MICROBIOLOGY

Central Nervous System

SHEET NO. 5

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CORRECTER:

Overview

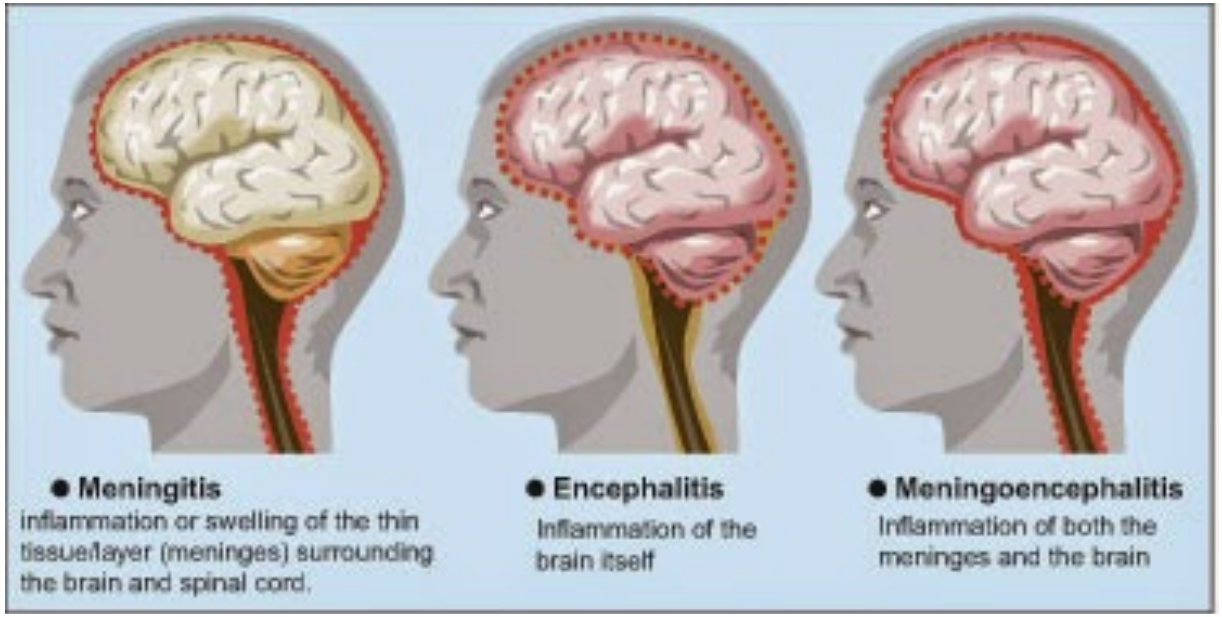
In this lecture we will discuss the following :

- Encephalitis
- Transmissible spongiform encephalopathies

Please focus on the underlined

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.

