



VIRAL INFECTION

VIRAL INFECTION OF THE CNS



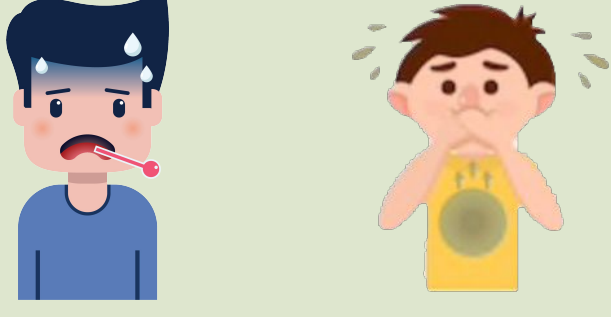

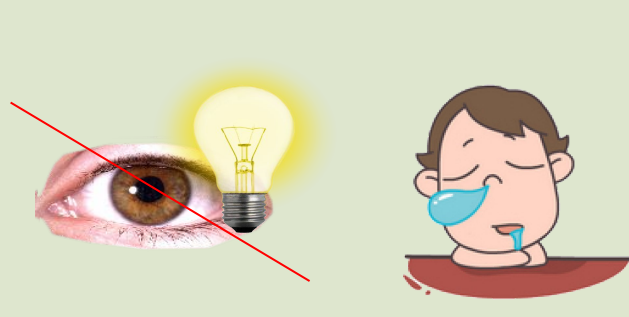

Objectives:

- ★ Acute viral infections of the CNS.
 - Aseptic meningitis, Paralysis & Encephalitis
 - Etiological agents
 - Enteroviruses & polioviruses.
 - Herpes simplex virus 1.
 - Rabies virus.
 - Arboviruses (West Nile virus).
 - For each one you should know the structure, epidemiology, pathogenesis, clinical presentations, lab diagnosis, treatment & prevention.

Causes of Meningitis

Infectious				Non- infectious
Viral	Bacterial	Fungi	Protozoa	
<p>★ Aseptic meningitis</p> <ul style="list-style-type: none"> ○ Less severe ○ Resolve without specific treatment within a week or two 	<p>★ Septic meningitis</p> <p>★ Severe and may result in:</p> <ol style="list-style-type: none"> Brain damage Hearing loss Learning disability <p>★ It would cause death</p>			

Signs & Symptoms

Vomiting	Headache	Light aversion	Joint pain
Fever	Neck stiffness	Drowsiness	Fitting
			

Cerebrospinal fluid (CSF) analysis

	Normal	Aseptic Meningitis	Septic Meningitis
Color	Clear	Clear	Cloudy ₁
Cells/ mm³	<5	Increase 100-1000 lymphocytes	Increase 200-20000 neutrophils
Glucose mg/dl	45-85	Normal or slightly changed	Low <45
Causes	-	Viruses or others	Bacteria

₁ Because of the presence of pus cells and protein



Viral Meningitis (Aseptic Meningitis)

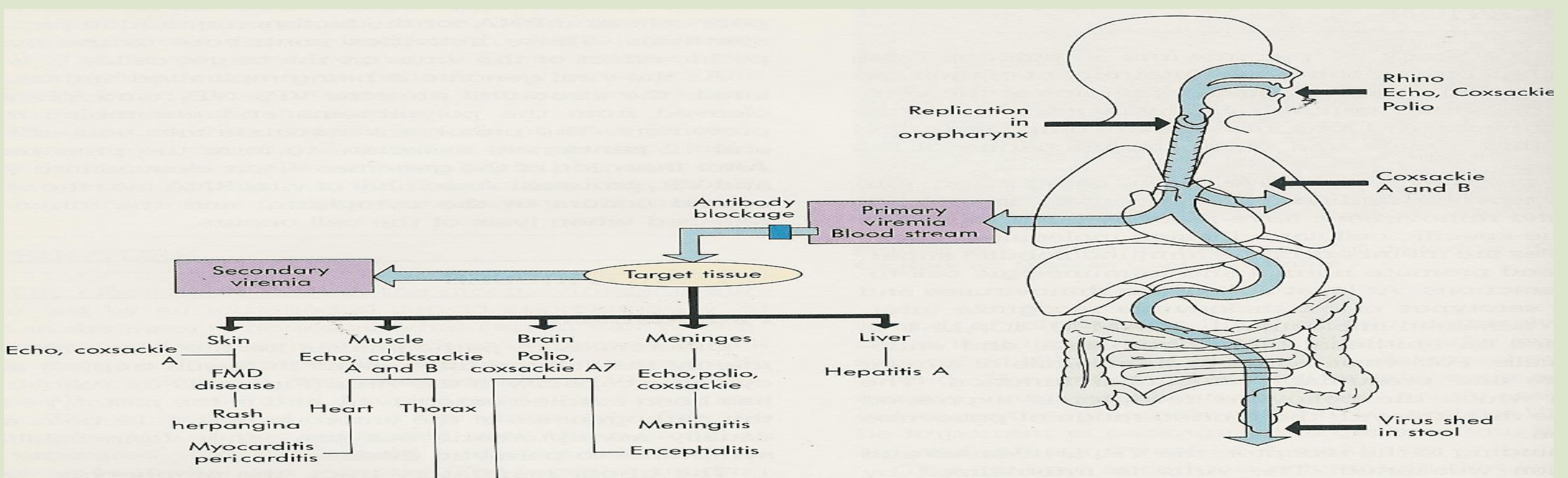
Etiology

- ★ It's mainly caused by **Enterovirus** and other viruses such as:
 - Mumps virus
 - Arboviruses.
 - Herpes viruses.
 - Human Immunodeficiency Virus.
 - Lymphocytic choriomeningitis virus.
- ★ **Enterovirus** belong to the **Picornaviridae**₁ family which is a non enveloped, icosahedral, positive single stranded RNA genome (+ ssRNA)₂
 - ★ Which includes: :
 - Poliovirus (Type 1,2 & 3)
 - Coxsackieviruses (A&B)
 - Echoviruses
 - Entroviruses (68-71)

