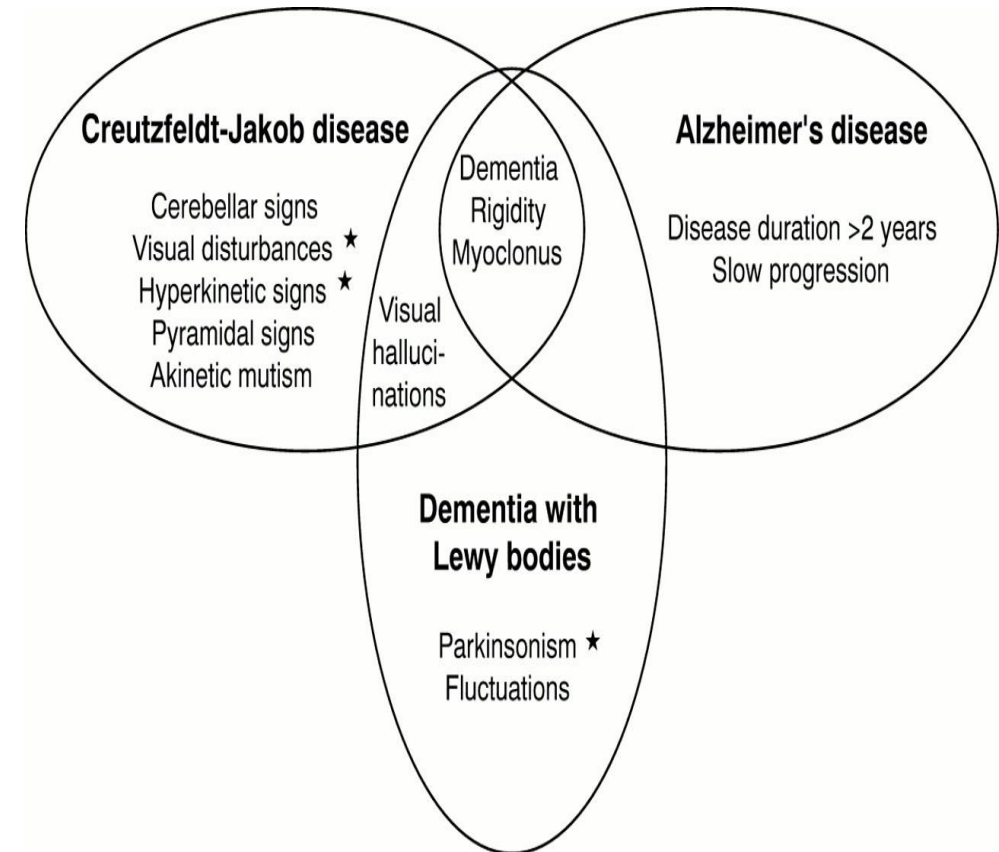
- If the prion protein gene is altered in a person's **sperm or egg cells**, the mutation can be **transmitted** to the person's offspring.
- The particular mutation found in each family affects **how frequently the disease appears** and what **symptoms are most noticeable**.

## acquired (iCJD)/(vCJD)

- **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 **BSE, "mad cow" disease**.

# Signs & Symptoms of CJD

- **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 such as:
  - Ataxia.**
  - speech impairment.**
  - changes in gait.**



## Myoclonus

- **Definition** : 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.



