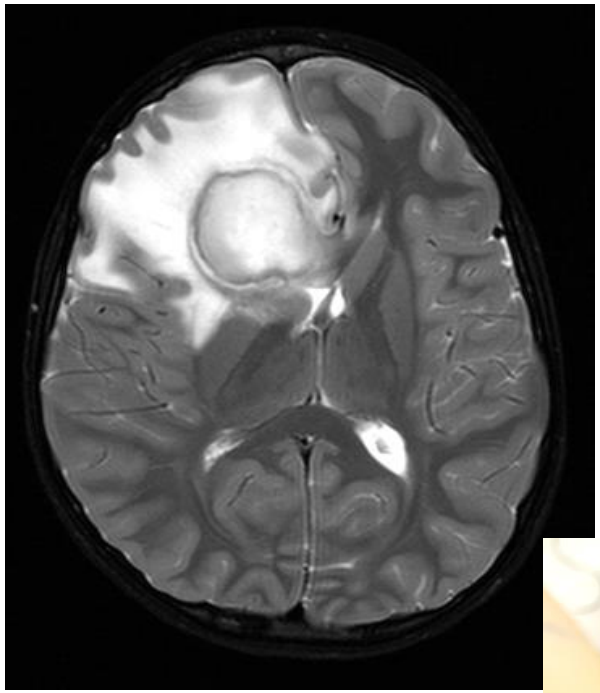
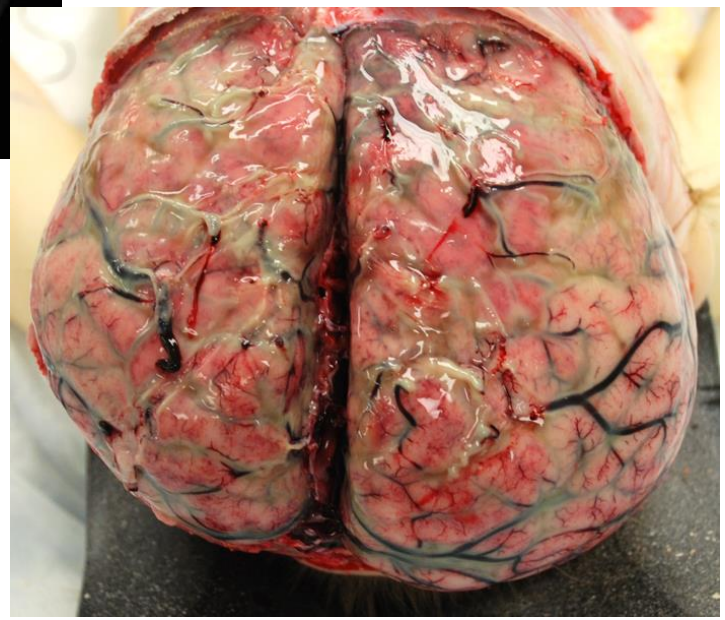
Microbiology of the central nervous system





Done by :Aya batayneh

Anas Abu-Humaidan
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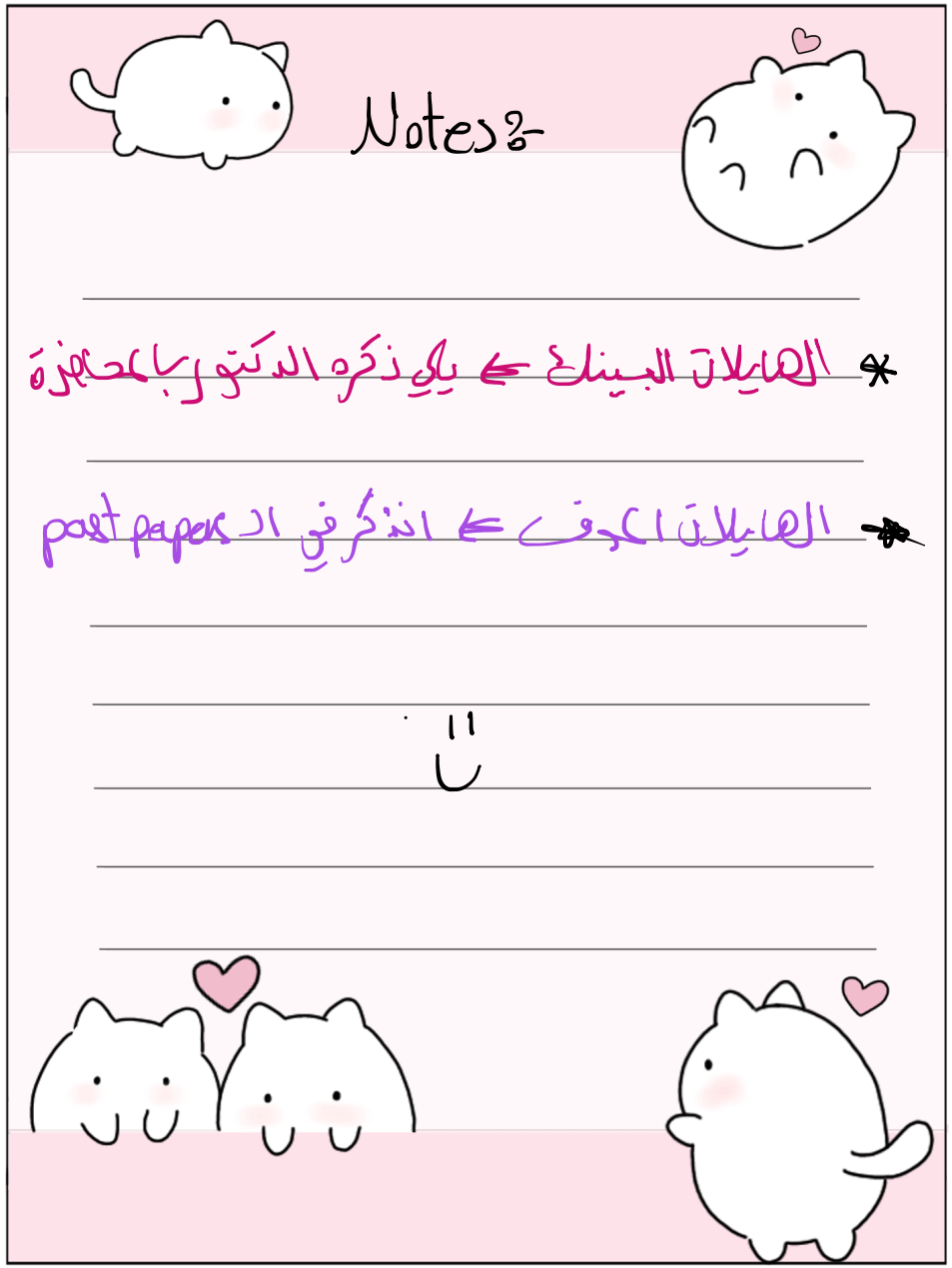
Lecture 5

