MICROBIOLOGY
TEAM 432

Lecture (3)

Viral Infections of CNS

Color guide:

- Very important
- Additional information
- Male doctor's notes
- Female doctor's notes
- Gray not mentioned

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Viral Infections of CNS

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Objectives:

Acute viral infections of the CNS.

1. **Aseptic meningitis & paralysis ;**
   - A. **enteroviruses & polioviruses**
2. **Encephalitis;**
   - A. **herpes simplex virus**
   - B. **Rabies virus.**
   - C. **arboviruses (West Nile virus) .**

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

Mind map
(Viral Infections of CNS)

- **Enteroviruses**
  - Aseptic meningitis
  - Flaccid paralysis
  - Asymptomatic
  - Encephalitis
- **Poliovirus**
  - Aseptic meningitis
  - Flaccid paralysis
  - Asymptomatic
  - Abortive poliomyelitis
- **Herpes simplex virus -1**
  - Encephalitis
- **Arthropod-Borne Viruses**
  - Encephalitis
- **Arboviruses**
  - Aseptic Meningitis
  - Encephalitis
  - Asymptomatic
  - Fever, Rash & arthralgia
  - Hemorrhagic fever with or without hepatitis

Virus neurological diseases:

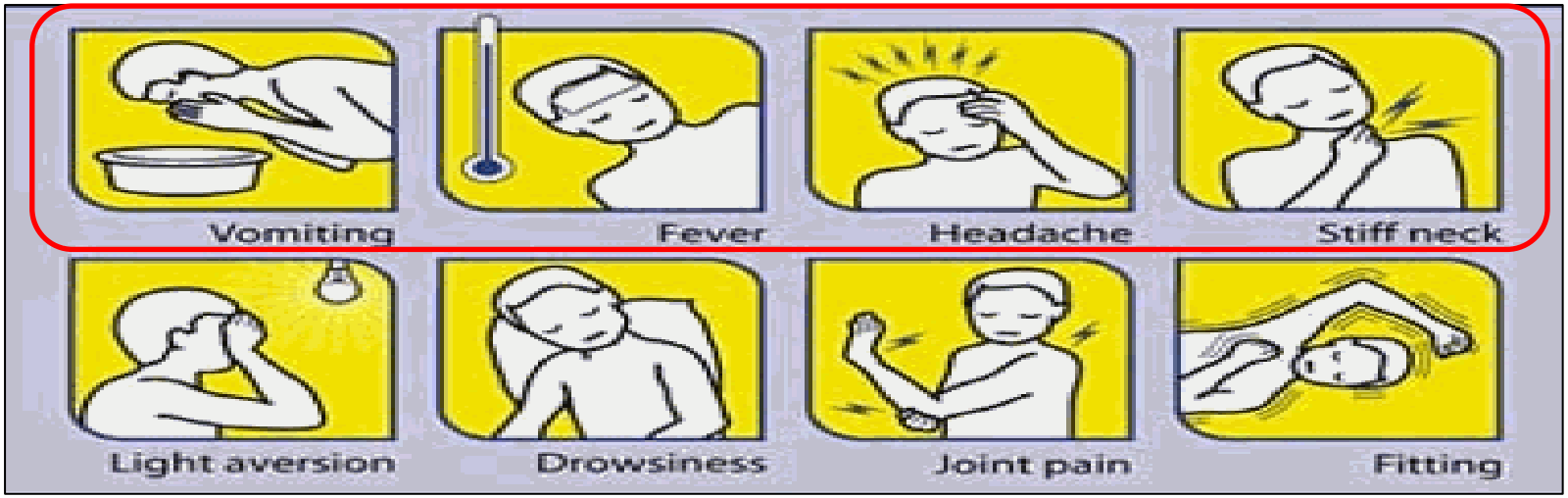
- Acute viral infections of the CNS.
- Chronic virus neurological diseases.
- Neurological diseases precipitated by viral infections.

Meningitis

Etiology

Infectious agents ;	Non-infectious agents
•bacteria*" most sever"* ,viruses *"most common"* ,fungi protozoa	

Symptoms



Viral Meningitis	Bacterial Meningitis
• Aseptic* meningitis • Caused by virus. • Less severe • Resolves without specific treatment within a week or two	• Caused by bacteria • Quite severe and may result in a) brain damage b) hearing loss c) learning disability • It would also causes death

Aseptic* :organism will not be identified by **routine** CSF stain and culture.