Epidemiology

Reservoir	Spread	Age	Seasonal Distribution
Human	<ul style="list-style-type: none"> - Fecal - oral route (mainly) - Inhalation of Infectious aerosols (Crowded, poor hygiene & sanitation) 	Children > adults	Summer & fall

Pathogenesis:



The main route for enterovirus is the fecal oral route → replicate in the GIT → reaches the blood (viremia) → it targets many organs such meninges, brain, muscles and askin.

₁ Pico means small and rna is its genome while viridae means virus

₂ +ssRNA translate into protein directly while -ssRNA (like rabies) has to go through transcription 1st

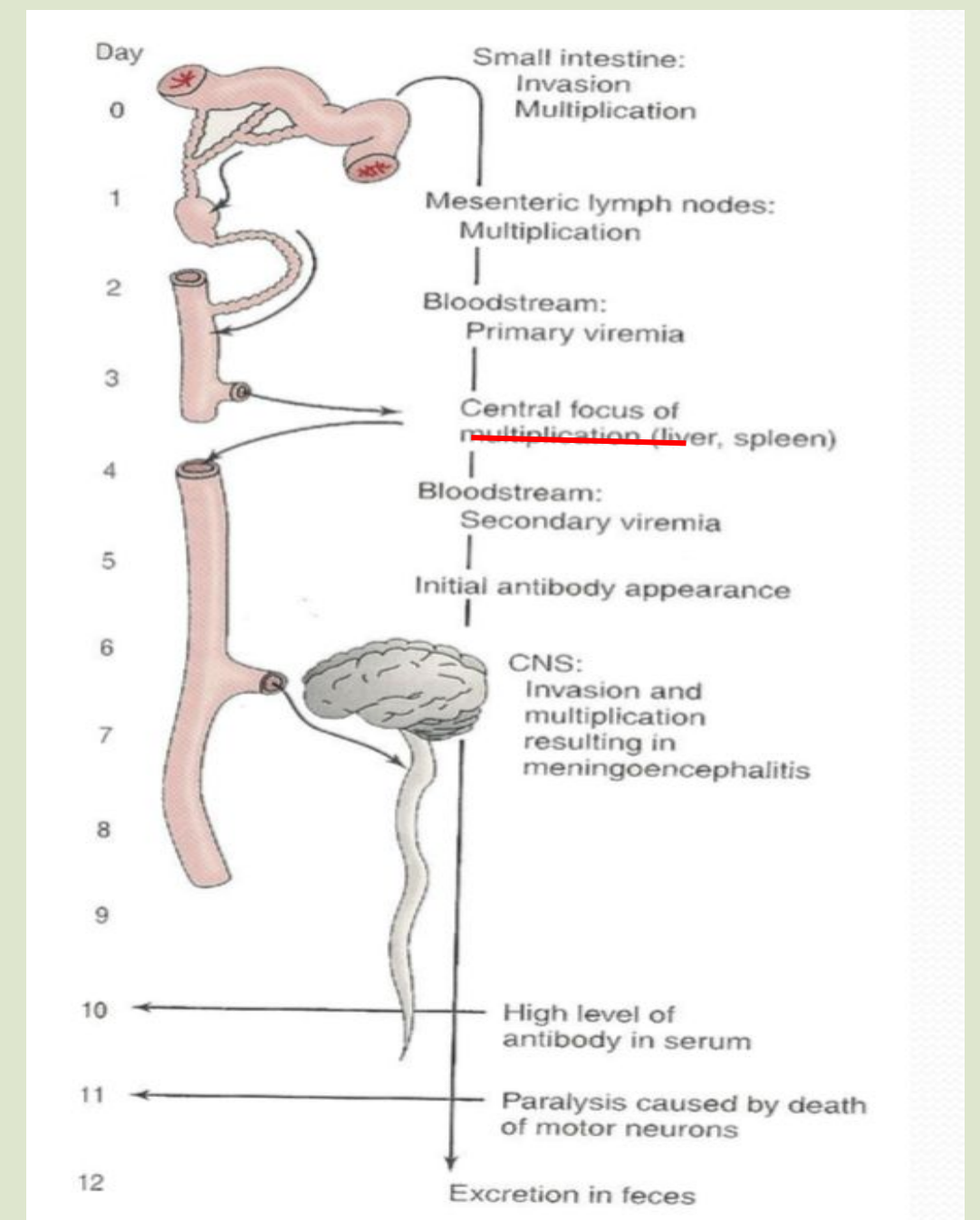


Enteroviral Infection (Asymptomatic Infections)