Overview

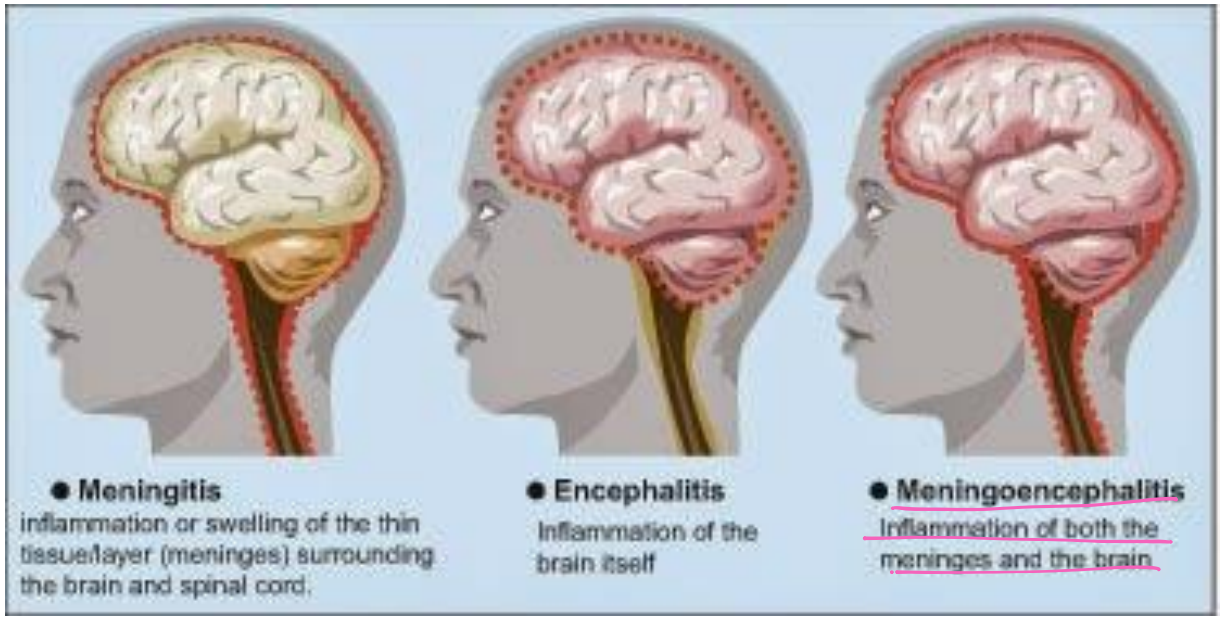
In this lecture we will discuss the following :

- Encephalitis
- Transmissible spongiform encephalopathies



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.



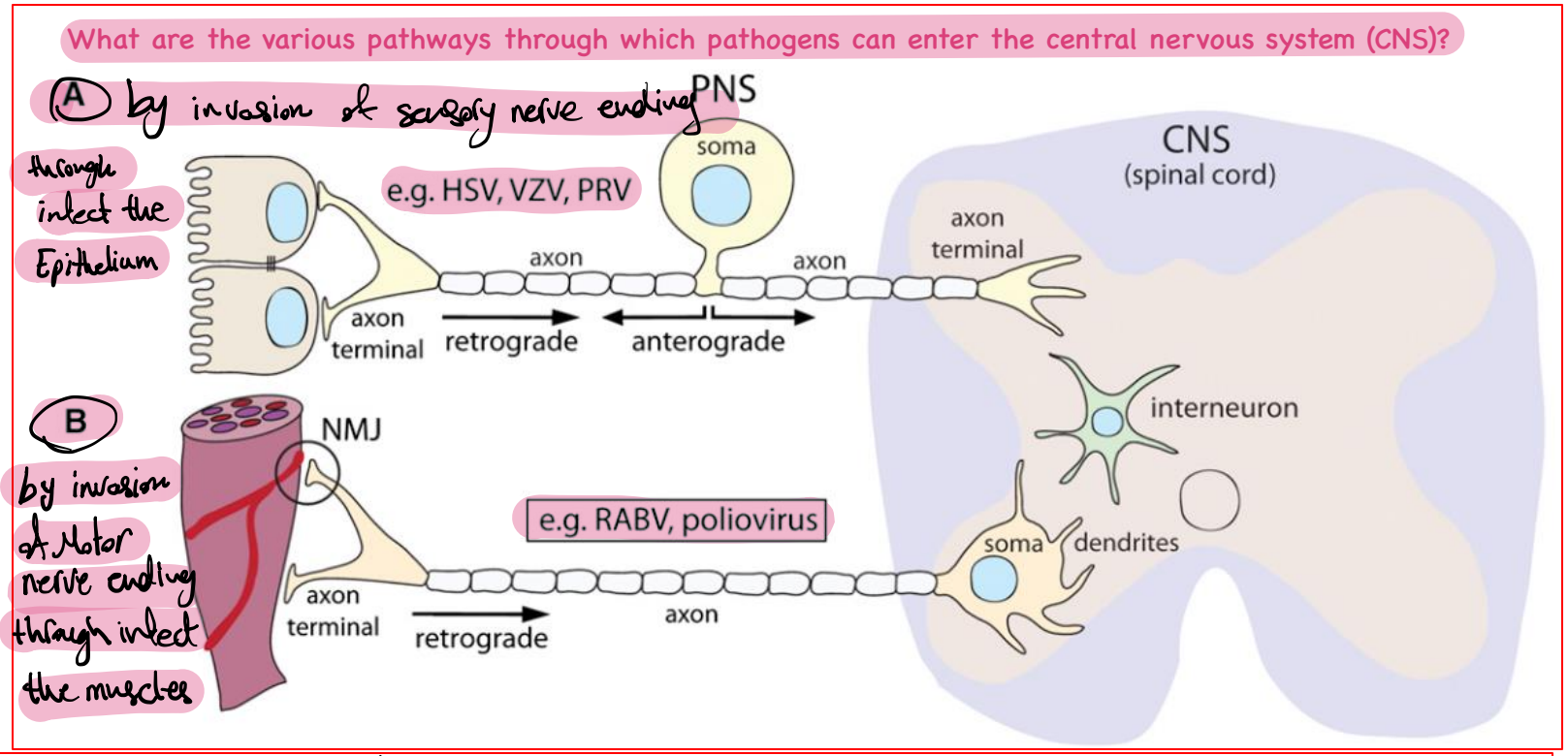
* viruses are the most causative agents of encephalitis.

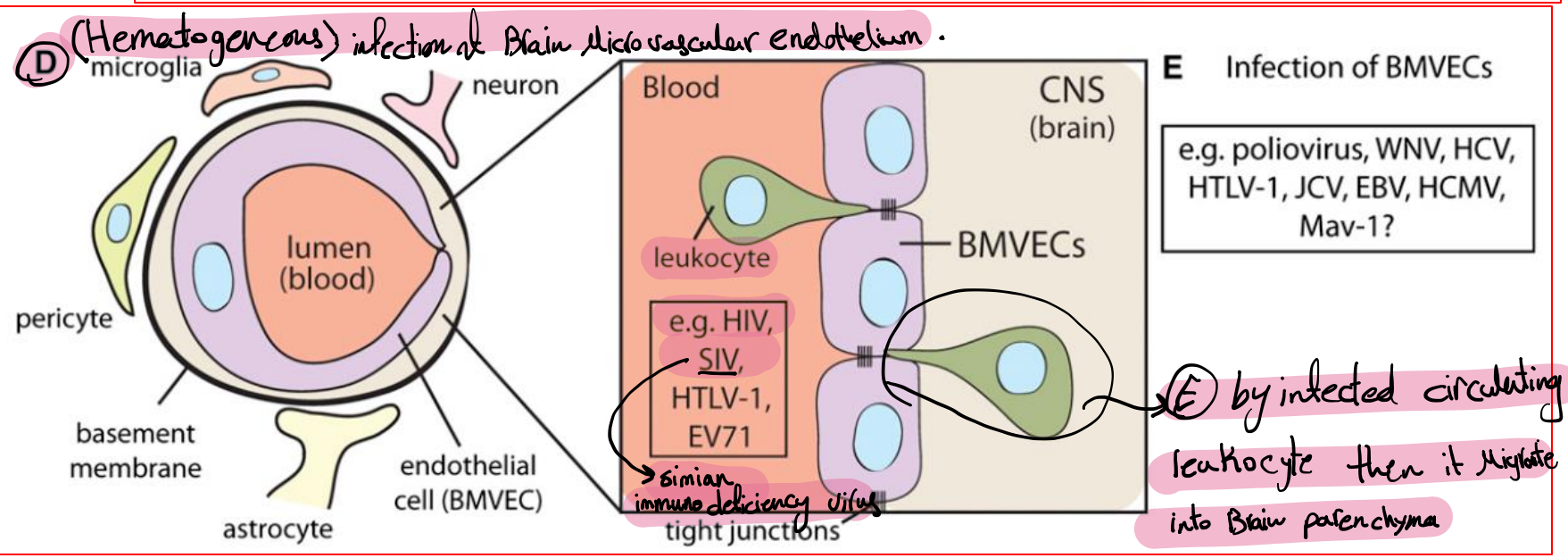
Viral spread to the CNS

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

important note:

Herpes simplex virus (HSV) is indeed one of the most common pathogens that can cause encephalitis. While encephalitis due to HSV infection is relatively rare, it can occur, especially in individuals with weakened immune systems or certain risk factors. However, not all individuals infected

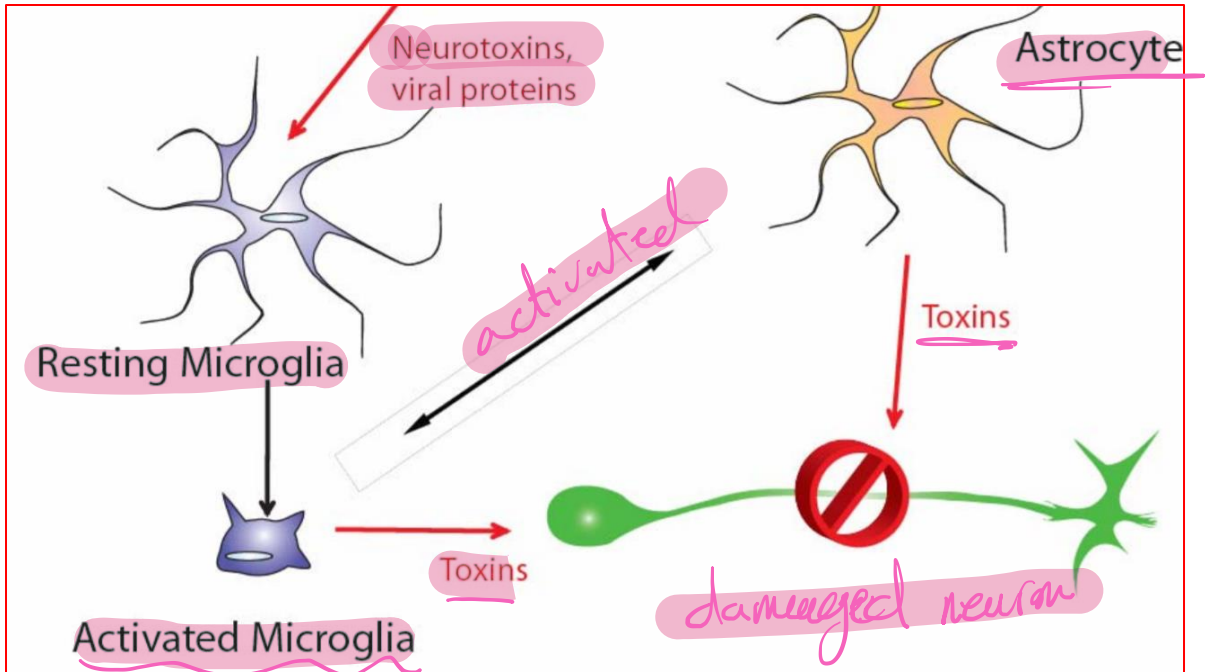




Virus Induced Immune-Mediated CNS Pathogenesis

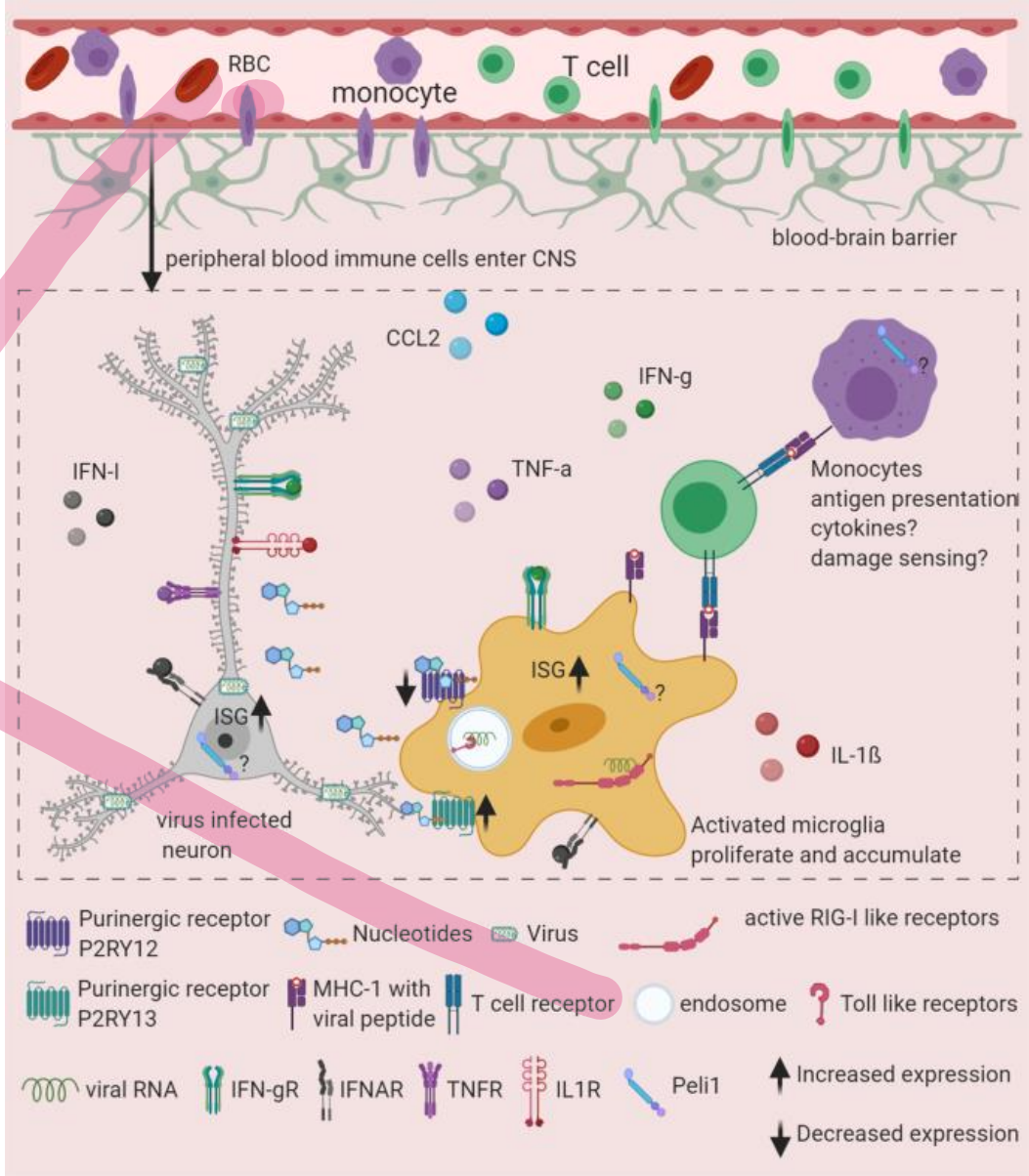
Synchronous Neutrophil Extravasation During VSV Encephalitis

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 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 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.

