MEDICINE
KING SAUD UNIVERSITY

MICROBIOLOGY436

تمت المراجعة
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LECTURE: VIRAL INFECTION OF THE CNS

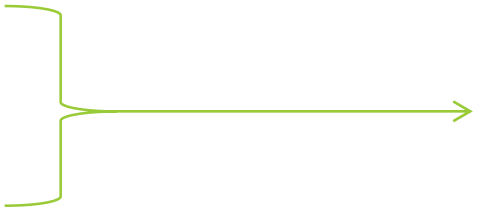
Editing File

- Important
- Doctor's notes
- Extra explanation
- **Only F** or **only M**

"لا حول ولا قوة إلا بالله العلي العظيم" وتقال هذه الجملة إذا داهم الإنسان أمر عظيم لا يستطيعه ، أو يصعب عليه القيام به .

OBJECTIVES:

- Acute viral infections of the CNS.
- Aseptic meningitis , Paralysis &Encephalitis
- Enteroviruses & polioviruses.
- Herpes simplex virus 1.
- Rabies virus.
- Arboviruses (West Nile virus).



- ✓ structure
- ✓ Epidemiology
- ✓ Pathogenesis
- ✓ clinical presentations
- ✓ Lab diagnosis
- ✓ Treatment & prevention

- Virus neurological diseases: Three groups of infection

  - Acute viral infections of the CNS.
    - ✓ **Meningitis, paralysis & encephalitis**
  - Chronic virus neurological diseases**.**
    - ✓ **SSPE, PML, C-J disease, tropical spastic paraparesis, HIV dementia.**
  - Neurological diseases precipitated by viral infections.
    - ✓ **Reye's syndrome, Guillian-Barré syndrome.**

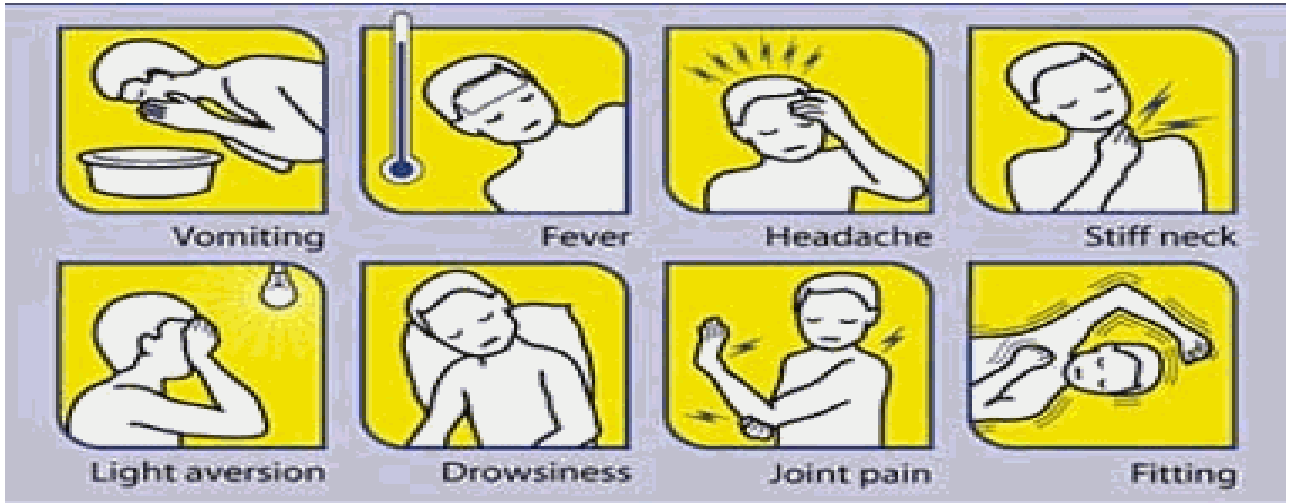
- **Meningitis:** -It includes the inflammation caused be an infection to the meninges or CSF

  - Caused by:

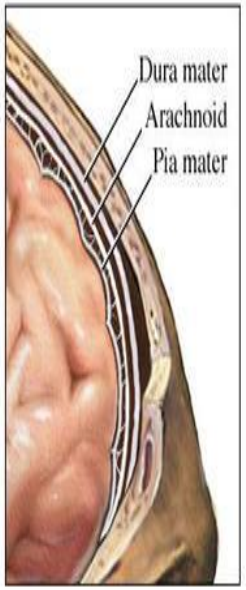
  ✓ Infectious agents:
  -bacteria
  -viruses
  -Fungi
  -protozoa

  ✓ Non-infectious agents.

  - Symptoms:



Viral meningitis* (we will talk about it in this lecture)	Bacteria meningitis*** (another lecture)
• Aseptic meningitis • Caused by virus. • Less severe • Resolves without specific treatment within a week or two**	• Septic meningitis •Caused by bacteria •Quite severe and may result in **a)** brain damage **b)** hearing loss **c)** learning disability • It would also causes death!