Neurologic Diseases	Non- Neurologic Diseases
<ul style="list-style-type: none"> ★ Aseptic Meningitis₁ ★ Paralysis ★ Encephalitis₂ 	<ul style="list-style-type: none"> ★ Respiratory Tract Infections ★ Skin & Mucosa Infections <ul style="list-style-type: none"> ○ Herpangina, Hand-foot-and-mouth disease, & Exanthems ★ Cardiac Infections <ul style="list-style-type: none"> ○ Pleurodynia (epidemic myalgia), Myocarditis, & Pericarditis ★ Acute hemorrhagic conjunctivitis ★ Others

Pathogenesis of Poliovirus:

1. Pathway to CNS by:
 - a. Blood
 - b. Peripheral nerves
2. Causing destruction of motor neurons of AHCs₃
3. Rarely affects brainstem (bulber poliomyelitis)
4. Immunity: IgA & IgG
 - lifelong type-specific immunity₄



Poliovirus Infections

1-2%	4-8%	90-95%
Major illness	Minor illness	No illness
<ol style="list-style-type: none"> 1. Nonparalytic poliomyelitis (Aseptic meningitis) 2. Paralytic poliomyelitis₅ (Flaccid paralysis) 	Abortive poliomyelitis (no CNS involvement)	Asymptomatic ₆

₁ Most common form of CNS infection caused by enterovirus

₂ Rarely caused by poliovirus

₃ It causes a lower motor neuron lesion → results in paralysis

₄ When someone get infected they will later on develop a lifelong immunity

₅ Paralytic poliomyelitis: it is asymmetrical, may have residual paralysis of the affected muscle. It's a disease of children but the risk of paralysis increase w/ age. So it mostly present it kids but might be seen in adult and in a more severe form.

₆ Can be transmitted to others.



Lab Diagnosis of Enteroviruses

Virus isolation	CSF in aseptic meningitis	Serology
<ol style="list-style-type: none"> Samples: <ol style="list-style-type: none"> Stool (best), rectal or throat swabs & CSF Inoculate in cell cultures: <ol style="list-style-type: none"> all enteroviruses grow expect some strands of Cox A viruses Observe for CPE (cytopathic effect) Identify the type 	<ol style="list-style-type: none"> Lymphocytosis Glucose levels N to slightly ↓ Protein levels N or slightly ↑ Isolation rate is variable RNA detected in CSF by RT-PCR 	Limited value

Management

Treatment (Rx)	No antiviral
Prevention	<ol style="list-style-type: none"> Sanitation and hygienic measures Poliovirus vaccines: <ol style="list-style-type: none"> Inactivated polio vaccine (IPV): (salk, killed) (S/C or IM) Live attenuated polio vaccine (OPV): (sabin, oral)
Doses	4 doses of PV; 2,4, 6-18 months & 4-6 years
Combination Vaccine	IPV, DTaP, Hib & HB vaccines
Adverse Reactions	<ul style="list-style-type: none"> IPV → local reactions Vaccine-associated paralytic poliomyelitis (OPV), therefore adults and immunocompromised need to get the killed one
Indication of Polio Vaccination of Adults (IPV)	Adults should get the IPV one. <ul style="list-style-type: none"> Travelers to polio-endemic countries Health Care Workers

Features of Polio Vaccines

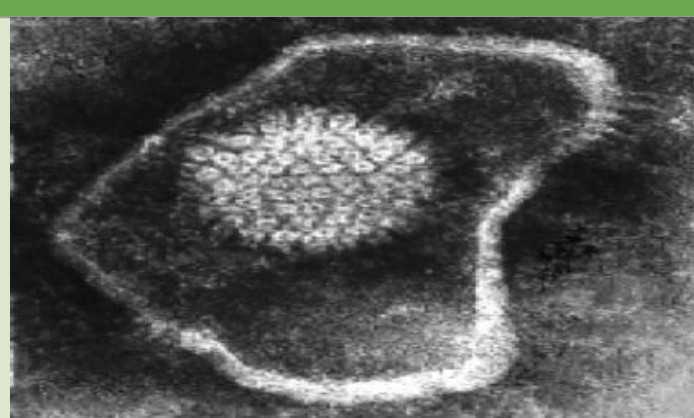
Attribute	Killed (IPV) injected	Live (OPV) orally
3 types (trivalent)	Yes	Yes
Prevent disease	Yes(short duration)	Yes (long duration)
Induce humoral IgG	Yes	Yes
Route of administration	Injection	Oral
Transmission others	No	Yes
Affords secondary protection by spread to others	No	Yes
Reverts to virulence	No	Yes (rarely)
Cause disease in immunocompromised	No	Yes