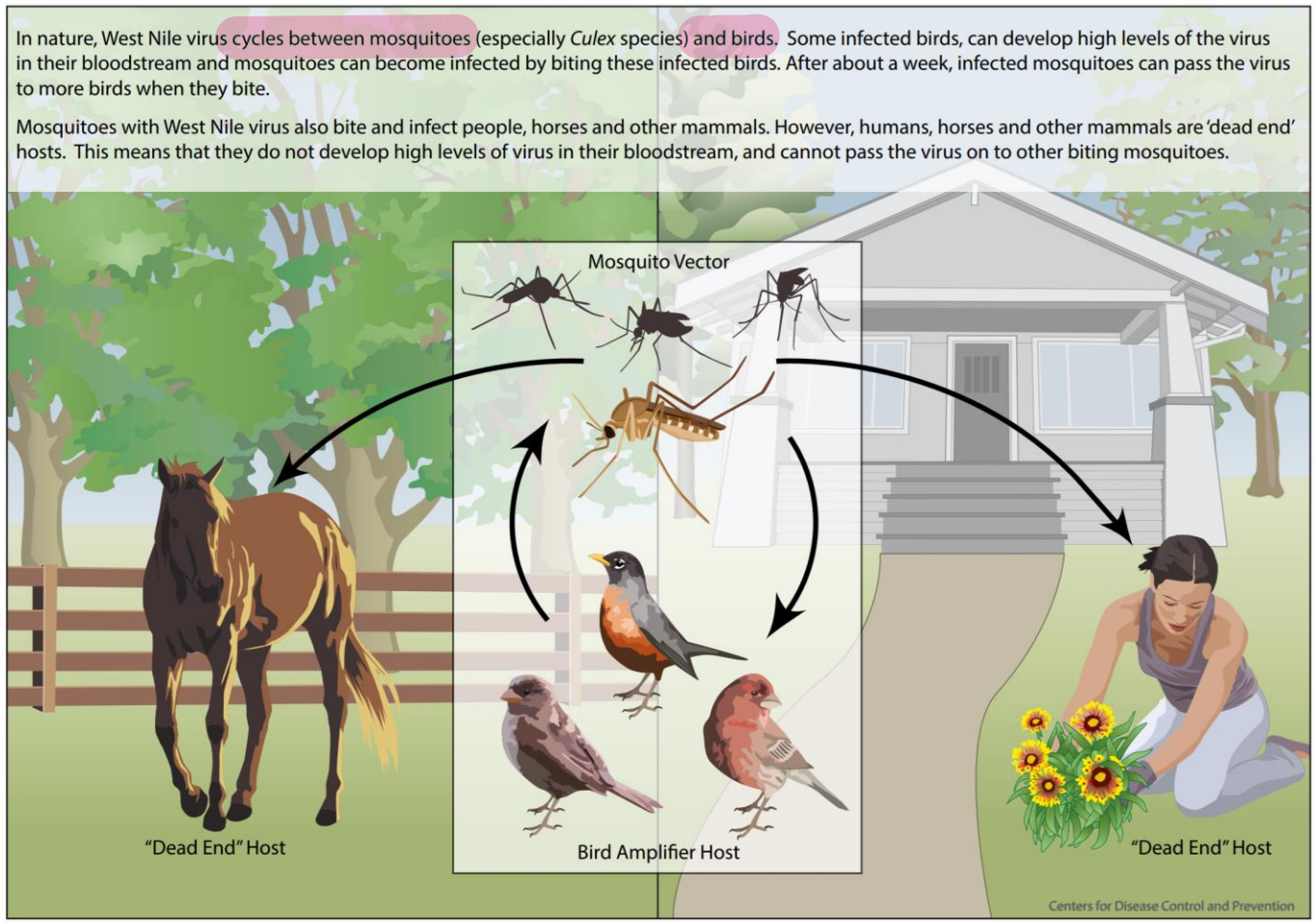
Neurotropic viruses typically cause pathologic injury in distinct regions of the CNS. But cannot be distinguished only by clinical examination.

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.



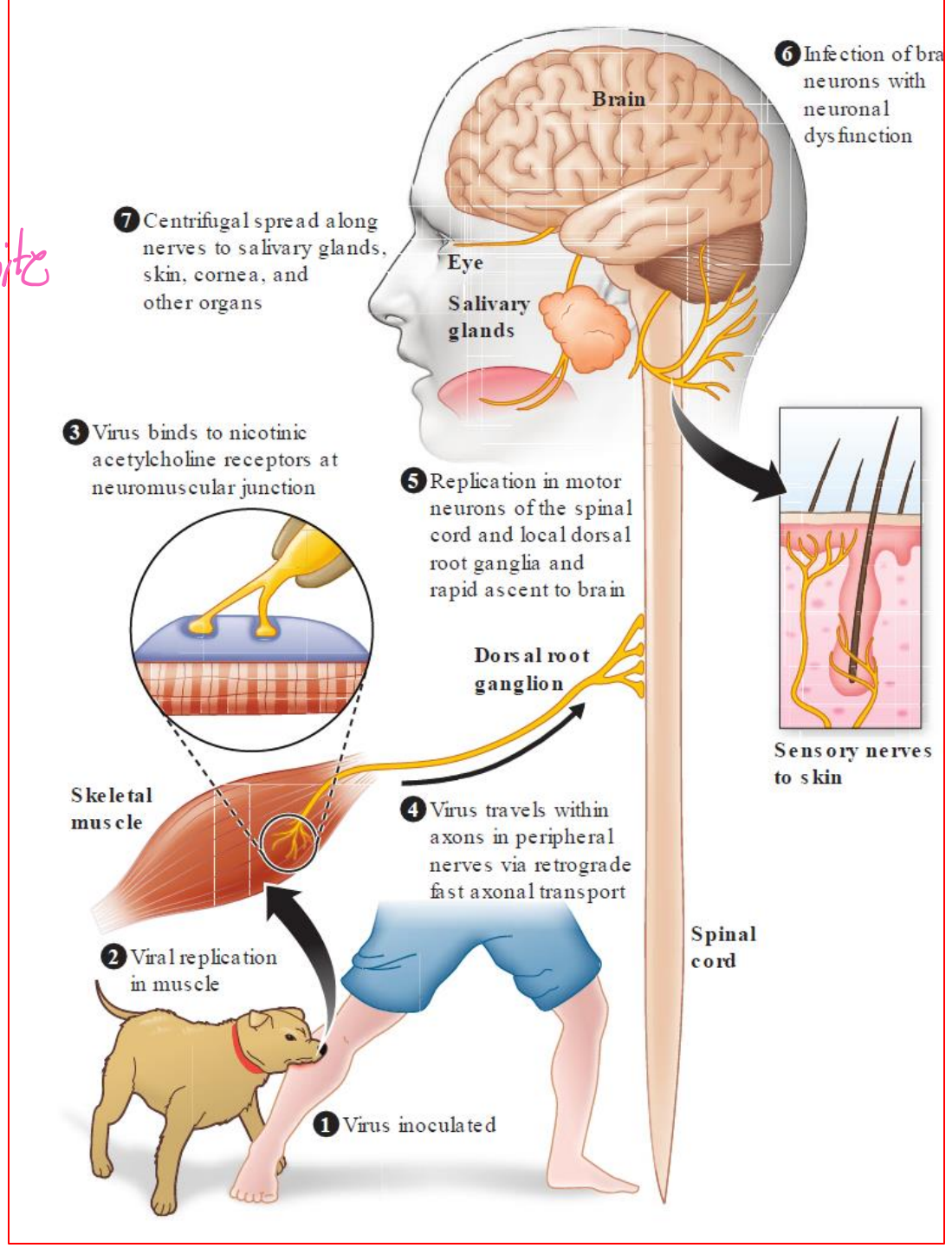
Rabies virus as a cause of encepahlitis

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

- 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 (→ clarity) that become shorter as the disease progresses

- if Brainstem dysfunction (→ too late stage) progresses rapidly, and coma— followed within days by death—is the rule unless the course is prolonged by supportive measures.