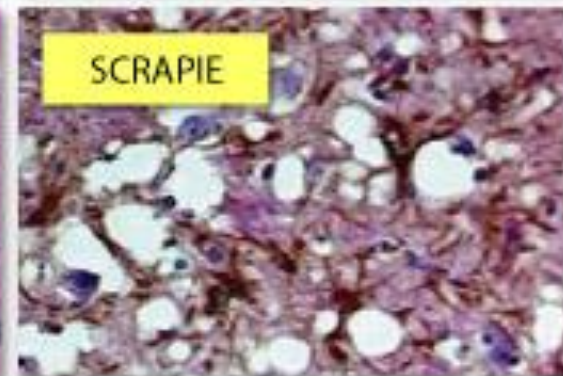
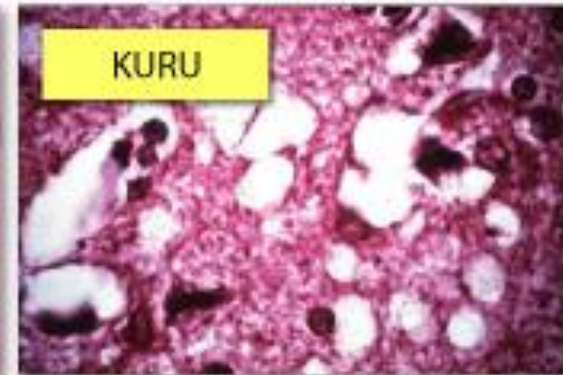
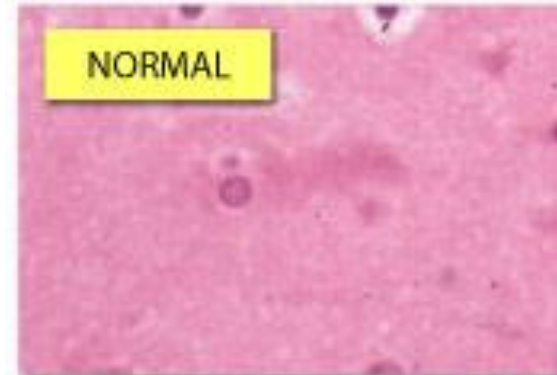


## How is CJD diagnosed?

- **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**.



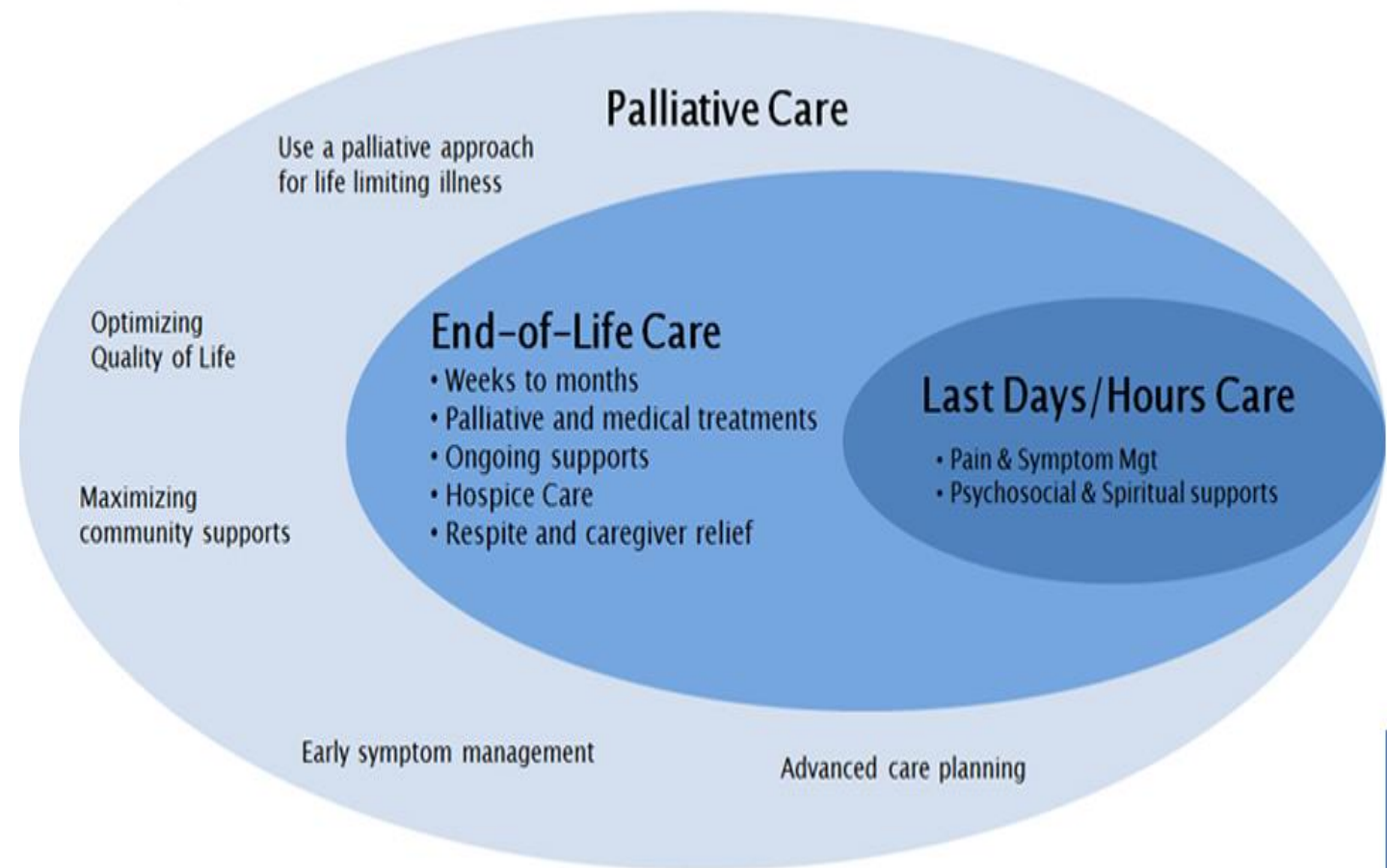
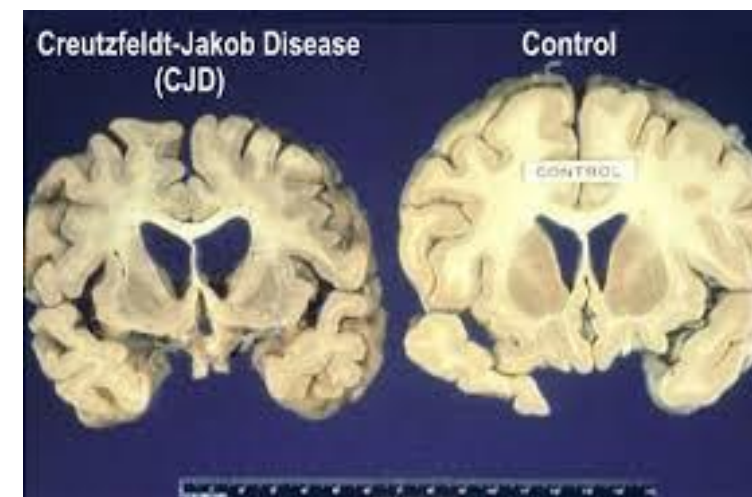
Brain histology of host infected with prions.  
**Sponge like**