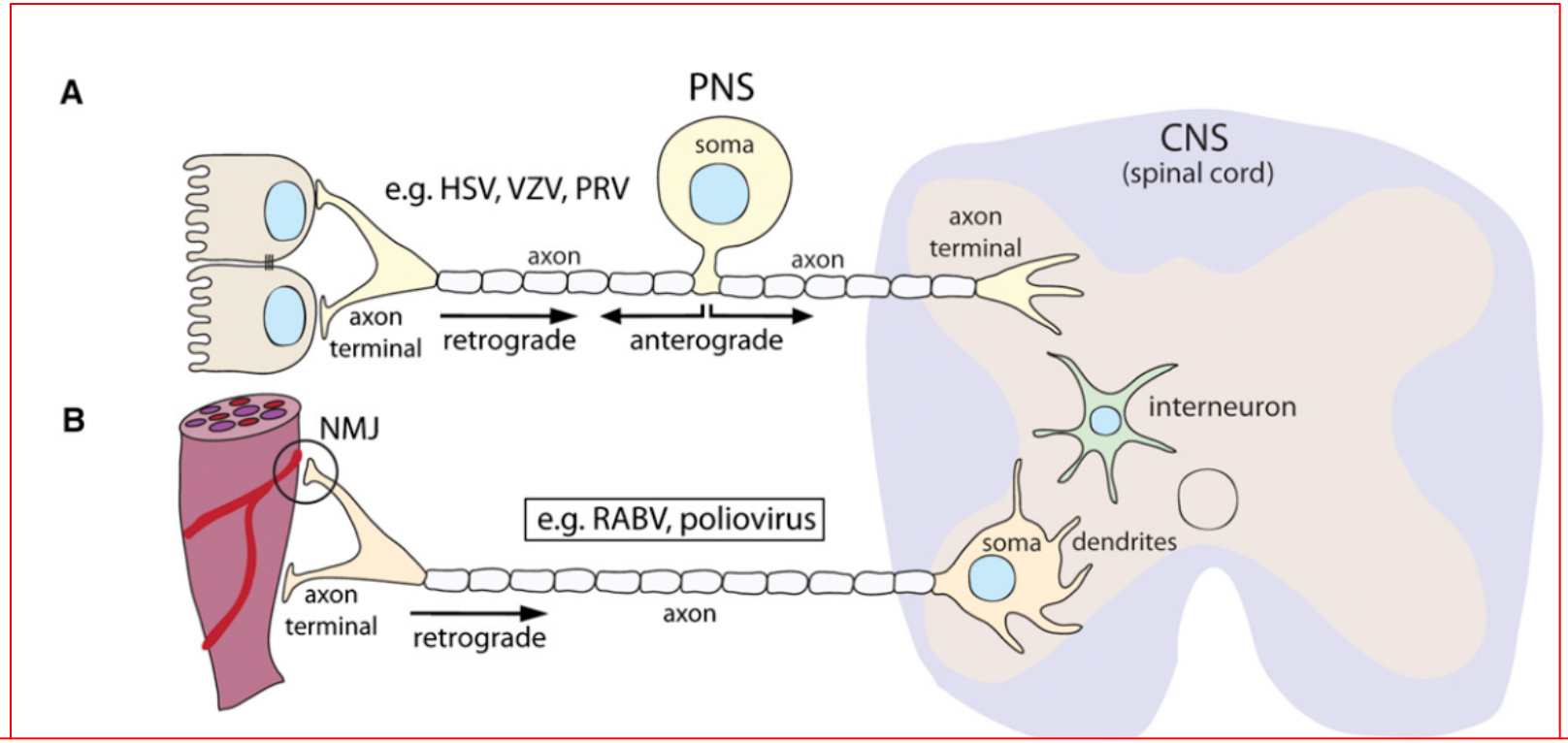


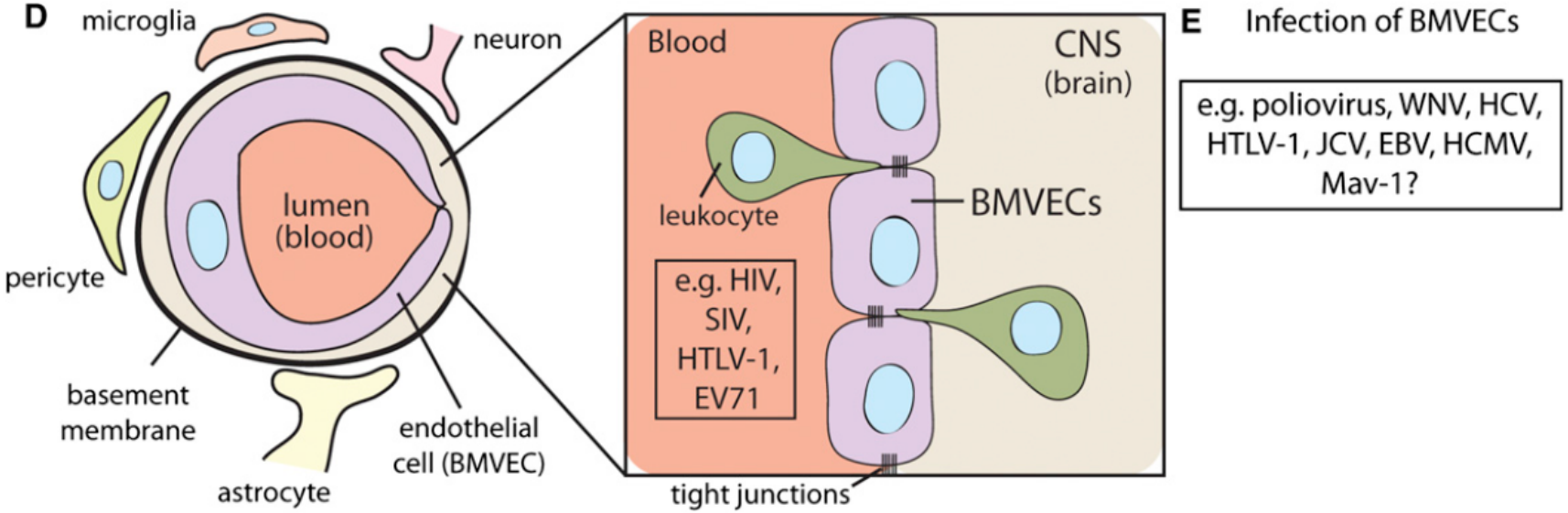
-Viral causes of encephalitis are more common than bacterial causes

Viral spread to the CNS

- 1.Invasion of **Sensory and motor Nerve Endings.**
- 2.Infection of **Brain Microvascular Endothelium**
- 3.Invasion by Infected **Circulating Leukocytes**

Proceed to next slide





- 1.Invasion of **Sensory and motor Nerve Endings**.

As in the case in herpes, it invades the epithelium then run through the axons of the peripheral nerves to settle in the cell body of the neurons ,but in this case (encephalitis) they reactivate and move to the CNS tissue to induce inflammation.

- 2.Infection of **Brain Microvascular Endothelium.**

So the viruses might invade the endothelium of the micro vessels of the brain then move to reach the adjacent brain parenchyma directly.

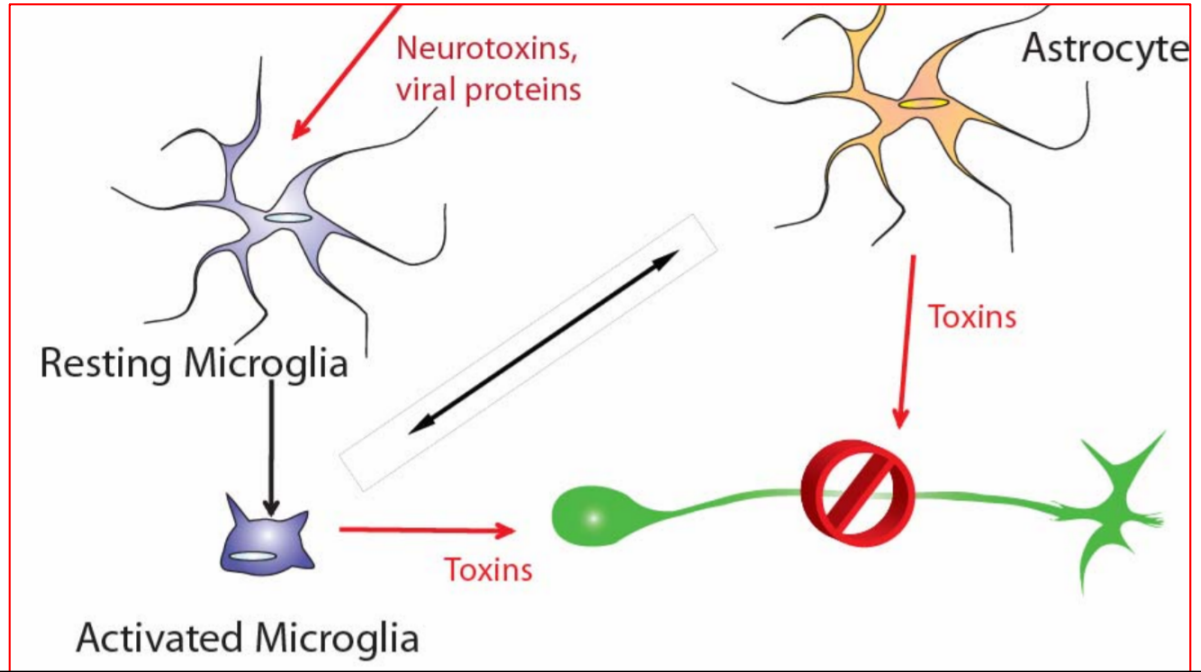
- 3.Invasion by Infected **Circulating Leukocytes**

As the name indicates, viruses infect the leukocytes in the blood then they move along with them to the CNS