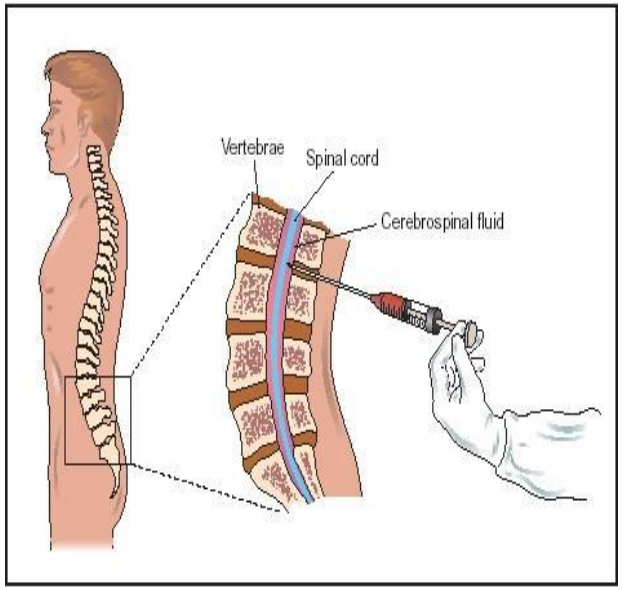
*Usually cause by virus and the CSF finding is negative (Aseptic) **spontaneously ***Its an emergency case and need empirical treatment

- ## Viral Meningitis (Aseptic meningitis):
  - Etiological Agents:
    - ✓ Enteroviruses The most common cause of viral meningitis

  Other :
    - ✓ Mumps virus . Incident has been decreased due to the vaccination
    - ✓ Arboviruses.
    - ✓ Herpes viruses.
    - ✓ Human Immunodeficiency Virus
    - ✓ **Lymphocytic choriomeningitis virus.**

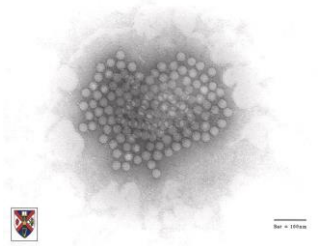
- ## Cerebrospinal fluid (CSF) analysis:

	Normal	Aseptic meningitis	Septic meningitis
Colour	Clear	Clear	Cloudy
Cells/mm^3	< 5	increase 100-1000 Lymphocytes	High/v. high 200-20,000 Neutrophils
Glucose mg/dl	45-85	Normal	Low<45*
Protein mg/dl	15-45	Normal/high 50-100	High>100
Causes		Viruses , others	Bacteria



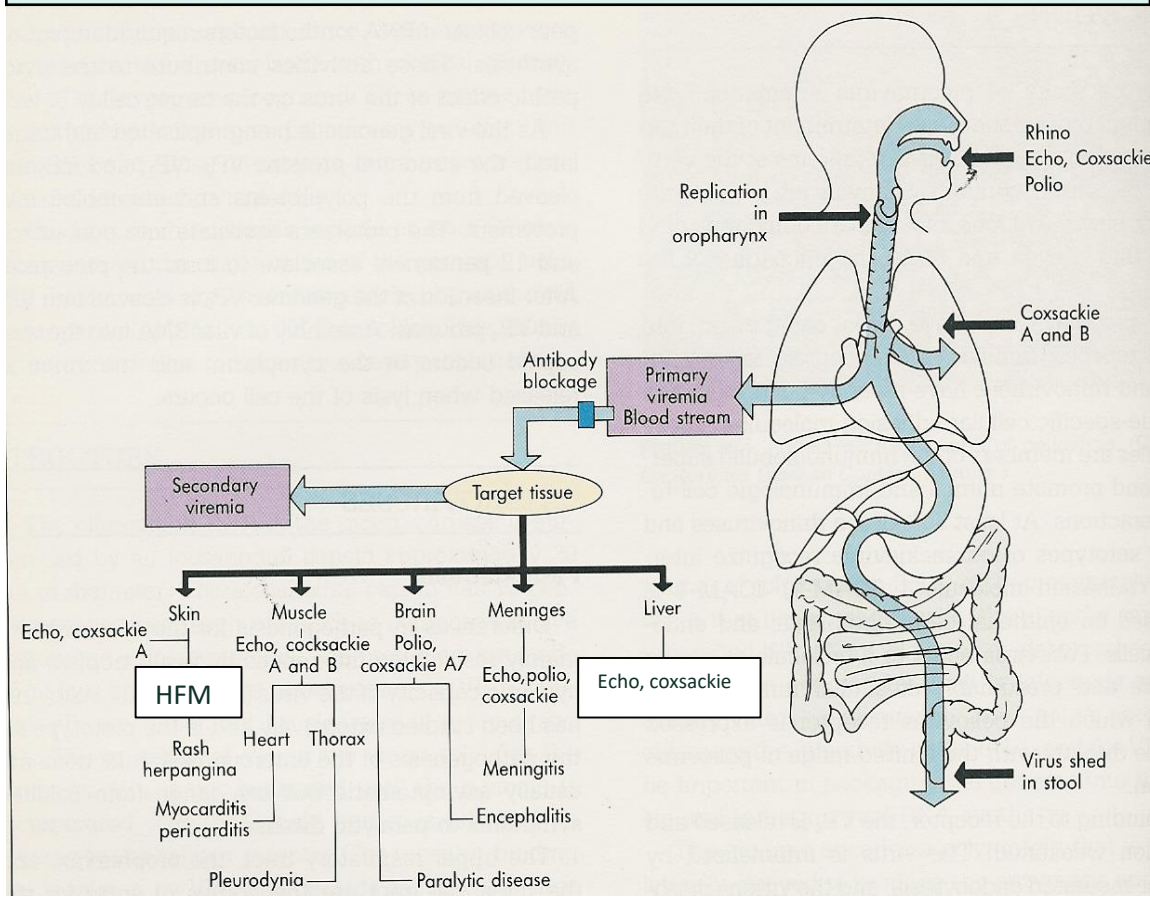
*consumes by the bacteria

- Enteroviruses:



Nonenveloped , icosahedral , ss (+) RNA	
Family :	Picornaviridae
Include:	• Poliovirus(1, 2&3 types) • Coxsackieviruses (A&B) • Echoviruses • Enteroviruses (68-71)
Epidemiology:	
Reservoir:	Human
Spread :	• Fecal - oral route (mainly) • Inhalation of Infectious aerosols (Crowded, Poor hygiene & Sanitation)
Age :	children > adults
Seasonal distribution*:	summer & fall

Pathogenesis:



*Major seasons for enteroviruses infection

- Enteroviral infections
  - Asymptomatic Infections
  - Diseases:

Neurologic Diseases	Poliovirus Types 1-3	GP A COX. Types 1-24	GP B COX. Types 1-6	Echovirus Types 1-34	Enterovirus Types 68-71
Aseptic meningitis*	1-3	Many	1-6	Many	71
Paralysis**	1-3	7,9	2-5	2,4,6,9,11,30	70,71
Encephalitis***		2,5-7,9	1-5	2,6,9,19	70,71

NON-Neurologic Diseases:

- ✓ Respiratory tract infections.
- ✓ Skin and mucosa infections;
- ✓ Cardiac infections
- ✓ Acute hemorrhagic conjunctivitis
- ✓ Others

2-Cardiac and muscular:
- ✓ Pleurodynia (epidemic myalgia)
- ✓ Myocarditis, pericarditis

3- Skin and mucosa infections;
- ✓ Herpangina
- ✓ Hand-foot-and-mouth disease
- ✓ Exanthems

3-Acute hemorrhagic conjunctivitis

4-Respiratory tract infections.

5-Others

*Self limiting disease **flaccid paralysis ***sever

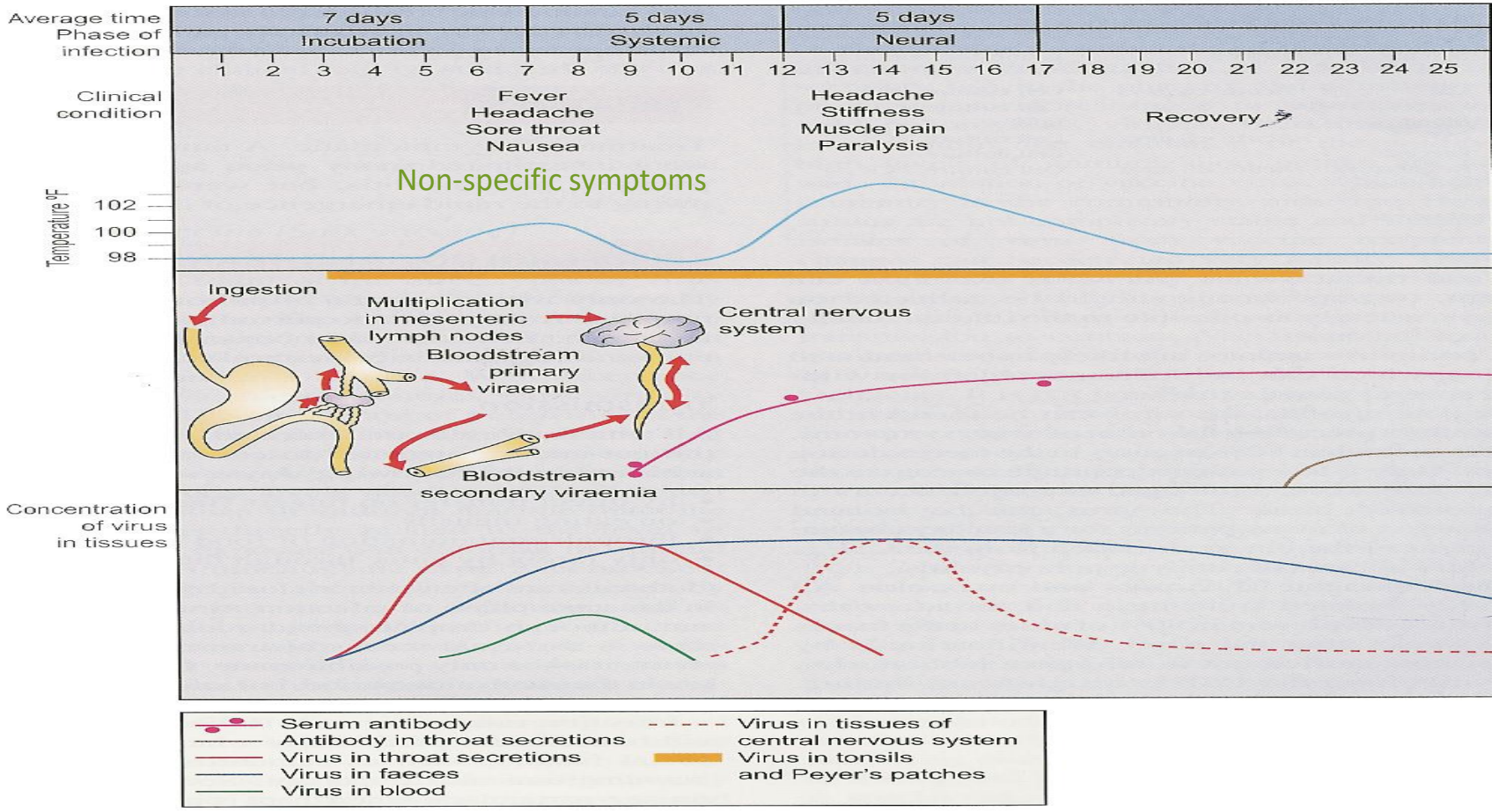
- ## Pathogenesis of polio:
  - Pathway to CNS by:
    - Blood
    - Peripheral nerves
  - Causing destruction of motor neurons **of AHCs**
  - Rarely affects brain stem (bulber poliomyelitis) شلل الاطفال