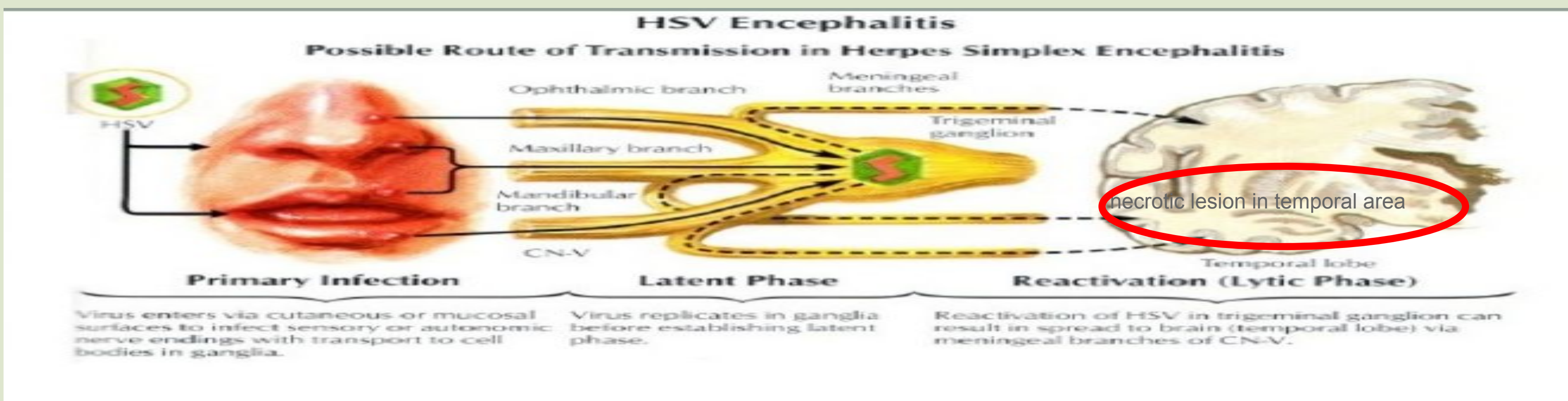
Viral Encephalitis

★ Enteroviruses, Herpes viruses, Rabies virus, Arboviruses, Others

Herpes Simplex Encephalitis

Caused by	<ul style="list-style-type: none"> - Herpes simplex virus -1(HSV-1) - dsDNA, enveloped, icosahedral virus 	
Clinical Findings	<ul style="list-style-type: none"> - Fever, headache, vomiting, seizures & altered mental status. - High mortality rate - The only treatable viral CNS infection 	
Diagnosis	<ul style="list-style-type: none"> - MRI → Reveal the temporal lesion - CSF → Lymph, glucose is normal & Protein is high - PCR → Detection of HSV-1 DNA 	
Treatment	Acyclovir.	

Pathogenesis:



It presents as skin lesions around the mouth and the nose → go to the sensory ganglion where it will replicated there → peripheral nerve → reaches the temporal area of the brain → result in a **temporal lesion**

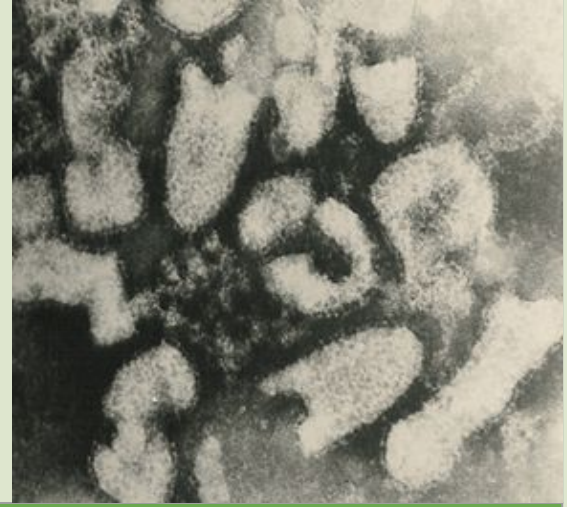


Rabies Encephalitis

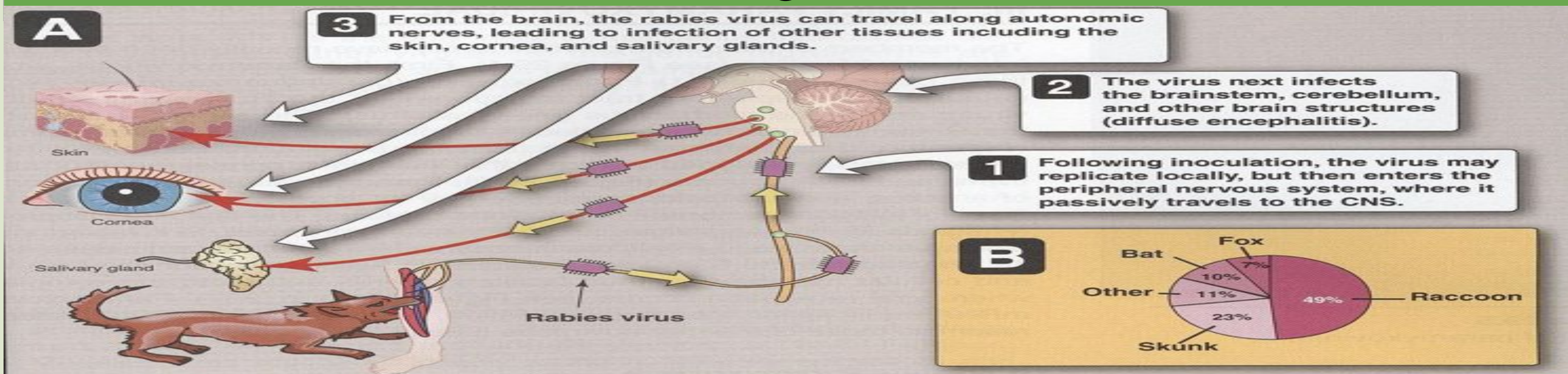
★ **Rhabdoviridae:** ss (-) RNA genome, helical, nucleocapsid, enveloped & bullet shaped virus

Epidemiology

Reservoir	Major; Raccoons , foxes, wolves, bats, cats & dogs
Transmission	<ul style="list-style-type: none"> - Common route: Bite of a rabid animal - Uncommon route: <ul style="list-style-type: none"> - Corneal transplant <small>most common mode of transmission</small> - Inhalation while in a bat infested cave



Pathogenesis



After getting a bite from a rabid animal that is infected rabies → the virus will enter the PNS → reaches spinal cord, medulla & brain → from the brain it travel down to infect other tissues like the cornea, skin & salivary glands .