Virus Induced Immune-Mediated CNS Pathogenesis

Synchronous Neutrophil Extravasation During VSV Encephalitis

Microglia Activated by a CNS Viral Infection



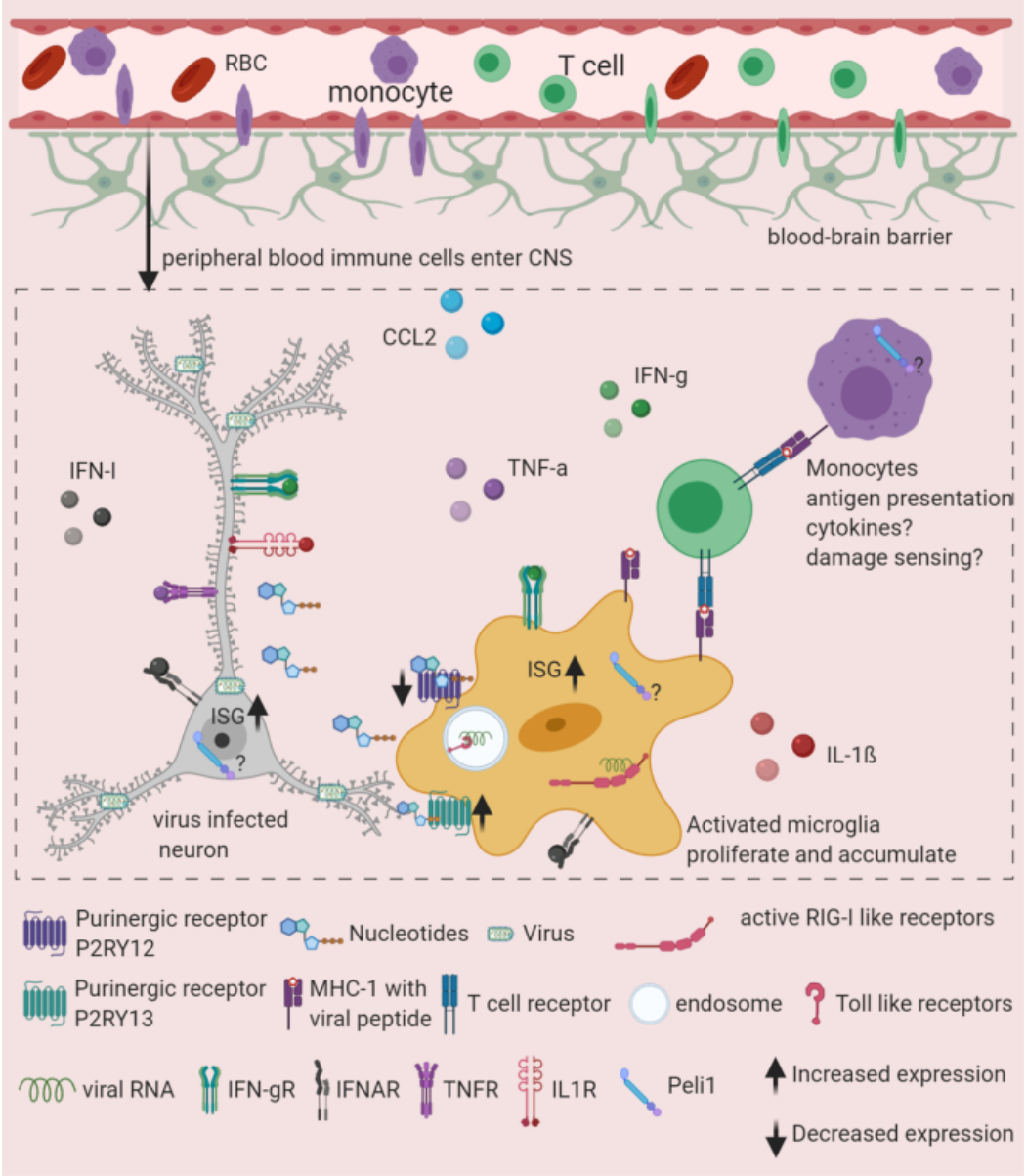
Virus Induced Immune-Mediated CNS Pathogenesis

- 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 (Redundant in this context means “replaceable ” so nonredundant here means that there is are other APCs in CNS) 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.

Pathogenesis in general isn’t well understood



The roles of microglia in viral encephalitis: from sensome 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), The patient with encephalitis commonly has;

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

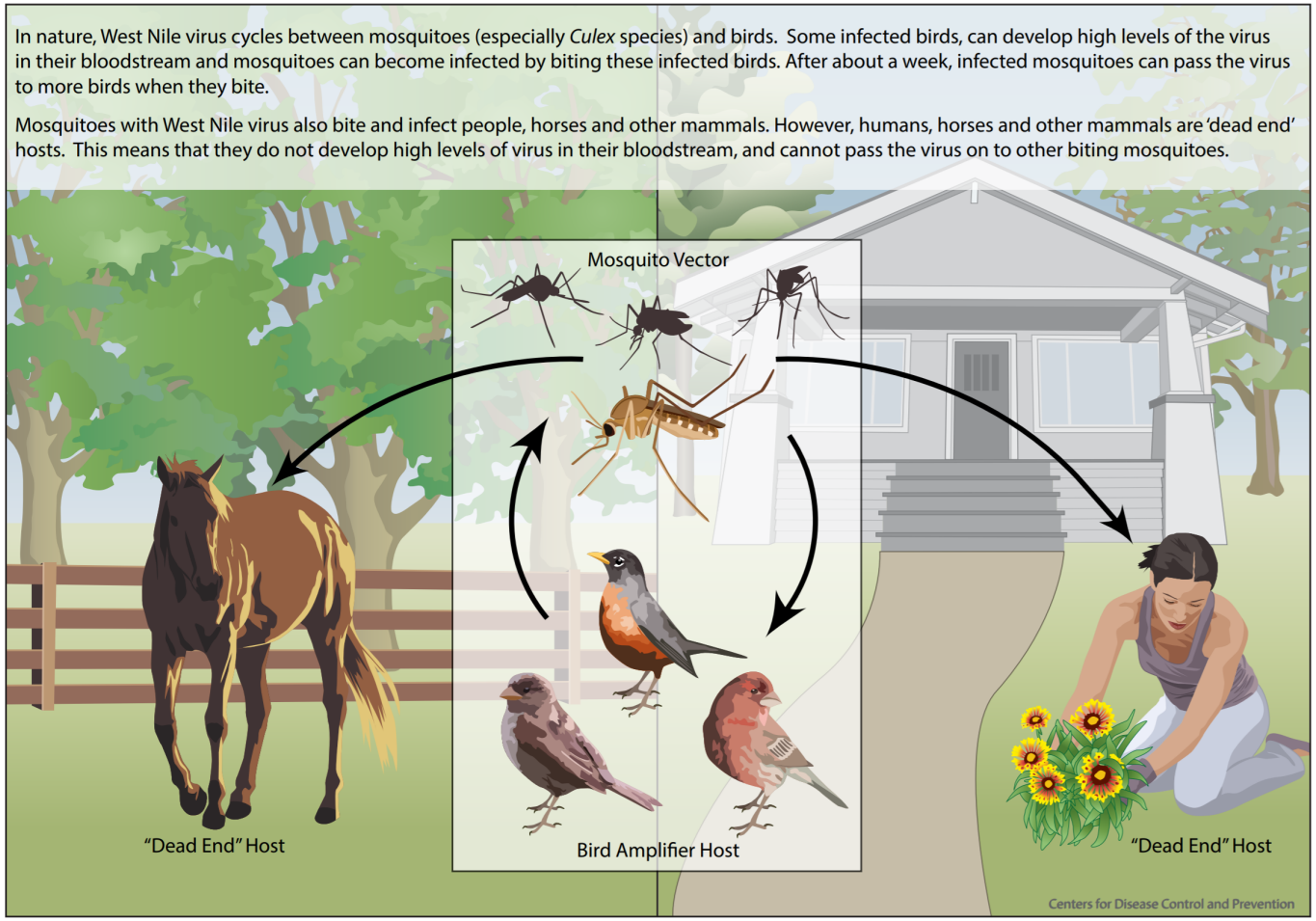
Neurotropic viruses typically cause pathologic injury in distinct regions of the CNS. But cannot be distinguished only by clinical examination. (There are no specific symptoms to distinguish encephalitis from the other infections of CNS(e.g meningitis), So your first management would be is to take CSF sample along with empirical antibiotics therapy)

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 majority of outbreaks.