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

Viral Meningitis (Aseptic meningitis)

Etiological Agents:

- **Enteroviruses** "most common"
- Other :
  - -Mumps virus .
  - -Arboviruses.
  - -Herpes viruses.
  - -Human Immunodeficiency Virus.
  - -Lymphocytic choriomeningitis virus.

Enteroviruses

Picornaviridae

- Pico = small , rna =RNA
- A family of viruses.
- Nonenveloped , icosahedral , ss (+) RNA

Include ;

- Poliovirus(1, 2&3 types)
- Coxsackieviruses (A&B)
- Echoviruses
- Enteroviruses (68-71) **most common**

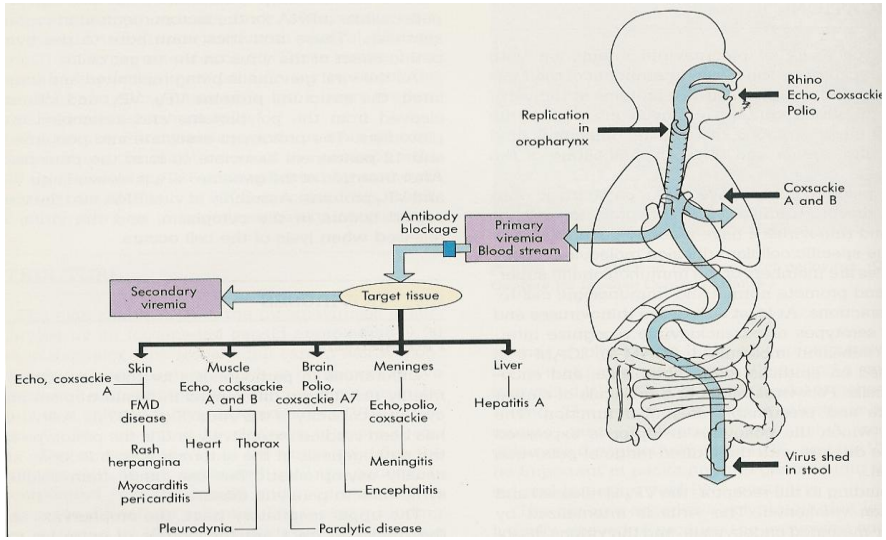
Epidemiology

Reservoir : Human	Spread : Fecal - oral route (mainly) Inhalation of Infectious aerosols (Crowded, Poor hygiene & Sanitation
Age : children > adults	Seasonal distribution: summer & fall

Enteroviral infections

Pathogenesis

1. Viruses replicate in the GIT lymph nodes
2. Migrate to blood = primary viremia
3. reach targeted organ in the CNS or excreted in the stool
4. secondary viremia



Asymptomatic Infections mainly

Diseases:

- *Neurologic Diseases*
- *NON-Neurologic 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
Acute Flaccid Paralysis	1-3	7,9	2-5	2,4,6,9,11,30	70,71
Encephalitis	rarely	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

Aseptic meningitis :

- **Comments neurologic disease**
- **Usually mild symptoms and recovery is complete except in neonates and if its associated with encephalitis.**

Poliovirus

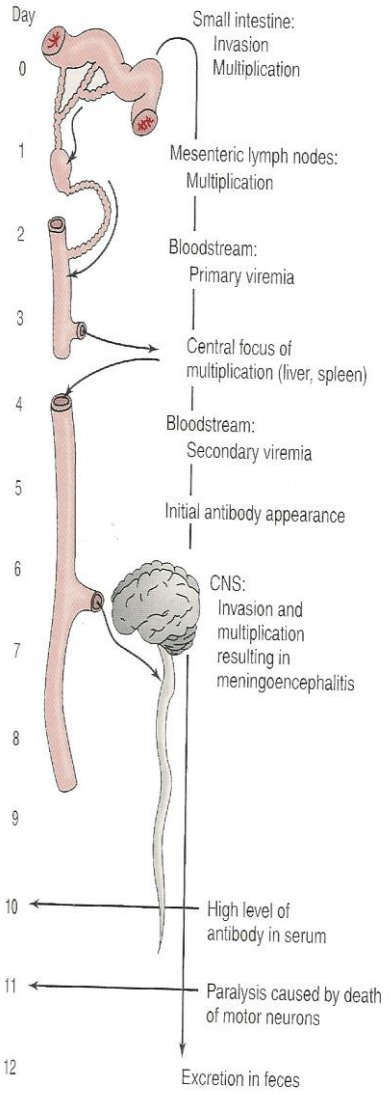
Pathogenesis of polio:

Pathway to CNS by: -Blood -Peripheral nerves

Causing destruction of motor neurons of AHCs =paralysis

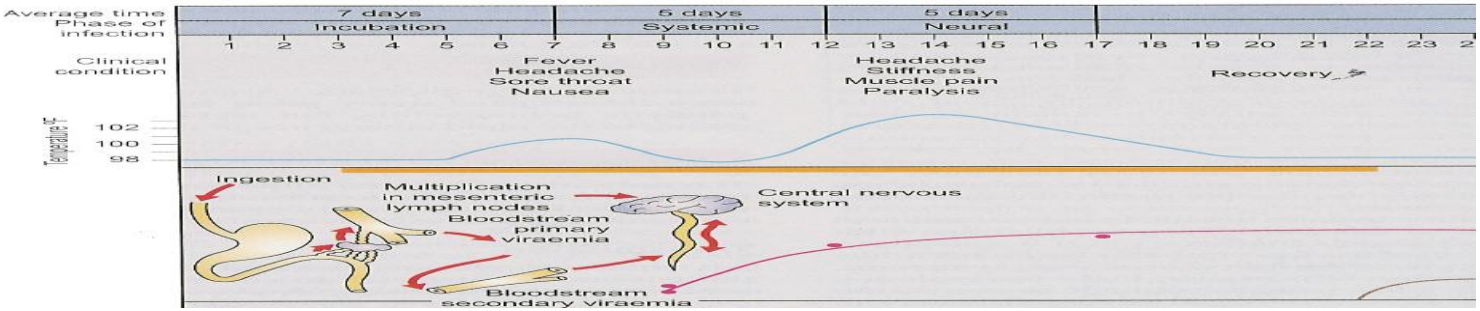
Rarely affects brain stem (bulber poliomyelitis)

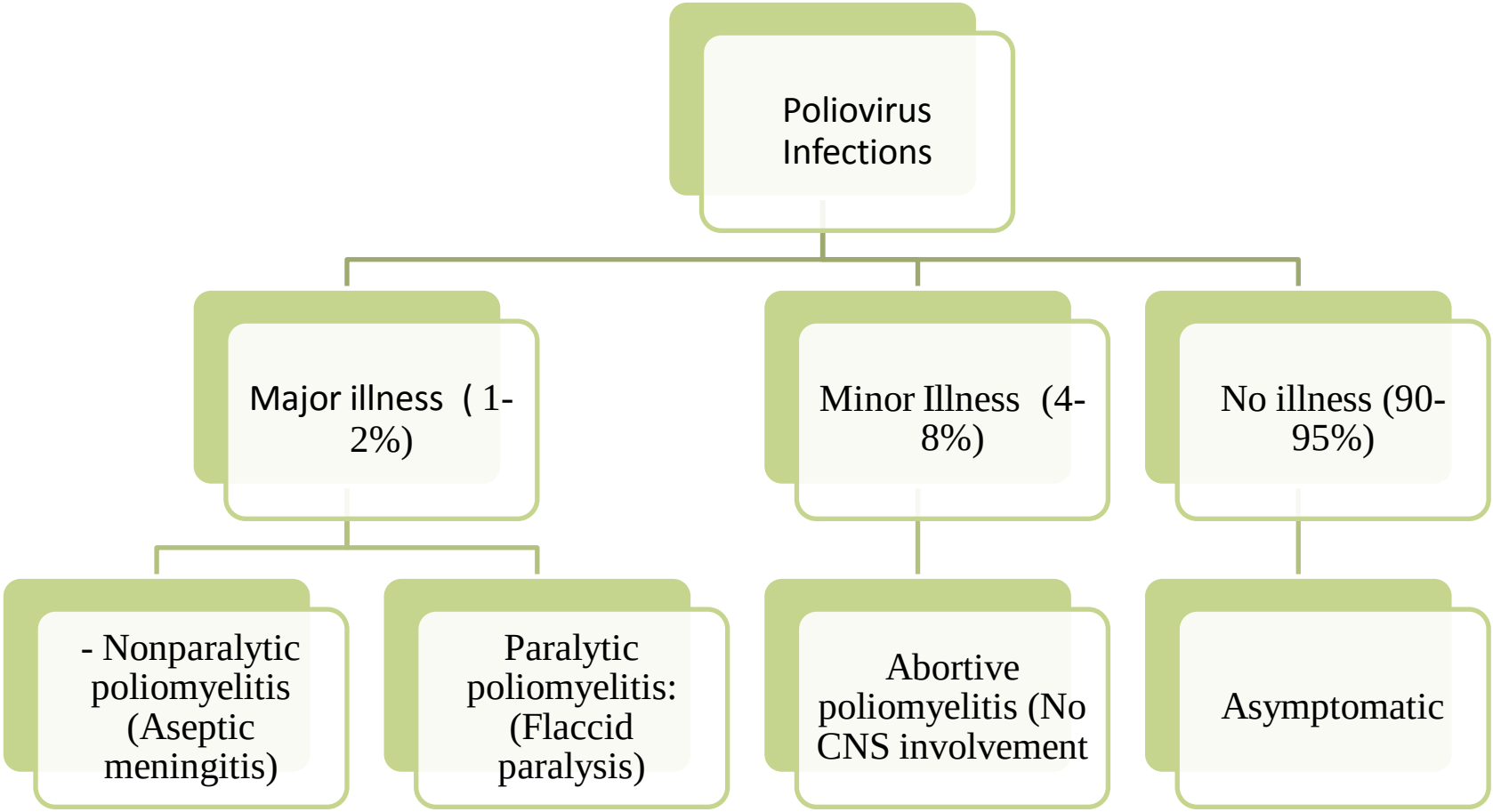
Immunity: • **IgA & IgG** = Lifelong type-specific immunity specific for poli 1 or 2 depending on the agent.