- ## Poliovirus Infections:

No illness:	90-95%	Asymptomatic
Minor Illness*:	4-8%	Abortive poliomyelitis (No CNS involvement)
Major Illness:	1-2%	1- Nonparalytic poliomyelitis (Aseptic meningitis) 2- Paralytic poliomyelitis: (Flaccid paralysis)

*Non-specific signs and symptoms

- Pathogenesis of polio:



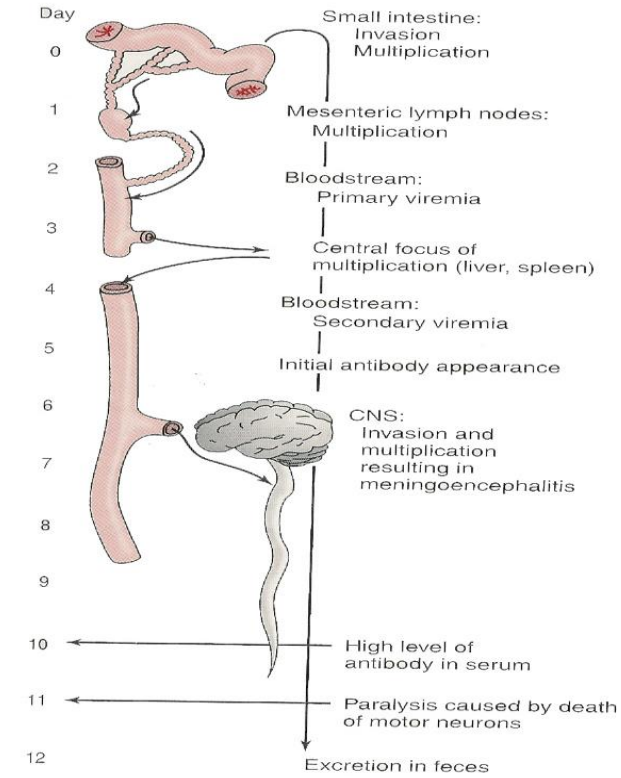
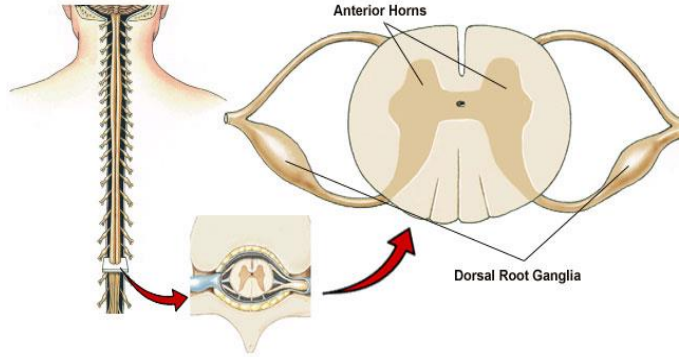


Figure F-6: Dorsal Root Ganglion & Anterior Horn



The dorsal root ganglion transmits *sensory* information while the anterior horn directs *motor* neurons.

Immunity: IgA & IgG = Lifelong type-specific immunity

• Lab Diagnosis of Enteroviruses

Virus isolation:	Samples:	• Stool (best) / Rectal / throat swabs / CSF • Inoculate **in cell cultures*** - in **MKC & HDF** All EVs grown except some strains of Cox A viruses
	Observe:	for CPE (cytopathic effect)
	Identify:	the type **by Neutralization Test**
	CSF in aseptic meningitis:	• lymphocytosis • Glucose level normal to slightly low • Protein level normal or slightly high • Isolation rate is variable Very low the appearance of enteroviruses • $EV_{(enteroviruses)}$ RNA detected in CSF by RT-PCR The best and gold standard to diagnose
Serology:	(limited value)	

• Management

treatment:	No antiviral treatment	
Prevention:	Sanitation & Hygienic measures	
	Poliovirus vaccines:	a- Inactivated polio vaccine (IPV) for adult (Salk, Killed) (S/C or IM) b- Live-attenuated polio vaccine (OPV) for children (Sabin, oral)