The majority of cases of acute encephalitis of suspected viral etiology **remain of unknown cause**.

Mostly diagnosis is accomplished by clinical manifestations (fever, headache, depressed consciousness...) and the patient then recovers completely without us knowing their exact pathogen involved, there are no positive pcr for the commonly known viruses.

But for confirmed cases, as reports show:

-If it was a sporadic case>> Herpes

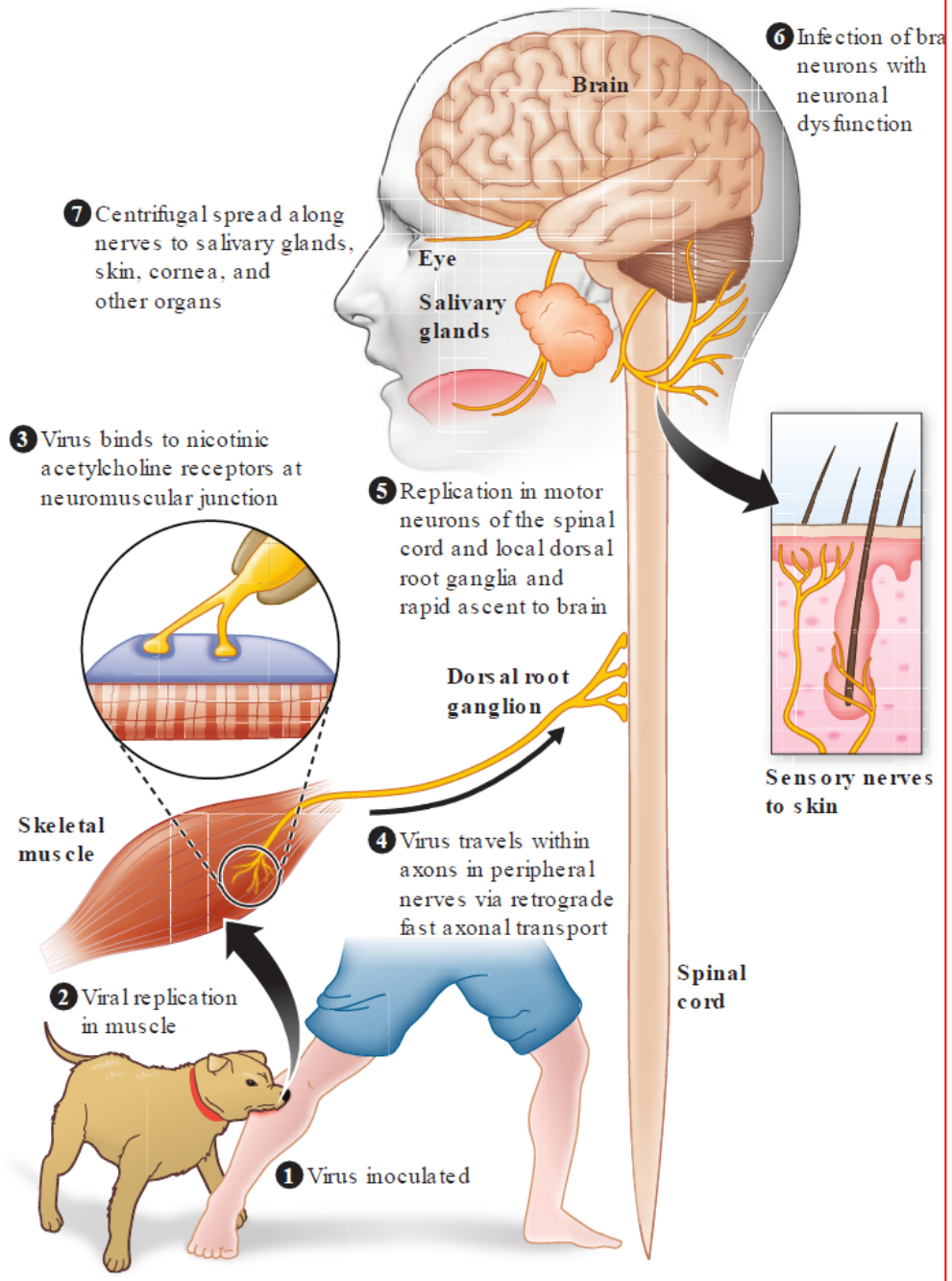
-If it was an epidemic case>> Arbovirus/ mostly West Nile Virus (WNV)

P.s:WNV cannot be transmitted between humans it is only transmitted by arthropods between animals to humans .. humans are a dead end host

Rabies virus as a cause of encepahlitis

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

- Incubation period ranges from days to less than a year.
- In addition to encephalitis symptoms, in encephalitic (furious) rabies, episodes of hyperexcitability 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.



How do you get infected with rabies (briefly)?

- You get bitten by an animal that carries the disease (dogs, squirrels ,etc..).
- The virus enters the muscles and rest in it, then move to the neuromuscular junction to move in the neurons to the CNS
- Infection of CNS neurons accompanied with neuronal malfunction.

-Might be transmitted from CNS to salivary glands or lacrimal gland, so it could be isolated from saliva or tears.

On the basis of exposure and local epidemiologic information, the physician must decide whether initiation of **post exposure prophylaxis** is warranted

Prophylaxis involves **wound care**, and passive immunization with rabies immune globulin.
(When the patient first get bitten you take care of the wound to sanitize it from any pathogen might be involved (i,e rabies) and stop any blood loss.
If rabies was suspected after the bite you might give IV Immunoglobulins against rabies to terminate its invasion)

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.

Negri bodies are Classic histopatholagic phenomena that occurs after infection with rabies (postpartum brain characteristic)

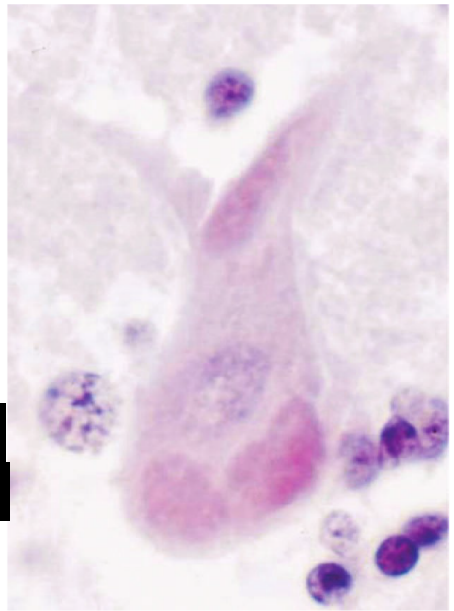


FIGURE 105-3
Three large Negri bodies in the cytoplasm of a cerebellar Purkinje cell from an 8-year-old boy who died of rabies after being bitten by a rabid dog in Mexico. (From AC Jackson, E Lopez-Corella: N Engl J Med 335:568, 1996. © Massachusetts Medical Society.)