★ **Rabies** → A fatal acute encephalitis **zoonotic**₁ disease

Phases

1. The incubation period ₂	1-3 months or longer
2. The prodromal phase	Fever, headache , malaise , anorexia, nausea & vomiting Abnormal sensation around the wound.
3. Neurological phase	<p>a. Encephalitis Nervous , Lacrimation , salivation, hydrophobia₃, convulsion, coma & death</p> <p>b. Paralytic illness; ascending, death, and it's associated with bat bite.₄</p>
4. Recovery	Extremely rare ₅

₁ Transmitted from animals

₂ If the patient visit the hospital during this period before the symptoms start they could treat them & saving them would be possible

₃ A classical sign of rabies, damage to the oropharyngeal muscles, the swallowing & breathing centers in the brain, the person infected with **rabies** is unable to swallow, especially liquid, & has the sensation of choking when they try to drink

₄ Less dramatic characterized by symmetrical paralysis associated with spinal cord infection and immediately lead to death

₅ Once signs and symptoms appear 99% will die



Laboratory Diagnosis

PCR

Rabies RNA in saliva

Rapid virus antigen detection (IF)

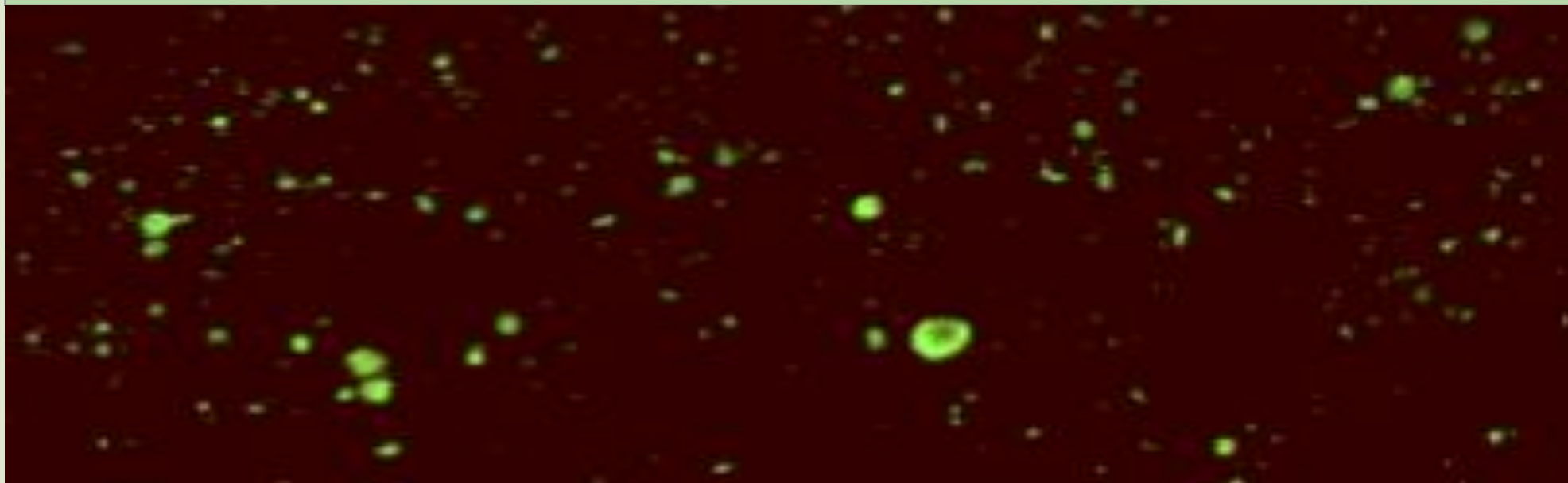
Neck skin biopsy, corneal impressions, & brain tissue