## 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 making patients comfortable and to help them function safely in their environment (**Palliative**).
- **Opiate drugs** can help relieve pain if it occurs, and the drugs **clonazepam** and **sodium valproate** may help relieve myoclonus.

We end up covering encephalitis and spongiform encephalopathies. See let's talk very briefly about infections within the spinal cord. ↓





The spinal cord can be involved in infections as well (infectious myelopathies) its quite rare, but it can happen

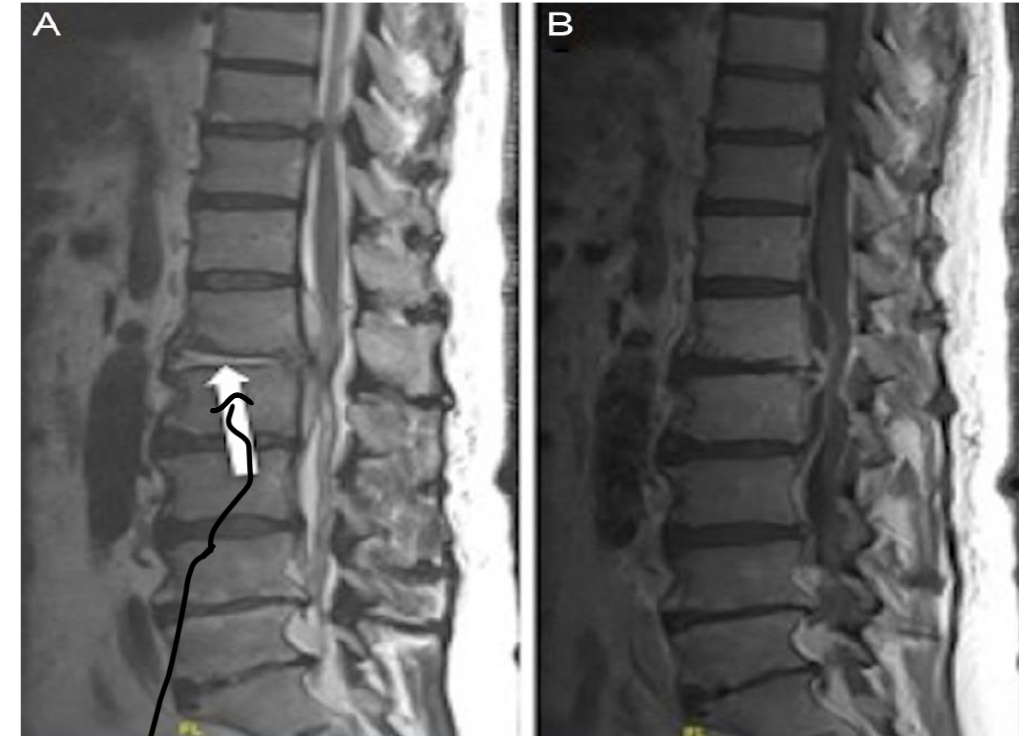
**Myelitis** arises from intrinsic infection and inflammation of the spinal cord.