Rabies 3/3

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Please play the video to see the hydrophobia sign (https://m.youtube.com/watch?v=9A8-CkrvZlQ&feature=youtu.be)

Hydrophobia is a common late-stage sign of rabies

How to diagnose a suspected encephalitis patient ?

- **Lumber puncture**: CSF profile is in indistinguishable from that of viral meningitis and 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**: Anti WNV IgM antibodies in the CSF are diagnostic for WNV encephalitis. (As an epidemic disease)

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

- **Brain biopsy [which is done postpartum]**

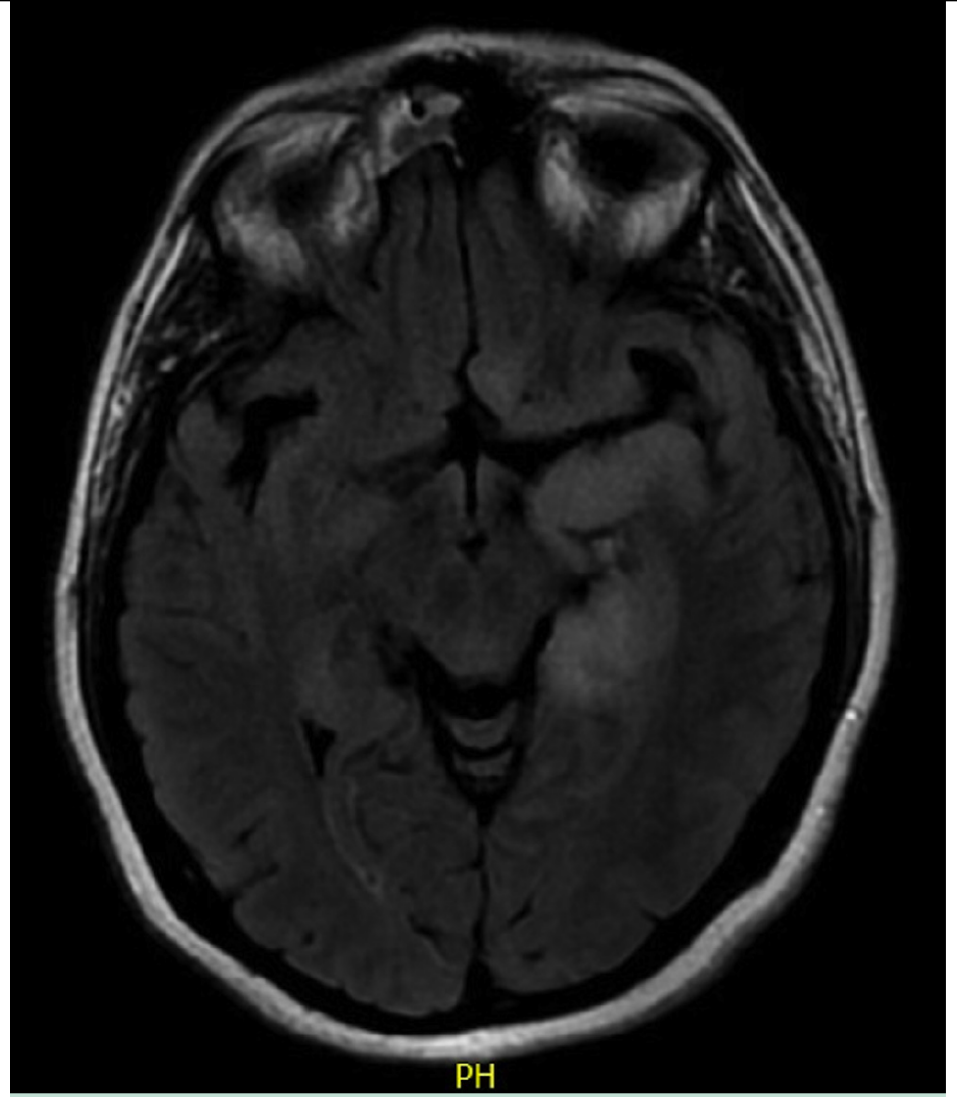


Figure 1 Herpes simplex virus (HSV) encephalitis. Brain magnetic resonance image of a patient who presented with memory impairment, headaches, and fevers. Axial T2 fluid-attenuated inversion recovery (FLAIR) imaging shows left hemispheric hyperintensity in the anterior and medial temporal lobe and mass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

Managment and sequelae of encephalitits

- 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) an should be **started empirically** in patients with suspected viral encephalitis, while awaiting viral diagnostic studies.

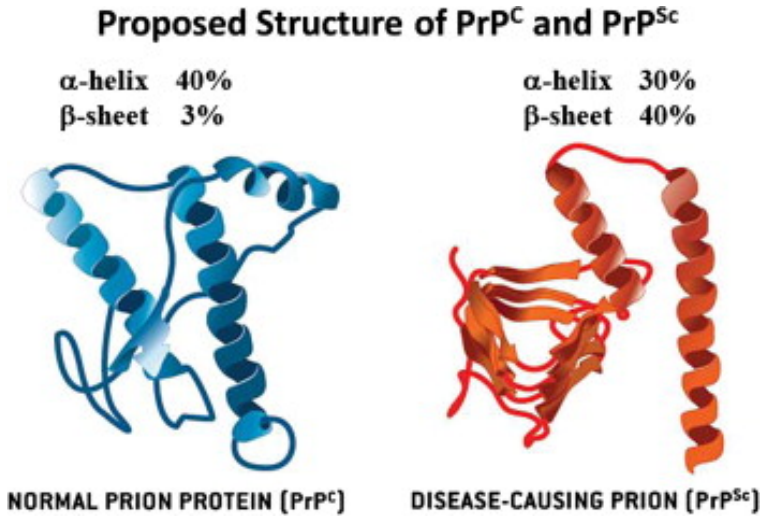
- There is considerable variation in the incidence and severity of sequelae in patients surviving viral encephalitis. Many patients with WNV infection have **sequelae**, including **cognitive impairment**; **weakness**; and hyper- or hypokinetic **movement disorders**, including tremor, myoclonus, and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