Phases:

1. **Incubation period (7-15 days) : non specific ilness "symptoms are not related to the CNS " due to primary viremia**
2. **prodromal period (2 days) :no illness**
3. **Specific illines period : symptoms are a result of invasion of the CNS "meningitis , acute flaccid Paralysis" due to secondary viremia**
4. **Recovery period**




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

Lab Diagnosis of Enteroviruses

- **Virus isolation (Gold standard):-**
  - Samples: Stool (best- because of the high concentration), Rectal, throat swabs & CSF.
  - Inoculate in monkey kidney cell liner (MKC) & humen diplococcic fibroblast (HDF).
    - * (All EVs grown except some strains of Cox A viruses).
  - Observe: for CPE (Cyto Pathological Effect).
  - Identify: the type by Neutralization Test

Because the Enteroviruses grow on live tissue, so it is cultured in tissue from monkey kidney cells & Human diplococcic fibroblast.

- **CSF in aseptic meningitis shows:-**
  - Lymphocytosis
  - Glucose level is normal to slightly decreases.
  - Protein level is normal or slightly increases.
  - Isolation rate is variable.
  - EV RNA detected in CSF by RT-PCR "faster" (special for RNA in which RNA is transferred into DNA).

- **Serology** (limited value).

Management

❖ **Treatment:-**

No antiviral therapy (just symptomatic treatment).

❖ **Prevention:-**

Sanitation & Hygienic measures.

Poliovirus vaccines (PV):

- Inactivated polio vaccine (IPV) – Killed: (called: Salk) (route: S/C or I.M)
- Live attenuated polio vaccine (OPV): (called: Sabin) (route: oral)

(4 doses of PV: at 2, 4, 6 or 18 ms. & 4 or 6 yrs.)

Polio Vaccination of Adults:

Indications:

- Travelers to polio-endemic countries
- Health care workers -They should receive IPV.

- IPV vaccine is given to Adult & Immunocompromised Pt.
- OPV vaccine is given to children.

Pediarix Vaccine:

is pediatric vaccine for intramuscular administration containing a combination of Diphtheria (D), Tetanus (T), Acellular Pertussis (aP), Hepatitis B (HB), and Inactivated Poliovirus Vaccine (IPV).