Clinical manifestations depend on the exact level and **location within the cord** (affect the nerve roots that are leaving the spinal cord at that level) **The herpesviruses and enteroviruses are common causative agents** ubiquitous, accounting for a substantial number of viral myelitis cases.

Other than viruses, we can have bacteria as well as space occupying lesion:

**Pyogenic epidural abscess**, a cause of extrinsic cord compression, requires immediate recognition, because permanent neurologic deficits may develop within 36 hours of symptom onset

***Treponema pallidum***, the causative agent of **syphilis**, is a rare etiology of myelopathy in the 21st century. In later stages of syphilis (secondary and tertiary )



**Figure 2** Discitis with associated ventral epidural abscess. Lumbar 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*.



We have ended our lecture.

Thank you



This is case scenario  
from our doctor.

A

write a case scenario for encephalitis



### Case Scenario for Encephalitis:



**Patient Profile:** Jane, a 32-year-old female, presents to the emergency department complaining of a severe headache, fever, and confusion.

**History of Present Illness:** Jane reports that her symptoms started approximately five days ago with a fever, headache, and body aches. Over the past two days, her headache has worsened, and she has become increasingly confused. She reports difficulty remembering things, and she has been experiencing visual hallucinations.

**Medical History:** Jane has a history of asthma and occasional migraines, but otherwise, she is generally healthy. She takes an over-the-counter migraine medication as needed and has not had any recent hospitalizations or surgeries.

**Physical Exam:** On examination, Jane appears confused and disoriented. She has a fever of 101.2°F, and her blood pressure is 130/90 mmHg. Her heart rate is elevated at 110 beats per minute. Neurological exam reveals that she has difficulty with orientation, memory, and speech. She also has a stiff neck and is sensitive to light.

Point out the mistakes in this case scenario written by chatgpt

**Diagnostic Testing:** A lumbar puncture is performed, and cerebrospinal fluid (CSF) analysis reveals elevated white blood cells, indicating inflammation in the brain. The CSF also shows a high protein level and a low glucose level, consistent with a diagnosis of encephalitis. A CT scan of the brain is also ordered to rule out other potential causes of her symptoms, such as a brain abscess or tumor.

**Diagnosis and Treatment:** Based on the history, physical exam, and diagnostic testing, Jane is diagnosed with encephalitis. She is started on intravenous antiviral medication and supportive care for her fever and pain. She is admitted to the hospital for close monitoring and further treatment.

**Outcome:** With prompt treatment, Jane's symptoms improve over the course of several days. She remains in the hospital for a week and then is discharged with a prescription for antiviral medication to complete at home. She follows up with her primary care physician and a neurologist for further evaluation and management of her symptoms.

## Further reading:

- Oxford handbook of infectious diseases and microbiology-  
Part4: Clinical syndroms  
Chapter 19: Neurological infections
- Harrison's Infectious Diseases 3rd Edition  
SECTION III Infections in organ systems  
Chapter 36