Keep in mind that encephalitis is a rare disease and even rarer than meningitis

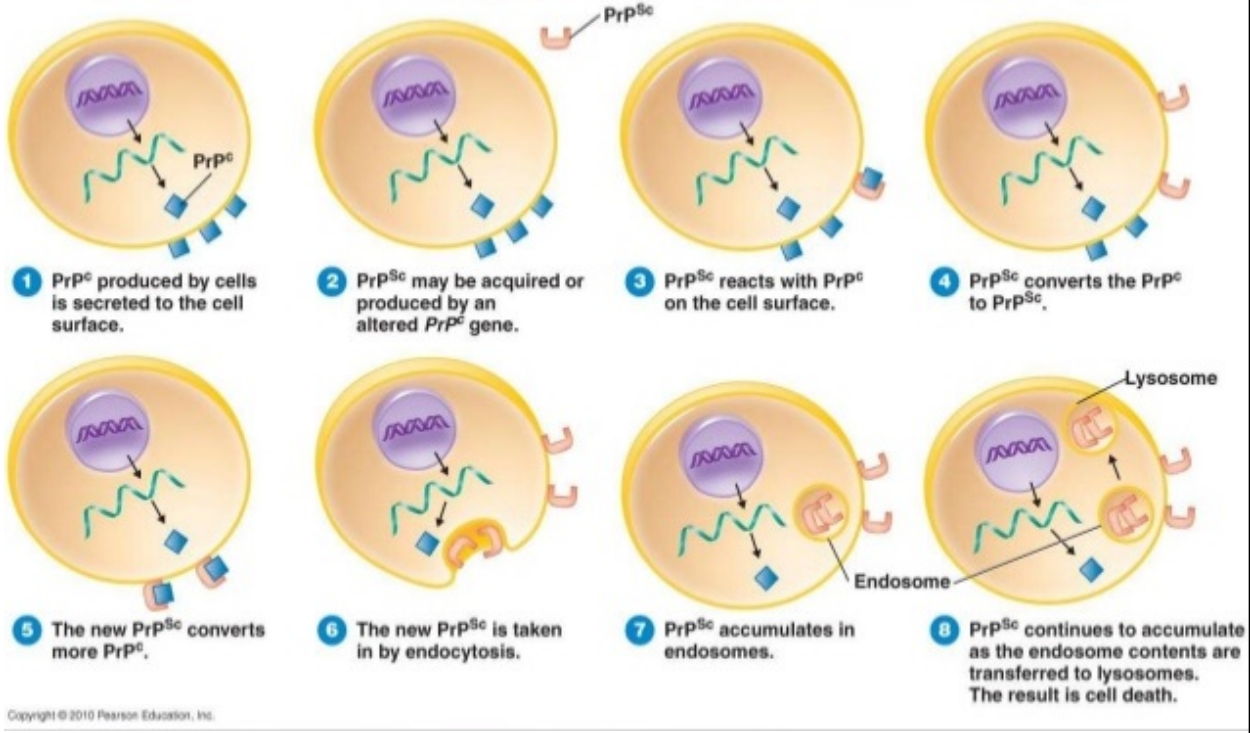
Prions

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.

Brain normally produce "normal" protiens but in some pathologic situations it becomes abnormal prions and causes damage to neurons, and these abnormal prions when the may meet the normal ones they make them also abnormal.



Prions composed of the prion protein (PrP) are hypothesized as the cause of **transmissible spongiform encephalopathies (TSEs).**
(Spongiform:Destruction of brain tissue so it becomes like a sponge)



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 characterised by a degeneration of cerebral cortex & cerebellum tissue giving it a sponge-like appearance.

- **TSEs** in humans include:
  1- **Creutzfeldt–Jakob disease (the most common) (4 forms):**
  the sporadic (sCJD) - the hereditary/familiar (fCJD)
  - the iatrogenic (iCJD) - the variant form (vCJD).
  2- **Kuru.**

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


Kuru


Scrapie

- **TSEs** in **animals** include:
  1- **Scrapie** in **sheep and goats**.

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

Forms of CJD

Sporadic (sCJD) elderly

- 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)

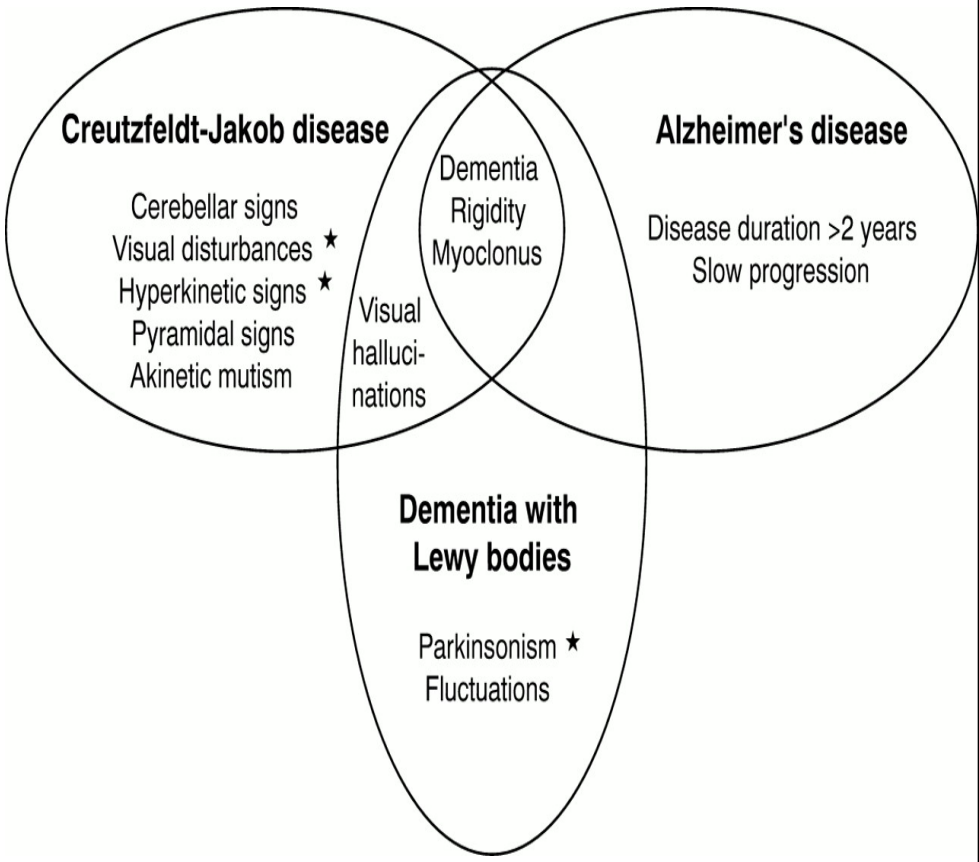
- If the prion protein gene is altered in a person's **sperm or egg cells**, the mutation can be **transmitted** to the person's offspring.
- The particular mutation found in each family affects **how frequently the disease appears** and what **symptoms are most noticeable**.

acquired (iCJD)/(vCJD)

- **Iatrogenic:** Accidental transmission o 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: (especially when cerebellum is involved)
  Ataxia.
  speech impairment.
  changes in gait.