Rabies is treated by ??

- 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.

* not treated by supportive care & Antibiotics
↳ bc its virus not a bacteria :-)

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.

histological sign of Rabies

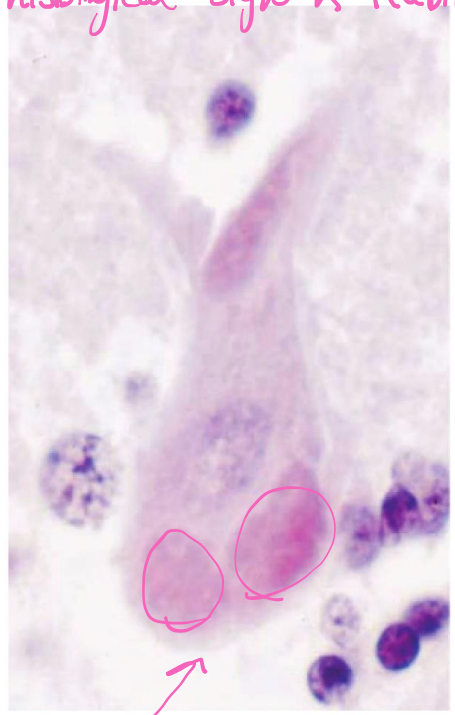


FIGURE 105-3
Three large Negri bodies in the cytoplasm of a cerebellar Purkinje cell from an 8-year-old boy who died of rabies after being bitten by a rabid dog in Mexico. (From AC Jackson, E Lopez-Corella: N Engl J Med 335:568, 1996. © Massachusetts Medical Society.)

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.

- **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 we can't found the causative agent

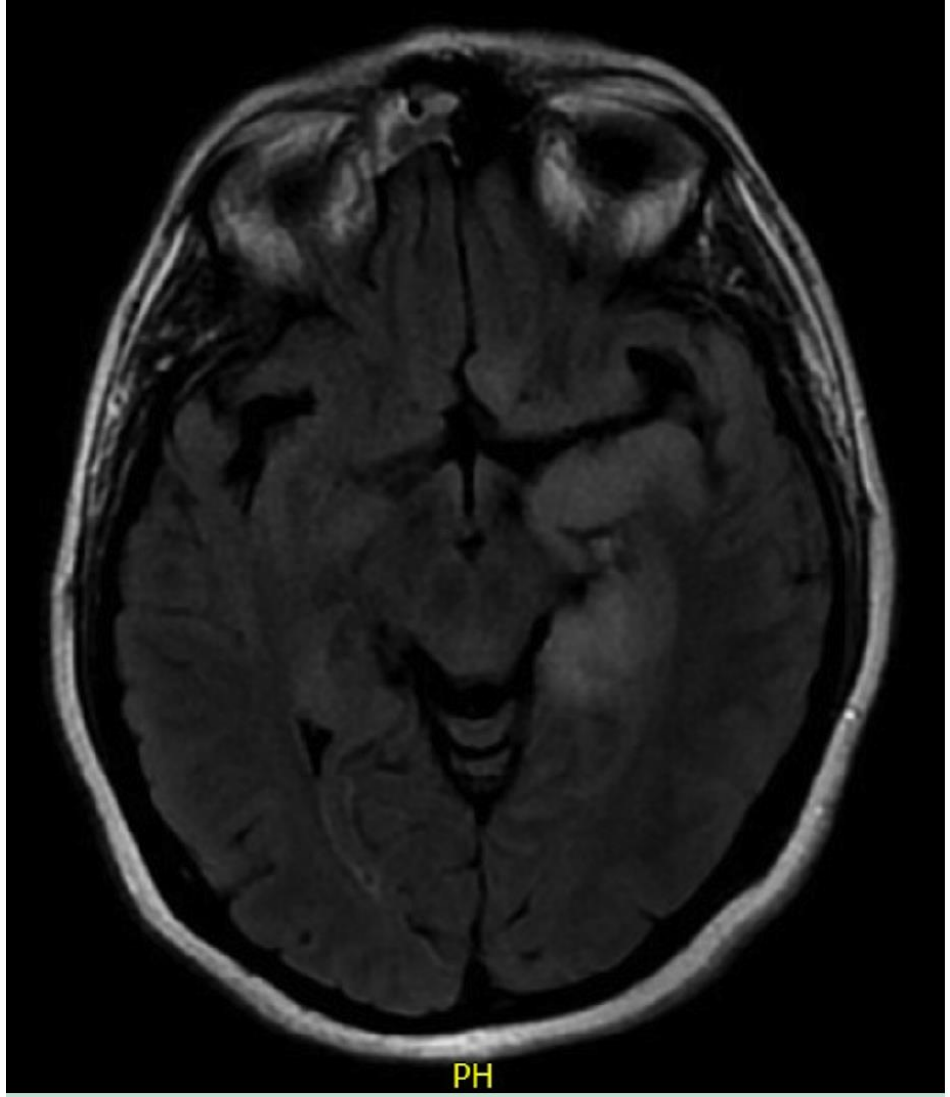


Figure 1 Herpes simplex virus (HSV) encephalitis. Brain magnetic resonance image of a patient who presented with memory impairment, headaches, and fevers. Axial T2 fluid-attenuated inversion recovery (FLAIR) imaging shows left hemispheric hyperintensity in the anterior and medial temporal lobe and mass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

Managment and sequelae of encephalitits

So we can prevented & treatment the encephalitis.

- 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**.

not treated at home

- **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.