*Not all of them grow **I**PV = **i**njection, **O**PV = **o**rally Cytopathic effect (CPE): Any possible change in the appearance of the infected cell (CPE can take several forms) *foundation*

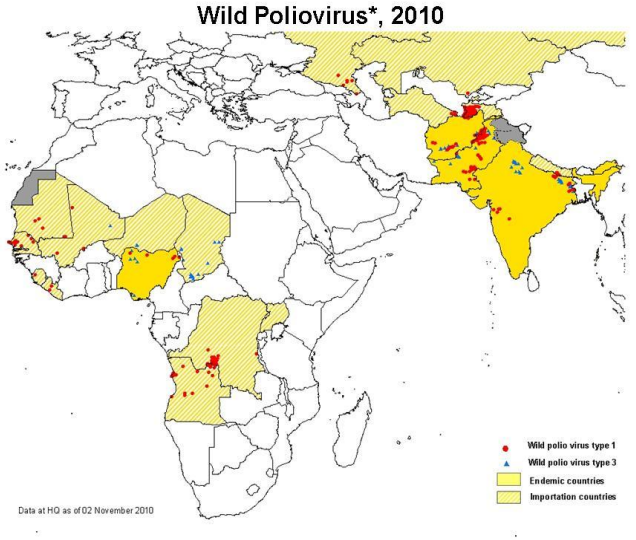
- Important Features of Polio Vaccines:

Attribute	Killed (IPV)	Live (OPV)
3 types (trivalent)*	Yes	Yes
Prevents disease	Yes	Yes
Induces humoral IgG Against viremia	Yes	Yes
Route of administration	Injection	Oral
Induces intestinal IgA	No	Yes
Interrupts transmission	No	Yes
Affords 2^{o} protection by spread to others	No	Yes
Reverts to virulance	No	Yes (rarely)
Causes disease in the immunocompromised	No	Yes
Co-infection with other EVs may impair immunization	No	Yes
Requires refrigeration	No	Yes
Duration of immunity	Shorter	Longer

Notes: 1- immunocompromised and Adult should take the Killed (IPV) type
2- Children take the Live (OPV) type which also oral administration 3- The Live (OPV) rarely cause paralysis while killed (IPV) not

*Protect against the three types of viruses

- Poliovirus Vaccine:
  - Adverse reactions ;
    - local reactions (IPV) At the site of injection
    - Vaccine -Associated Paralytic Poliomyelitis (OPV) adult , immunocompromised*
  - 4 doses of PV; 2, 4 , 6-18 ms & 4 - 6 yrs
  - **Combination vaccine** (Pediarix): contains **:**IPV, DTaP ,Hib & HB vaccines



- **Polio Vaccination of Adults**
  - Indications:
    - ✓ Travelers to polio-endemic countries Take KILLED(IPV) type
    - ✓ HCW Health care worker
  - IPV

The Incident has been decreased due to the using of universal vaccination

1988

- 350,000 cases
- 125 endemic countries
- World Health Assembly voted to eradicate polio

2016

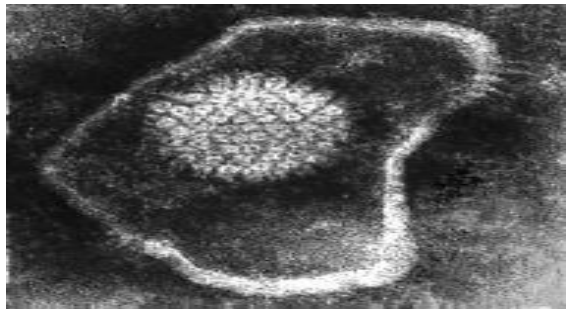
- 34 cases reported*
- 3 endemic countries