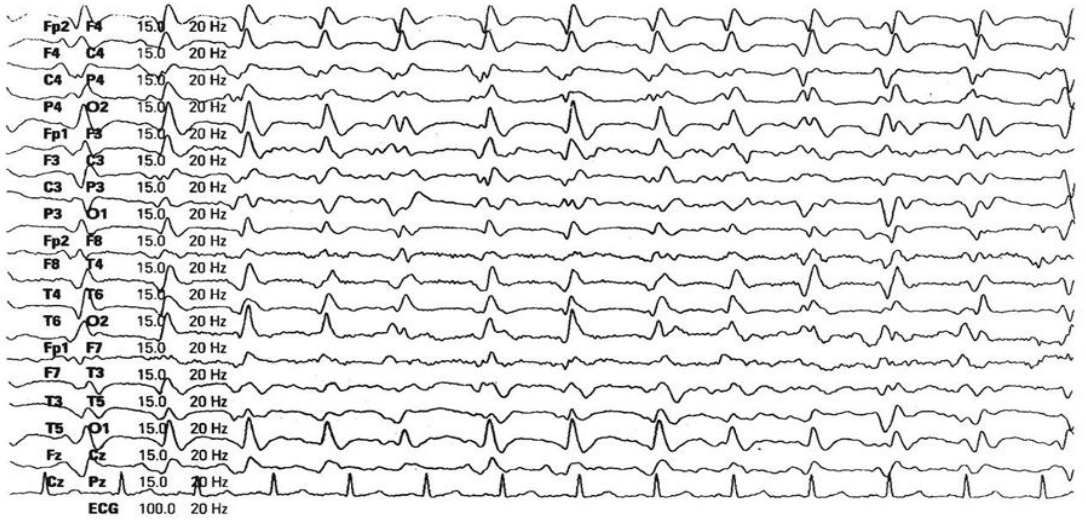
Myoclonus

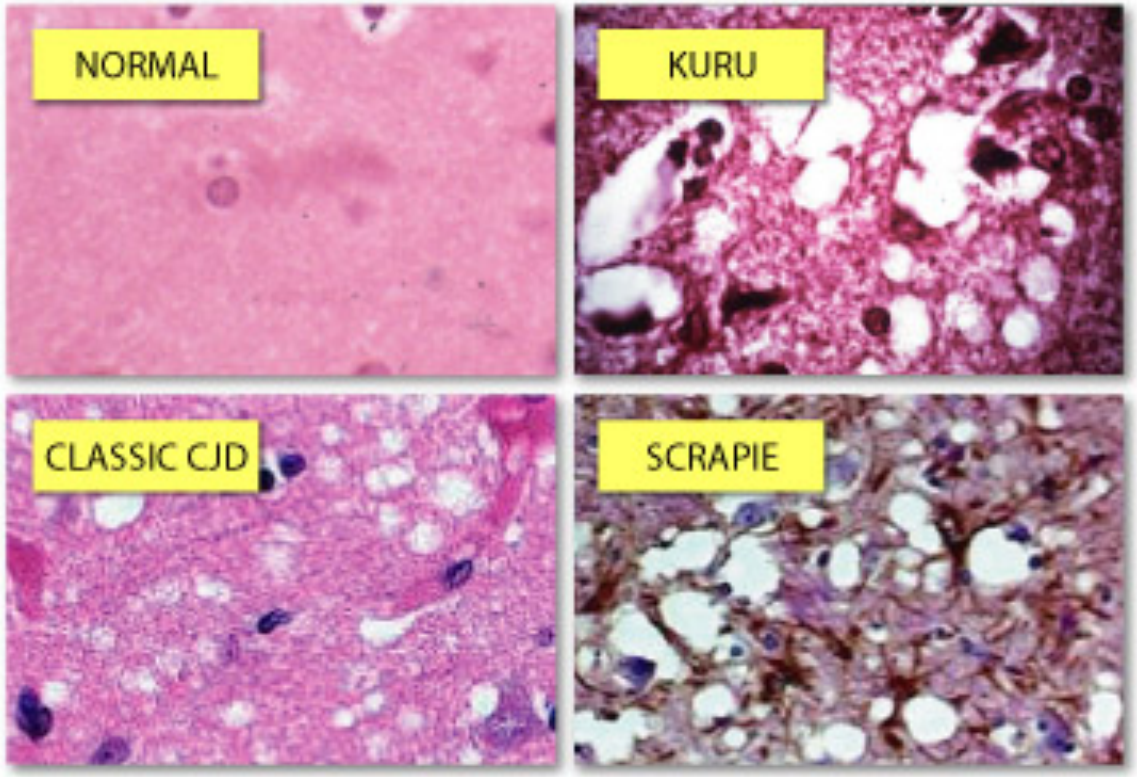
- **Definition :** is a brief, involuntary **twitching** of a muscle or a group of muscles caused by **sudden muscle contractions** (positive myoclonus) OR **brief lapses of contraction** (negative myoclonus).
- Most patients **(90%)** with CJD exhibit **myoclonus** that appears at **various times** throughout the illness.
- Myoclonus **persists** during sleep, **Unlike** other involuntary movements.

How is CJD diagnosed?

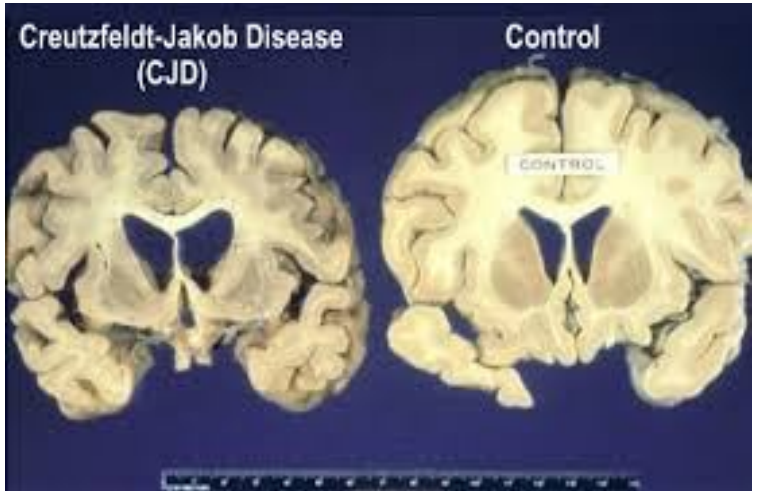
- **Electroencephalography (EEG)** can be particularly valuable because it shows a specific type of abnormality in major but not all types of CJD.
- **Magnetic resonance imaging (MRI)** has recently been found to be accurate in about 90 percent of cases.

- (Important)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**.