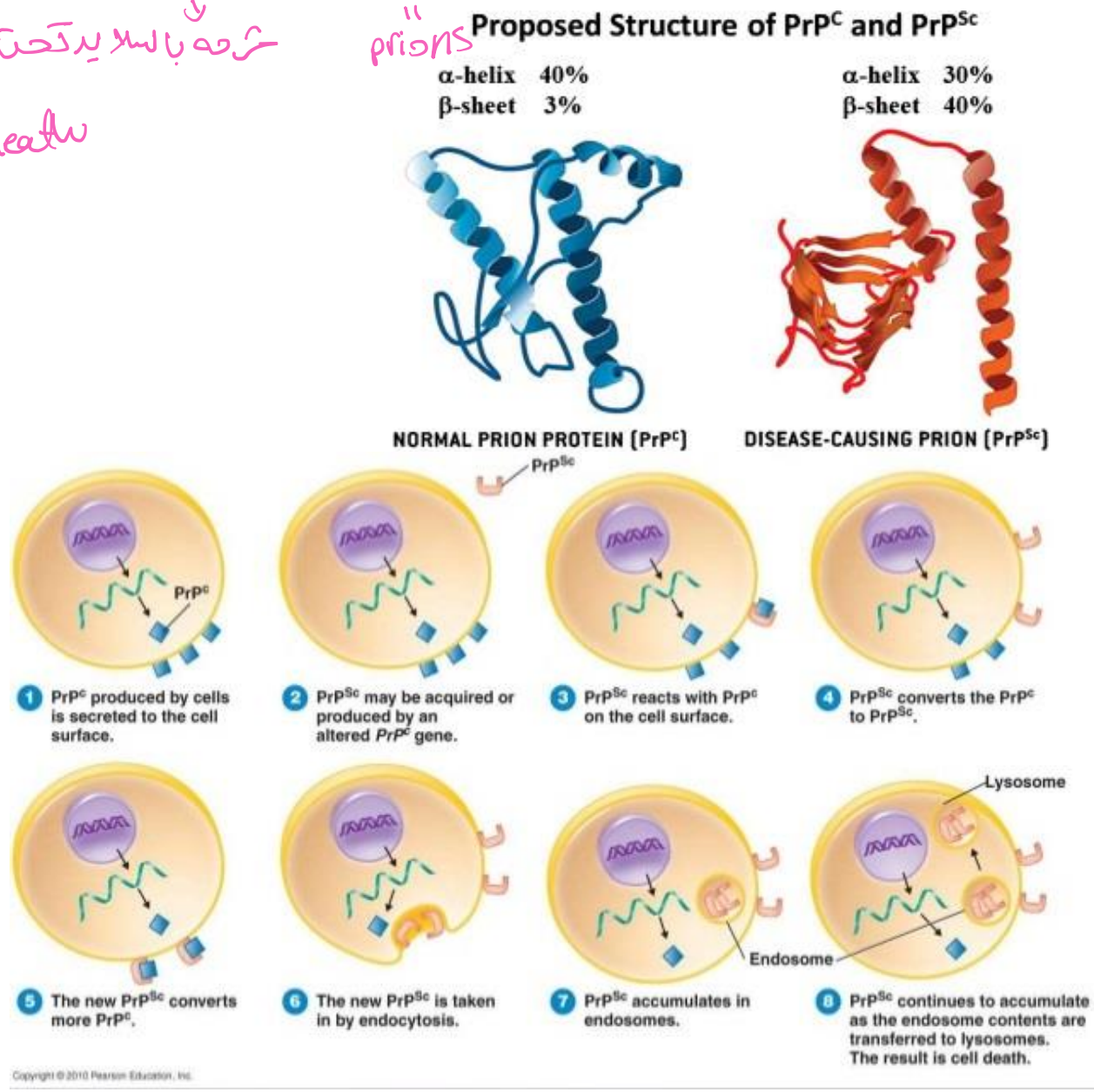
m/c pathogen

- 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.

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.

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



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 (4 forms):**
  the sporadic (sCJD) - the hereditary/familiar (fCJD)
  - the iatrogenic (iCJD) - the variant form (vCJD).
  2- **Kuru.**

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

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

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

Kuru

Scrapie

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)

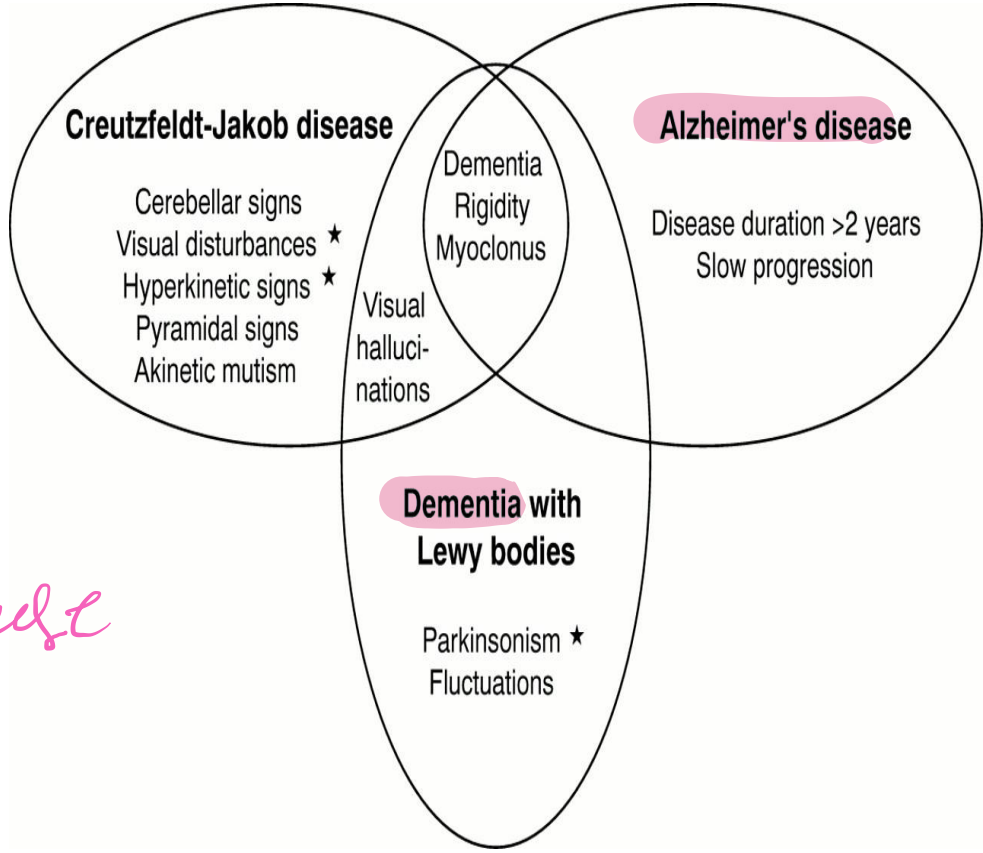
- **Iatrogenic:** Accidental transmission o CJD to humans appears to have occurred with **corneal transplantation, contaminated (EEG) electrode implantation, and surgical procedures**.
- **Variant:** Acquired by **eating meat** from cattle affected by **BSE,"mad cow" disease**.

Signs & Symptoms of CJD

- **Rapidly progressive dementia** (confusion, disorientation, and problems with memory, thinking, planning and judgment).
- **Rigidity**.
- Agitation, apathy and mood swings.
- **Myoclonus**. ⇒ شرحها بالسلايد تحت
- As the condition worsens physical manifestations such as:

Ataxia.
speech impairment.
changes in gait.