*Should take the killed (IPV) type

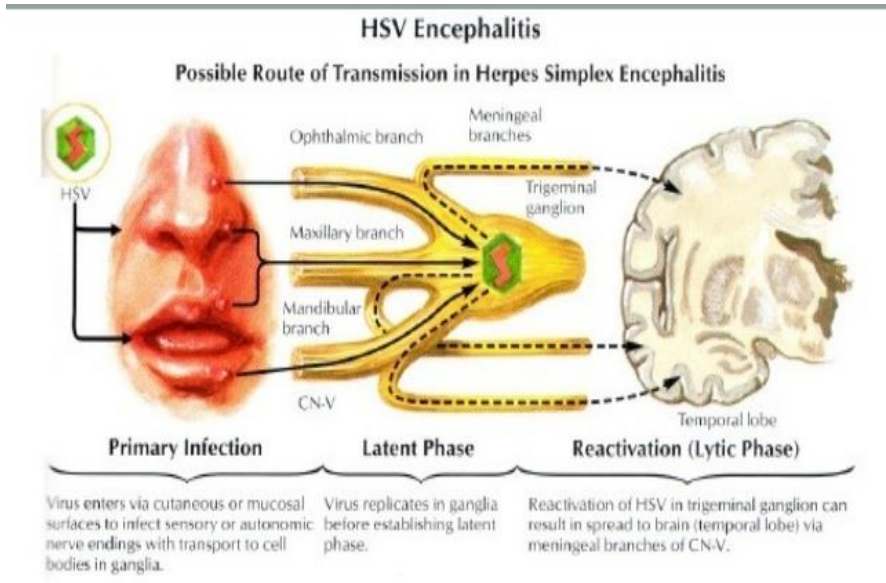
- **Viral Encephalitis:**

Enteroviruses	Herpes viruses.	Rabies virus	Arboviruses	Others

- **Herpes Simplex Encephalitis:**



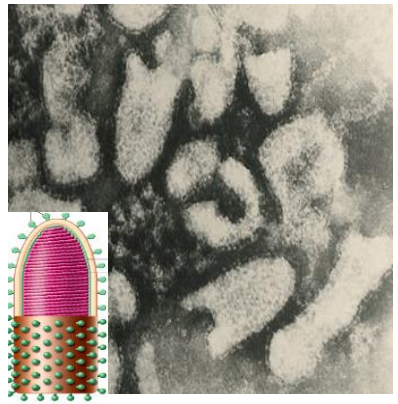
  - Caused by:
    - ✓ Herpes simplex virus -1(HSV-1) Type 1
      dsDNA , Enveloped , Icosahedral Virus
  - C/F:
    - ✓ Fever ,Headache ,Vomiting ,Seizures & altered mental status.
    - ✓ High mortality rate
  - Diagnosis:
    - ✓ MRI (magnetic resonance imaging) to find the lesion in the temporal lope
    - ✓ CSF: Lymph: high
      glucose: normal
      Protein: high
    - ✓ detection of HSV-1 DNA by PCR.
  - Treatment:
    - ✓ Acyclovir. this is the only virus (from this group) that can be treated.



-Can transmitted by saliva or direct contact with physclis then travel to the peripheral nerve to the trigeminal ganglia and it will affect the temporal lop (necrotic lesion)

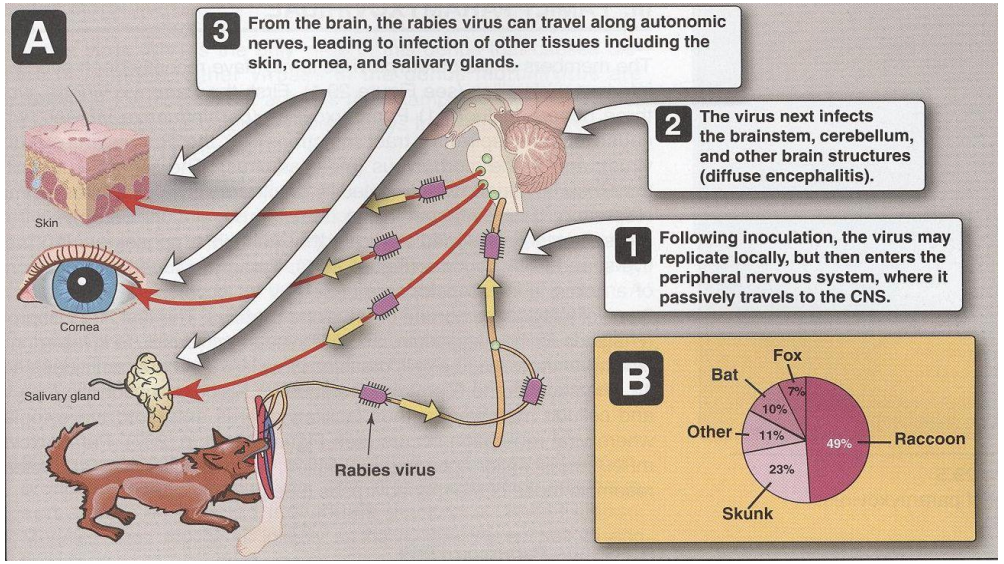
- # Rabies encephalitis:

s.s (-)RNA genome, Helical nucleocapsid, Enveloped virus.		
Family:	Rabies virus :Rhabdoviridae.	
Epidemiology;		
Reservoir:	a- Major: Raccoons , Foxes, Wolves & bats.	b- Imp: cats & dogs
Transmission:	a- Common route (usually dogs) • Bite of a rabid animal	b- Uncommon route • Inhalation while in a bat infested cave • Corneal transplant



Bullet shaped virus

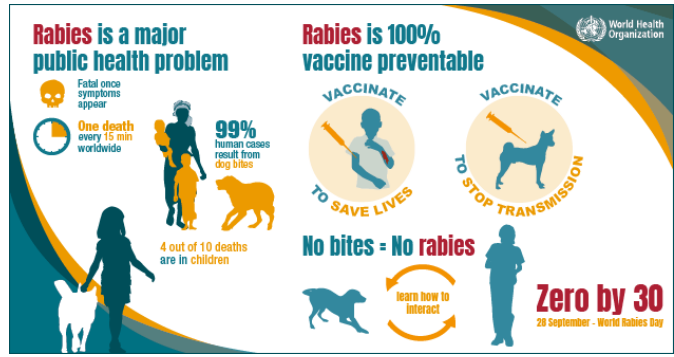
Pathogenesis:



From animals to human / In USA rarely conceder as reservoir for the rabies because they are immunized

- Rabies: داء الكلب
  - a fatal acute encephalitis
  - zoonotic disease .