Histopathology

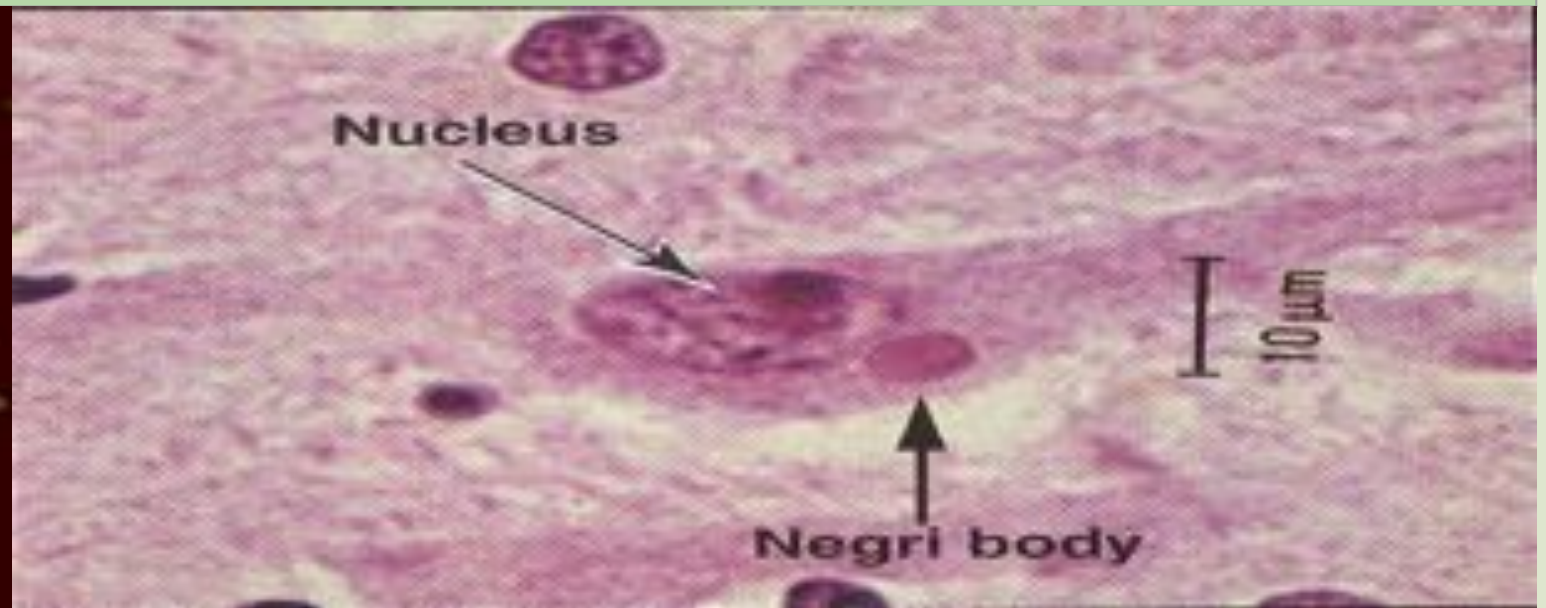
Neuronal brain cells
intracytoplasmic inclusions (Negri bodies)

Virus cultivation ₁

Serology



Rabid brain stained with Fluorescent anti-rabies antibody



Negri bodies are diagnostic of rabies.

Prevention

Control measures against canine rabies

- stray animals control
- Vaccination of domestic animals₂

Pre-exposure Prophylaxis (Vaccine):

People at increased risk of rabies
e.g. vets, animal handlers ... etc.

Post-exposure₃ Prophylaxis:

- wound treatment₄
- **passive immunization₅**:
 - Human anti-rabies immunoglobulin around the wound and IM
- **Active immunization₆**
 - Human Diploid Cell Vaccine (HDCV)
 - 5-6 doses

₁ It takes a long time so ppl don't use it anymore

₂ Like cats and dogs

₃ After the bite

₄ Cleaning the bite

₅ We give the patient antibodies

₆ We give the patient killed virus to induce the human response so it would form antibodies



Arthropod-borne Viruses

Arboviruses > 500 Vs

Reservoir	Wild birds & Mammals
Vector	Mosquito, ticks & Sandfly
Transmission	Bite of infected vector
Infections	<ul style="list-style-type: none"> ★ Asymptomatic Infections ★ Diseases 1. Fever, Rash & arthralgia 2. Hemorrhagic fever ± hepatitis 3. CNS disease (meningitis & encephalitis)

★ ArboVs associated with CNS disease:

Virus	Vector	Reservoir	Distribution
Eastern Equine Encephalitis (EEEV)	mosquito	birds	America
Western Equine Encephalitis (WEEV)	mosquito	birds	America
Venezuelan Equine Encephalitis (VEEV)	mosquito	rodent	America
Japanese Encephalitis V	mosquito	Birds pigs	Orient
Murray Valley Encephalitis V	mosquito	birds	Australia
West Nile V <small>Dr. said we'll only concentrate in this</small>	mosquito	birds	Europe, Africa, Middle East Asia, America

West Nile Virus

Features	<ul style="list-style-type: none"> ★ Flaviviridae: enveloped ssRNA ★ Causes Febrile illness → meningitis & encephalitis ★ Vector: mosquitoes ★ Reservoir: birds ★ 80% is asymptomatic & 20% might develop west nile fever 	
Laboratory Diagnosis	<ul style="list-style-type: none"> A. Isolation (Gold standard, reference lab) <ul style="list-style-type: none"> i. Samples: blood, CSF, & viscera ii. Cell culture: CPE & identify by IF B. IgM-AB → ELISA & IF (most used) C. Arbovirus RNA by RT-PCR 	
Prevention	<ul style="list-style-type: none"> ★ Vector Control: <ul style="list-style-type: none"> a. Elimination of vector breeding sites b. using insecticides c. Avoidance contact with vectors (repellants & net) 	<ul style="list-style-type: none"> 1) Vaccines: <ul style="list-style-type: none"> a. Tick-borne encephalitis vaccine b. Japanese encephalitis vaccine