} in late stages of disease

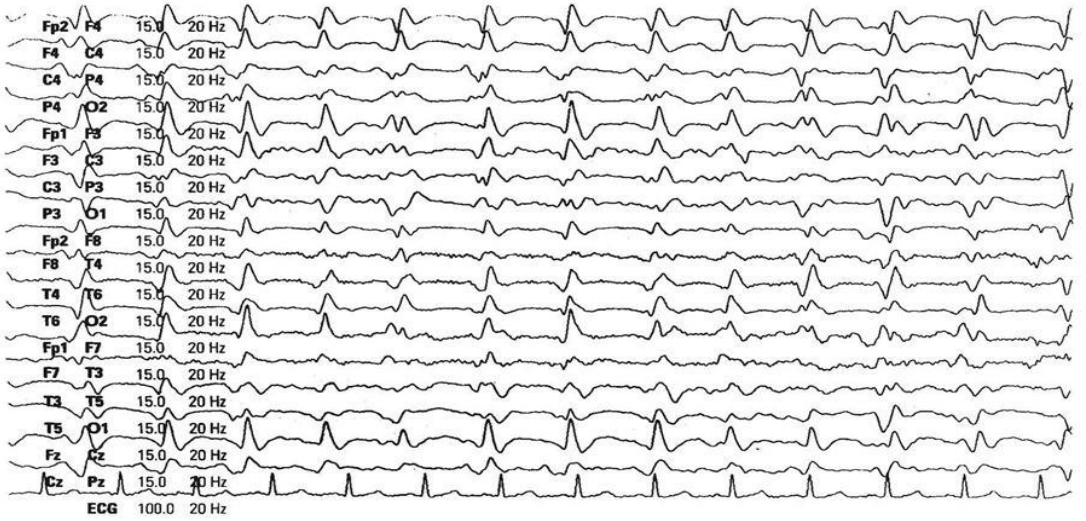


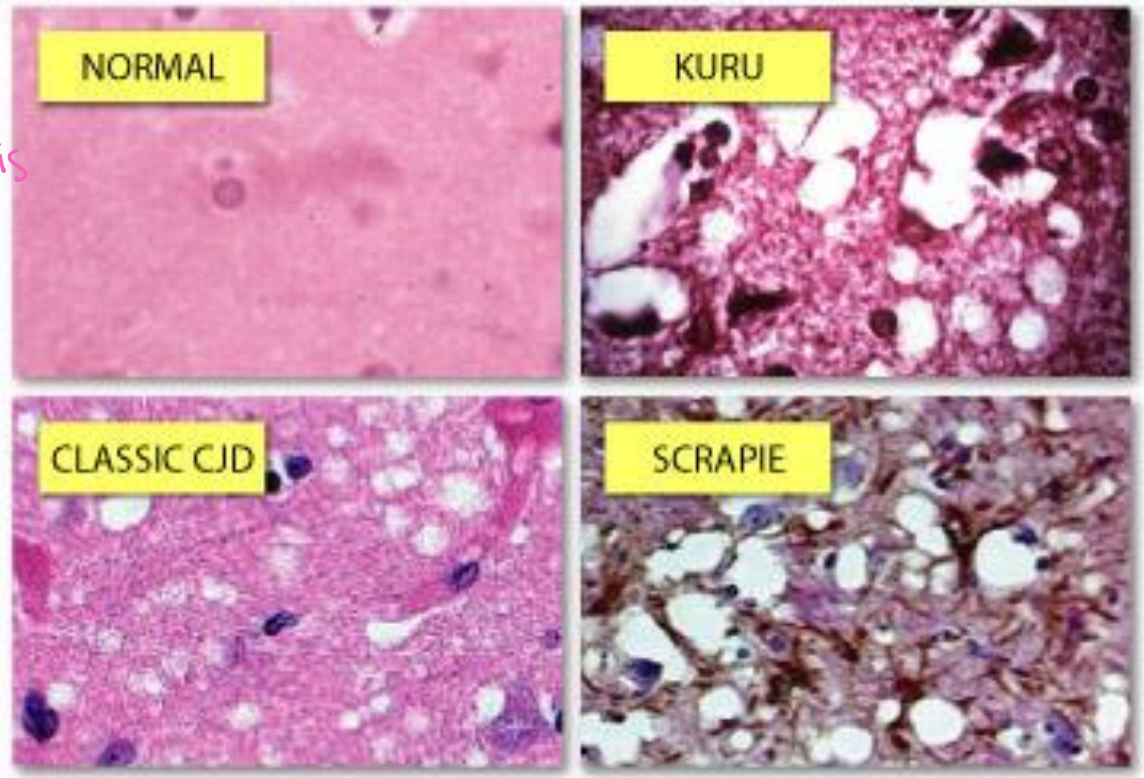
Myoclonus

- **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**.

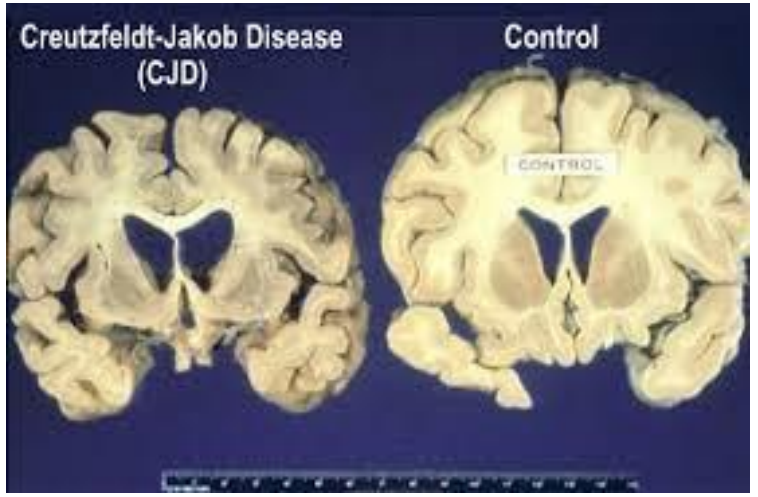


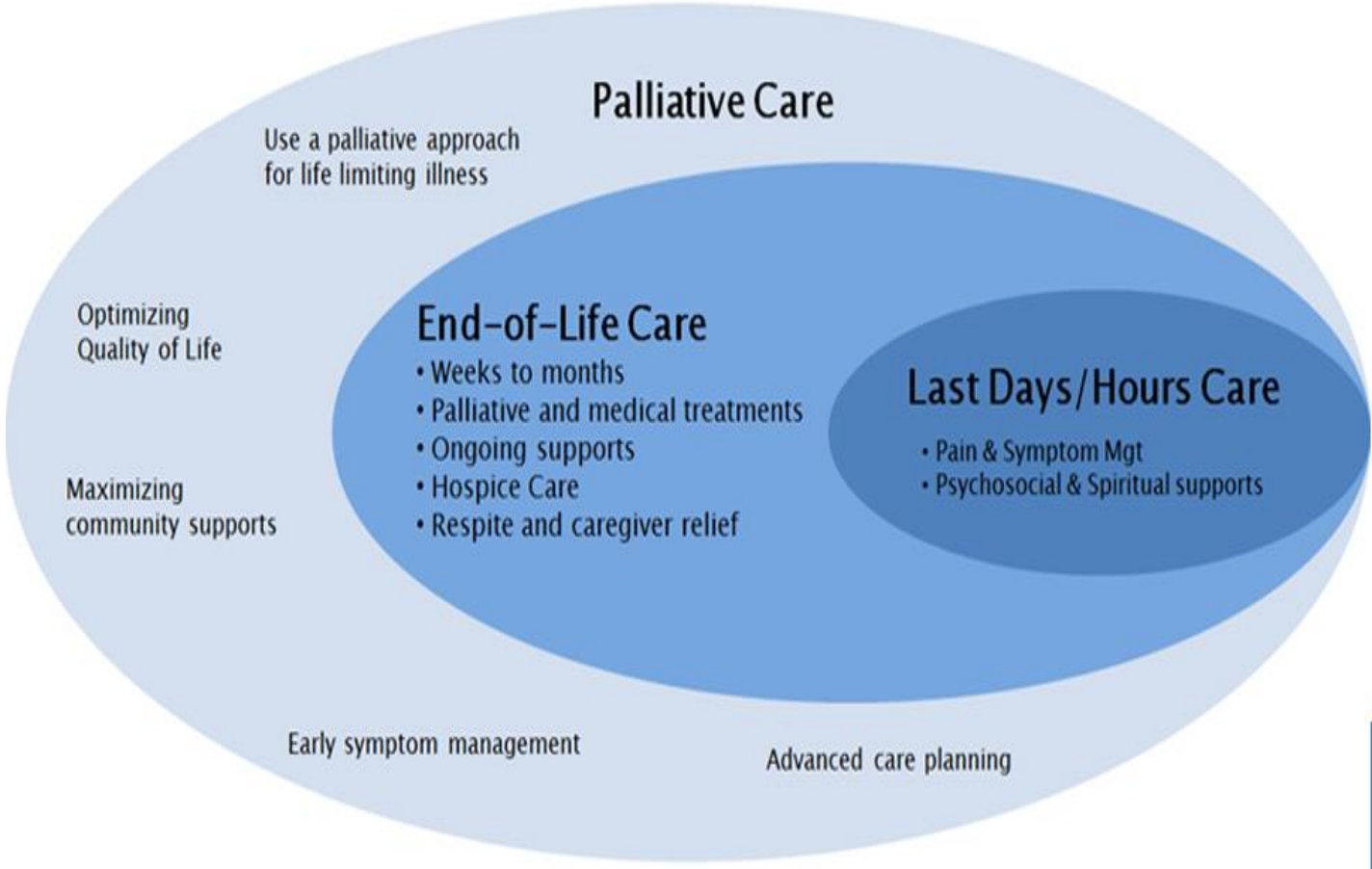


Treatment of CJD

the patient survival median is short
no treatment for this disease

- 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**.