4 phase :		
1-The incubation period:	1-3 m > longer *	
2-The prodromal phase: Non specific illness	• Fever, Headache, Malaise, Anorexia, Nausea & Vomiting. • Abnormal sensation around the wound.	
3-Neurological phase:	A- encephalitis: Majority of illness • Nervous , Lacrimation , salivation, Hydrophobia** , Convulsion ,coma & death .	B- Paralytic illness: • Ascending , Death , associated with Bat bite. Due to infection of the spinal cord rather than brain
4- Recovery:	Extremely rare	

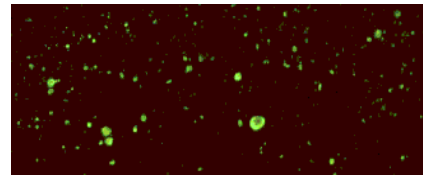


*Variable dependent on many factors including the location of the bite if it's in head it will be shorter than in leg

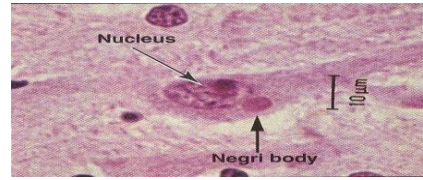
**Fear from water due to painful spasm of pharyngeal muscles

• Laboratory Diagnosis:

• PCR:	R. RNA in saliva The most sensitive and specific detection
• Rapid virus antigen detection* (IF):	✓ Neck skin biopsy Back of neck ✓ Corneal impressions ✓ Brain tissue
• Histopathology:	✓ neuronal brain cells ✓ intracytoplasmic inclusions (Negri bodies)
• Virus cultivation	
• **serology**	



Rabid brain stained with Fluorescent anti-rabies antibody



Negri bodies are diagnostic of rabies.

• Prevention: Untreatable but preventable

• Control measures against canine rabies include**:	✓ Stray animals control.	✓ Vaccination of domestic animals.	
• Pre-exposure prophylaxis (Vaccine):	✓ Persons at **increased risk** of rabies e.g. vets, animal handlers etc. Such as people contact with animals		
• Post-exposure prophylaxis: who exposed to the virus	✓ Wound treatment water and antiseptic solution	✓ **Passive immunization*****: human anti-rabies immunoglobulin around the wound & I M.	✓ **Active immunization******: Human Diploid Cell Vaccine (HDCV), 5 - 6 doses

*appear as a bright fluorescent apple green color when viewed with a fluorescence microscope

**Vaccine of animal

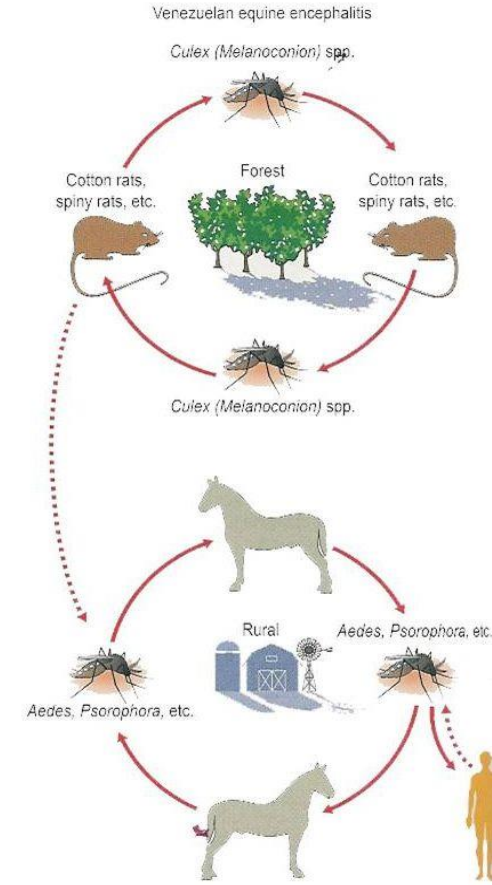
***Immediate protection

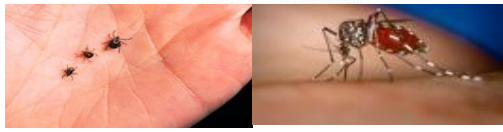
****Prolong immunity

/ Passive and active giving at the same time after exposure but different side

- **Arthropod –borne Viruses:**
  Arboviruses > 500 Vs

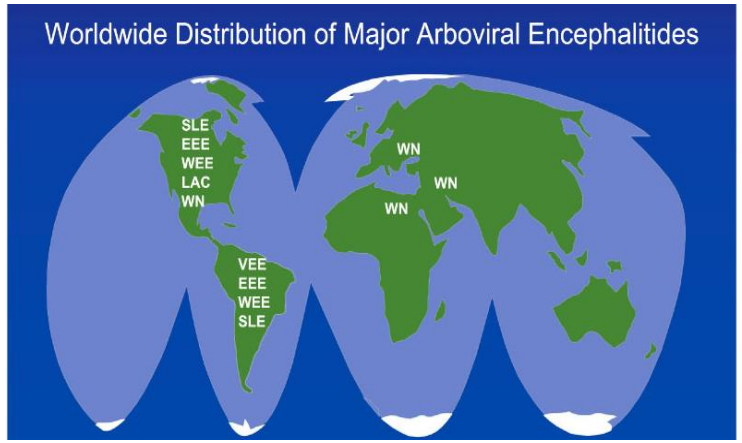
Epidemiology;			
Reservoir:	Wild birds & Mammals		
Vector:	Mosquito, ticks& Sandfly		
Transmission:	bite of infected vector		
Infections:	Asymptomatic Infections		
Diseases:	1- Fever, Rash & arthralgia	2- Hemorrhagic fever ± hepatitis	3- CNS disease (meningitis & encephalitis)