Notes

- Aseptic meningitis is mostly self-limiting and need no treatment
- Septic meningitis is serious and need immediate treatment
- The main cause of aseptic meningitis **Enterovirus**
 - Infections caused by poliovirus are decreasing why? Because of vaccination
 - It's important to know that enterovirus replicate in the GIT.
- Entero means intestinal tract
- Poliovirus is an enterovirus thus it occurs via the fecal-oral route → replicates in the GIT:
 - After it might get excreted with feces (asymptomatic infection) or it might reach the blood → abortive poliomyelitis
- Or from the blood it could reach the CNS and either cause → non paralytic poliomyelitis (aseptic meningitis) or paralytic poliomyelitis (rarely)
- Pay a very good attention to the questions; when they ask about the **most common poliovirus infection** your answer should be **asymptomatic** but if the question was the **most common clinical presented poliovirus infection** your answer should be **abortive poliomyelitis**
 - 7.days incubation period(no symptoms)-5.days prodromal(systemic symptoms)-5.days neural symptoms
- **Poliovirus vaccination:**
 - Why don't we use the OPV with immunocompromised patients? Bc it can reverse to its natural virulence state and it will cause paralysis
 - The live vaccine is live attenuated and in very rare cases will cause paralytic illness in immunocompromised patients so they are given killed vaccine
 - For adults the killed is better to avoid the complications
 -
- **What characterizes HSV encephalitis? Temporal lesion**
- **HSV encephalitis is the only treatable CNS viral infection**
- **There's no viremia stage in rabies**
- **Poliovirus → prevented but not treated**
- **HSV → treated but not prevented**
- **Rabies → prevented but not treated**



Summary

Viral Meningitis (Aseptic meningitis)

Pathogen:	Enteroviruses - Herpes viruses - HIV - Arboviruses - Mumps virus		
Enteroviruses			
Family	Picornaviridae	Include:	Poliovirus (1, 2,3 types) Coxsackieviruses (A&B) Echoviruses Enteroviruses (68-71)
Character	ss (+) RNA Nonenveloped , icosahedral Affect children more		
Reservoir	Human	Spread:	Fecal - oral route (mainly) - Inhalation.
Enteroviral infections	Asymptomatic Infections:	Neurologic Diseases	Aseptic meningitis - Paralysis Encephalitis
		Non-Neurologic Diseases	
Poliovirus	Pathogenesis	- GIT → spread to CNS by blood or peripheral nerves → destruction of AHCs (LMNL) → paralysis. - Rarely affect brainstem → bulber poliomyelitis Immunity: IgA & IgG Lifelong type-specific immunity	
	Poliovirus infection	- 90% → Asymptomatic. (but can transmit the virus) - 4-8% → minor illness → Abortive poliomyelitis (No CNS involvement).(children) - 1-2% → major illness: 1- Nonparalytic poliomyelitis (Aseptic meningitis). 2- Paralytic poliomyelitis: (Flaccid paralysis). (adult)	
Lab Diagnosis	Virus isolation	Samples: Stool , Rectal, throat swabs & CSF → Inoculate in cell cultures (all EV grow except some strains of Cox A) → Observe for CPE → Identify the type.	
	CSF in aseptic meningitis	Lymphocytosis - Glucose level normal to slightly ↓ - Protein level normal or slightly ↑	RT-PCR test: To detecte EV RNA in CSF
Management	<ul style="list-style-type: none"> ❖ No antiviral Rx ❖ Prevention: <ol style="list-style-type: none"> 1)Sanitation & Hygienic measures 2)Poliovirus vaccines 	Poliovirus Vaccine: A- Inactivated polio vaccine (salk) (best for adult and immunocompromised) B- Live-attenuated polio vaccine (sabin) (may cause vaccine-associated paralytic poliomyelitis in adult and immunity)	

Viral Encephalitis

Pathogen	Enteroviruses - Herpes viruses - Rabies virus - Arboviruses.		
	Herpes Simplex Encephalitis	Rabies encephalitis (zoonotic disease)	
Caused by	Herpes simplex virus -1 dsDNA , Enveloped , Icosahedral Virus	Rabies virus Rhabdoviridae, s.s (-)RNA, Enveloped virus.	
Symptoms	Seizures and altered mental status	-The prodromal phase: Abnormal sensation around the wound -Neurological phase - Hydrophobia	
Diagnosis	MRI (temporal lesion) CSF: Lymph, Protein PCR	PCR: from saliva Rapid virus antigen detection(IF): from neck skin, and corneal impression. Histopathology: Negri bodies	
Treatment	Acyclovir (only CNS viral infection that is treatable) (no vaccines)	Vaccination only : 1-Vaccination of domestic animals 2-Pre-exposure prophylaxis: to people at risk of rabies 3-Post-exposure prophylaxis: -Passive immunization: human anti-rabies immunoglobulin -Active immunization: Human Diploid Cell Vaccine .	

Arthropod –borne Viruses (Arbovirus) : Associated with CNS Disease (West Nile virus)

	West Nile V → Flaviviridae.→ meningitis, encephalitis (transmission by birds)		
Diagnosis	A-Isolation (Gold standard) B -IgM -AB* - ELISA, IF C - Arbovirus RNA by RT-PCR		
Prevention	<ul style="list-style-type: none"> ❖ Elimination of vector breeding sites using insecticides ❖ Vaccines: <ul style="list-style-type: none"> Tick-borne encephalitis vaccine Japanese encephalitis vaccine 		



MCOs:

1- What is the most common form of CNS infection caused by enterovirus?

- A- Encephalitis.
- B- Acute hemorrhagic conjunctivitis.
- C- Aseptic meningitis.
- D- Paralysis.

2- Which of the following is found in herpes simplex encephalitis ?

- A- Hydrophobia.
- B- Lacrimation.
- C- Rash.
- D- Temporal lesion.