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.

→ Common causative agents

→ between dural & spinal column

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.

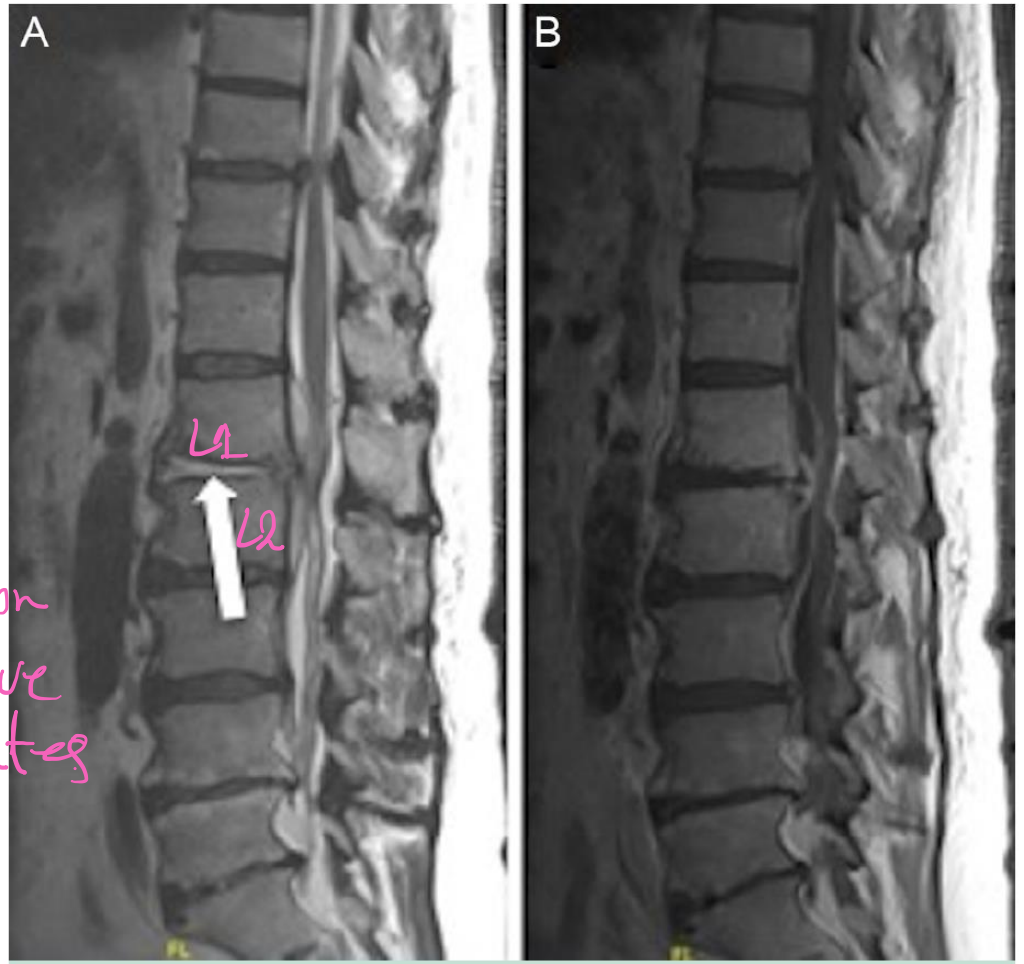


Figure 2 Discitis with associated ventral epidural abscess. Lumbosacral magnetic resonance image of a patient with diabetes mellitus who presented with acute on chronic low back pain, fevers, and weight loss. Sagittal T2 fluid-attenuated inversion recovery (FLAIR) imaging (**A**) and T1 postcontrast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

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

1- Choose the true sentence about encephalitis:

a. Rabies is treated by supportive care and antibiotics

b. Arboviruses are the most common cause of epidemic cases

C. Herpes cause encephalitis in 70% of cases

Answer: B

2. Which of the following is true about transmissible spongiform encephalopathies?

Answer: The only way to confirm a diagnosis is a brain biopsy

- True about familial Creutzfeldt-Jakob:

a. Acyclovir is important as empirical treatment

b. Brain biopsy has no importance in diagnose

C. There is no treatment for this disease

Answer: C

3. A patient came with a headache, fever, and focal neurologic deficits. CSF investigations have shown leukocytosis with predominance of lymphocytes and normal glucose and protein levels, the most appropriate diagnostic method is?

A. PCR

B. viral culture

C. biopsy

D. CT imaging

Answer: A

-Wrong statement about encephalitis:

Answer: It cannot be prevented or treated

-Which of the following is true regarding encephalitis ?

a. Streptococci are the most identified pathogens in sporadic cases of encephalitis .

b. Encephalitis patients are usually treated at home with anti-pyrectics and painkillers .

Persons infected with Herpes simplex type-1 commonly develop encephalitis

d. SF culture is necessary to confirm the diagnosis of encephalitis .

e. Arboviruses are associated with epidemics of encephalitis .

Answer: E

- right about TSEs

Answer: sporadic more common mostly in adult > 60 years old

-False statement about meningitis (or encephalitis):

Answer: Brain biopsy is usually acquired for diagnostic purposes

-Wrong about a patient with CJD:

Answer: His survival median is very long

-The most common cause of sporadic encephalitis:

Answer: HSV

-A 53-year-old woman develops fever and focal neurologic signs. Magnetic resonance imaging shows a left temporal lobe lesion. Which of the following tests would be most appropriate to confirm a diagnosis of herpes simplex encephalitis in this patient?

(A) Brain biopsy

(B) Tzanck smear

(C) Polymerase chain reaction assay for viral DNA in cerebrospinal fluid

(D) Serologic test for viral IgM antibody

Ans: C

Book Questions "From Jawtez"

-The presence in neurons of eosinophilic cytoplasmic inclusion bodies, called Negri bodies, is characteristic of which of the following central nervous system infections?

(A) Borna disease

(B) Rabies

(C) Subacute sclerosing panencephalitis

(D) New variant Creutzfeldt-Jakob disease

(E) Postvaccinal encephalitis

Ans b

- A 20-year-old man, who for many years had received daily injections of growth hormone prepared from human pituitary glands, develops ataxia, slurred speech, and dementia. At autopsy the brain shows widespread neuronal degeneration, a spongy appearance due to many vacuoles between the cells, no inflammation, and no evidence of virus particles. The most likely diagnosis is
(A) Herpes encephalitis
(B) Creutzfeldt-Jakob disease
(C) Subacute sclerosing panencephalitis
(D) Progressive multifocal eukoencephalopathy
(E) Rabies
Ans: b

- Which one of the following is a recommended therapy for herpes simplex virus brain infection?
(A) Acyclovir
(B) Attenuated live virus vaccine
(C) Herpes immune globulin
(D) Interferon-a
(E) Ribavirin
Ans: A

- A 65-year-old man develops dementia, progressive over several months, along with ataxia and somnolence. An electroencepha- lographic pattern shows paroxysms with high voltages and slow waves, suggestive of Creutzfeldt-Jakob disease (CJD). By which of the following agents is this disease caused?

(A) Bacterium
(B) Virus
(C) Viroid
(D) Prion
(E) Plasmid

Ans: D