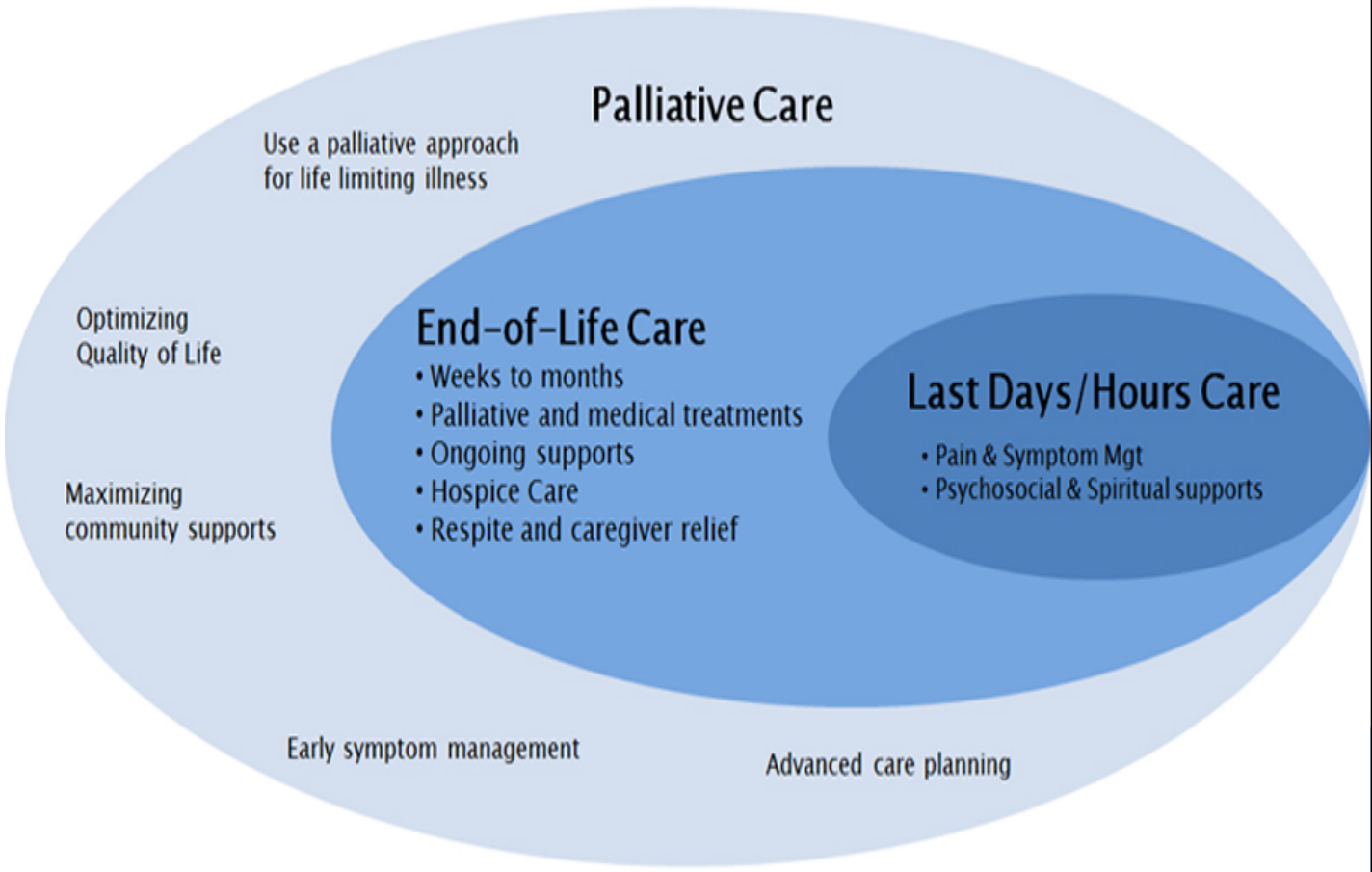




Treatment of CJD



- 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).**
  (relieving symptoms without dealing with the cause of the condition.because it got no cure)
- **Opiate drugs** can help relieve **pain** if it occurs, and the drugs **clonazepam** and **sodium valproate** may help relieve **myoclonus**.



The spinal cord can be involved in infections as well (infectious myelopathies)

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

Clinical manifestations depend on the exact level and **location within the cord**. The **herpesviruses and enteroviruses** are ubiquitous, accounting for a substantial number of viral myelitis cases.

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.

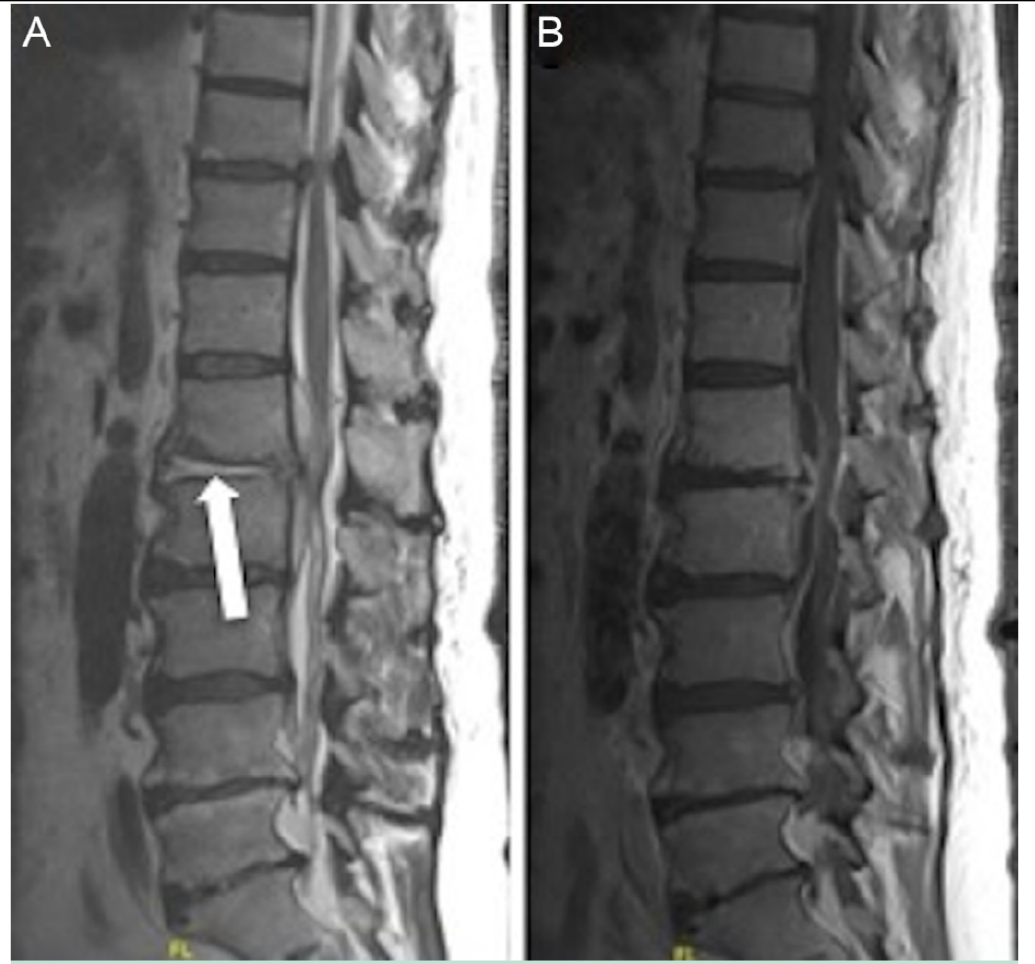


Figure 2 Discitis with associated ventral epidural abscess. Lumbosacral magnetic resonance image of a patient with diabetes mellitus who presented with acute on chronic low back pain, fevers, and weight loss. Sagittal T2 fluid-attenuated inversion recovery (FLAIR) imaging (**A**) and T1 postcontrast 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*.

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