3- Poliovirus affect which part of the CNS?

- A- Spinothalamic tract.
- B- Anterior horn cell.
- C- Descending tract.
- D- Lateral horn cell.

4- Which vaccine should not be given to HIV patients?

- A- Tick-borne encephalitis.
- B- Inactivated polio vaccine.
- C- Human diploid cell vaccine.
- D- Live-attenuated polio vaccine.

5- Which of the following viral CNS infection is treatable?

- A- Herpes simplex encephalitis.
- B- Brucellosis
- C- Rabies encephalitis.
- D- Enterovirus.

6- A patient has died of unknown cause, after autopsy, negri bodies was found in the brain tissue. What is the most likely cause of death?

- A- Rabies encephalitis.
- B- Viral meningitis.
- C- Herpes simplex encephalitis.

SAQ:

3-B
2-D
1-C
4-D
5-A
6-A

- A 10 years old boy brought to the hospital. He was complained of headache, fever. His mom said he was vomiting too. After taking the history she told you that he was bite by a dog 2 days earlier.

1- What is your diagnosis?

Rabies encephalitis

2- What further test would you order ?

PCR - Rapid virus antigen detection

3- what is the proper way to treat him?

Wound treatment

Post-exposure prophylaxis:

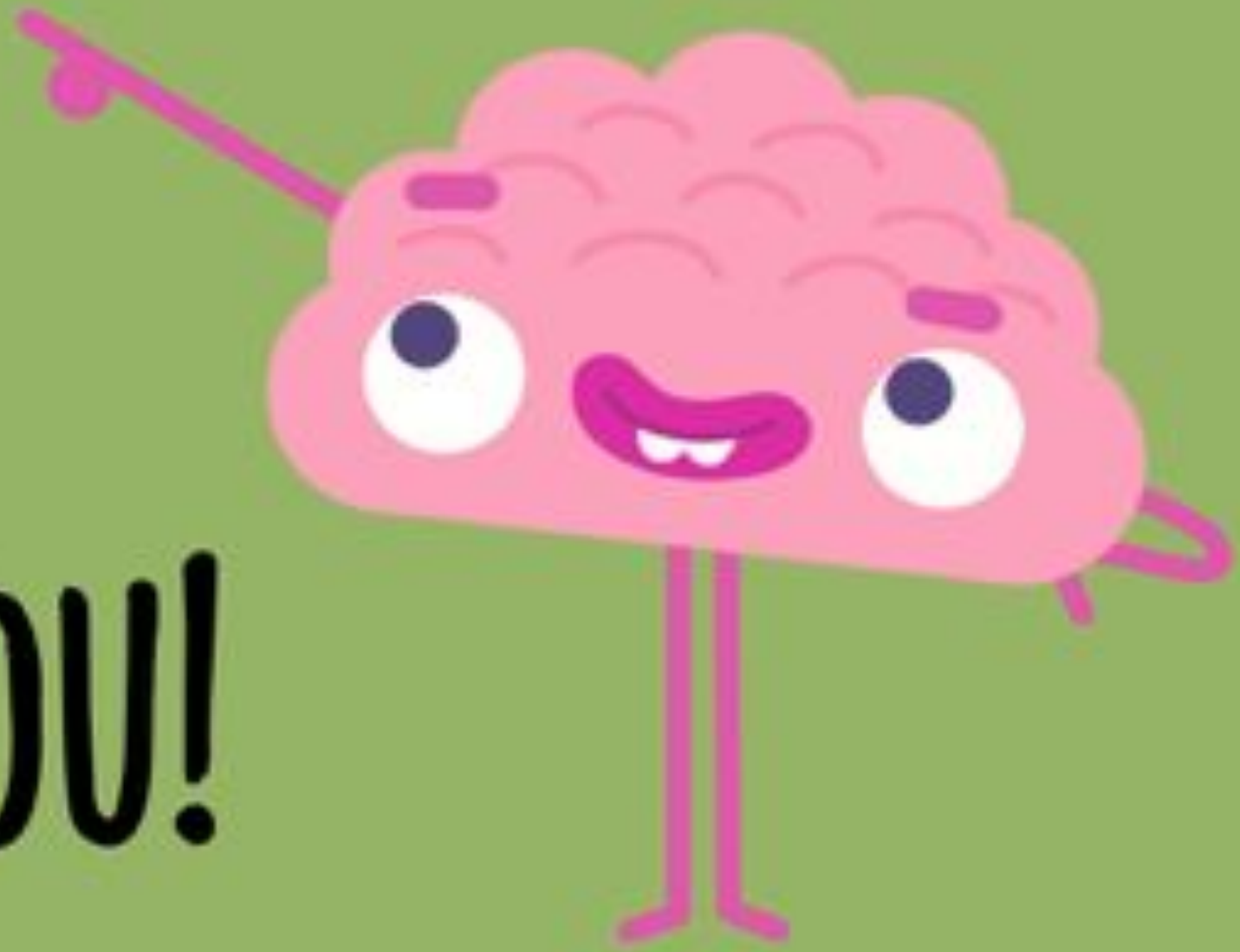
-Passive immunization: human anti-rabies immunoglobulin

-Active immunization: Human Diploid Cell Vaccine.

4- What stage of the disease do think he is in? What clinical manifestations are associated with the neurological phase of the disease?

Prodromal phase, nervous - lacrimation - salivation - hydrophobia





THANK YOU!



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