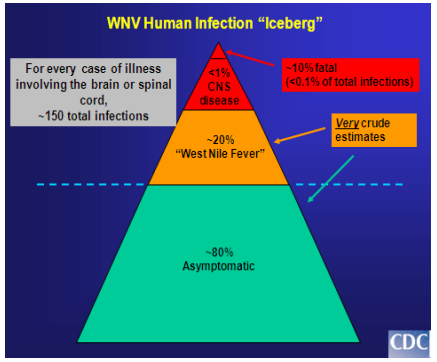


- ArboVs associated with CNS disease:

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	Transmitted by Mosquito	Birds	Europe, Africa Middle East, Asia, America

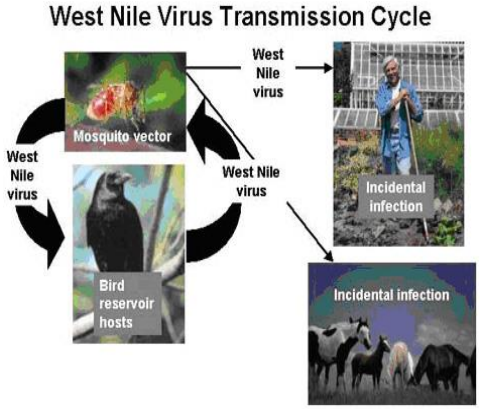


- **West Nile virus:** spread by infected mosquitoes
  - Flaviviridae **(enveloped +ssRNA)**
  - Febrile illness → meningitis , encephalitis



- **Laboratory Diagnosis:**

Lab methods:	
A- Isolation: (Gold standard) (Reference Lab)	Samples: blood, CSF, Viscera .
	Cell culture: → CPE → Identify
B- IgM -AB - ELISA, IF:	(most used) Most sensitive and rapid test
C - Arbovirus RNA:	by RT-PCR



- **Prevention:** There is no specific treatment

1-Vector Control:

- ✓ Elimination of vector breading sites
- ✓ using insecticides
- ✓ Avoidance contact with vectors (repellants , net)

2-Vaccines:

- ✓ Tick-borne encephalitis vaccine
- ✓ Japanese encephalitis vaccine

There is no vaccine against west Nile encephalitis or meningitis

SUMMARY:

Disease	Causative agent	Route of transmission	symptoms	Lab diagnosis	Management	Vaccine
Polio	Polio virus • ssRNA • non enveloped	Fecal-oral route or inhalation	Asymptomatic in most, rarely causes aseptic meningitis and flaccid paralysis	Samples: CSF, blood, stool Test: PCR • no serology	No antiviral	Adults: Inactivated polio vaccine Children: live-attenuated polio vaccine (gives IG-A immunity)
Viral encephalitis	Herpes • dsDNA • enveloped	--	Fever, headache, seizure, high mortality	CSF shows: • normal glucose • high protein • lymphocytosis	Acyclovir	--
Viral encephalitis	Rabies • Rhabdovirus • ssRNA • enveloped	Rabid animal bites (bats and dogs)	Stages: 1.Incubation 2.Prodromal (fever, malaise, etc) 3.Symptoms 4. recovery is rare	PCR for saliva IF for rapid detection Histopathology: negri bodies serology	--	For animals, prophylaxis, and after bite
West Nile	Arbo virus	Reservoir: birds Vector: mosquito	--	Isolation of blood, CSF, and saliva IgM AB	--	• Tick borne encephalitis vaccine • Japanese encephalitis vaccine

QUIZ:

1. Patient comes in with fever, headache, nausea, and a stiff neck. You test his CSF and its clear with lymphocytosis. After talking to the patient you discovered that he wasn't vaccinated as a child, and has recently travelled to India, a very crowded city with poor hygiene. What is the causative agent of his illness?
    a. Herpes
    b. Poliovirus
    c. Neisseria meningitidis
    d. Streptococcus pneumonaie

2. Herpes Simplex is a virus that is ..
    a. dsDNA
    b. ssDNA
    c. ssRNA

3. Which vaccine do you use for children?
    a. Inactivated polio virus
    b. Live attenuated polio virus

4. A vet comes into the ER with fever, headache, malaise, and hydrophobia. Upon further inspection you find that he has viral encephalitis due to a ssRNA virus. What could possibly be the route of transmission?
    a. Rabid animal bite
    b. Fecal-oral
    c. Inhalation
    d. Non of the above

Answers:
1. B
2. A
3. B
4. A

THANK YOU FOR CHECKING OUR WORK, BEST OF LUCK!

Hamad Alkhudairy

Shrooq Alsomali
Shatha Alghaihb
Rehab Alanazi
Najd Altheeb

Doctors slides

If the plan doesn't work, change the plan but never THE GOAL.