Important Features of Polio Vaccines

Attribute	Killed (IPV)	Live (OPV)	Notes
3 types (trivalent)	yes	yes	cover all 3 types of Polio "specific IgA & IgG for each type"
Prevents Disease	yes	yes	
Induces humeral IgG	yes	yes	
Route of administration	injection	oral	
Induces intestinal IgA	no	yes	prevent replication of polios, it interfere with fecal – oral transmission, which stops its transmission to community
Interrupts transmission	no	yes	
Affords secondary protection by spreading to others	no	yes	Means that when it is spread to another person, it provides protection called secondary protection
Reverts to virulence	no	Yes (rarely)	
Causes disease in immunocompromised pt.	no	yes	immunocompromised pt. IPV is used
Co-Infection with other EVs may impair immunization	no	yes	
Requires refrigeration	no	yes	
Duration of immunity	shorter	longer	
Adverse reaction	Local reaction at site of injection (no risk of paralysis)	Vaccine – associated paralytic poliomyelitis in adult, immunocomprised pt.	That's why adult & immunocompromised pt. should be given IPV

Viral Encephalitis

- Encephalitis:- is an acute inflammation of the brain.
- Etiological Agents:
  - Enteroviruses
  - Herpes viruses (Type 1)
  - Rabies virus
  - Arboviruses
  - Others

HSV Encephalitis

The only viral infection that is treated by anti-viral infection

- Caused by: Herpes simplex virus -1(HSV-1).
  - Characterized by: double strand DNA, Enveloped, Icosahedral Virus
- Clinical presentation:
  - Fever, Headache, Vomiting, Seizures & altered mental status.
  - High mortality rate.
- Diagnosis
  - Magnetic resonance imaging (MRI).
  - CSF analysis shows: Lymphcytosis, normal glucose & high Protein.
  - Detection of HSV-1 DNA by PCR.
- Treatment
  - Acyclovir (at least for 3 days).

Rabies Encephalitis

Is an acute fatal encephalitis

Caused by: Rabies virus , Rhabdoviridae

- Characterized by: single strand (-) RNA genom, Helical nucleocapsid, Enveloped virus
- Bullet shape

Epidemiology:

- Reservoir:
  - cats & dogs
  - Raccoons, Foxes, Wolves & Bats

Transmission:

- Common route:
  - Bite of a rabid animal
- Uncommon route:
  - Inhalation while in a bat-infested cave
  - Corneal transplant

Pathogenesis: after it enters through different routes → through PNS → CNS (forming negri bodies)

It goes under 4 stages:

Incubation Period	Prodromal Phase	Neurological Phase	Recovery

• 1-3 Ms > longer	• Fever, Headache, Malaise, Anorexia, Nausea & Vomiting
	• Abnormal sensation around the wound
		• Encephalitis
		  • Nervous, ↑lacrimation, Hydrophobia ↑convulsion, coma & death
		• Paralytic Illness
		  • Ascending, Death, Associated with bat bite.
			• Extremely Rare

Rabies Encephalitis

Laboratory Diagnosis:

- RT.PCR: Rabis RNA in saliva.
- Rapid virus antigen detection (Immunofluorescence '' IF '')
  - Neck skin biopsy.
  - Corneal impressions.
  - Brain tissue.
- Histopathology: neuronal brain cells intracytoplasmic inclusions (**Negri bodies**)
- Virus cultivation

Prevention:

- Control measures against canine rabies include:
  - Stray animals control.
  - Vaccination of domestic animals.
- Pre-exposure prophylaxis (Vaccine) :
  - Given to persons at increased risk of rabies e.g. vets, animal handlers etc.
- Post-exposure prophylaxis:
  - Wound treatment
  - Passive immunization: Human anti-rabies immunoglobulin applied around the wound & IM.
  - Active immunization: Human Diploid Cell Vaccine (HDCV) with 5 - 6 doses

Arthropod-Borne Viruses

Caused by:	Epidemiology:	Infections:	Diseases:
• Arboviruses > 500 Vs	• Reservoir: Wild birds & Mammals • Vector: Mosquito, ticks & Sand-fly • Transmission: bite of infected vector	• Asymptomatic Infections	• Fever, Rash & arthralgia • Hemorrhagic fever with or without hepatitis • 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	Mosquito	Birds	Europe, Africa Middle East Asia, America

West Nile virus

Family: Flaviviridae.

Febrile "fever" illness →meningitis , encephalitis

Laboratory Diagnosis

1. Isolation (Gold standard)
- Samples are taken from: blood, CSF, Viscera
- Cell culture:
  - →CPE (Cyto Pathological Effect)
  - →Identify by Immunoflurecence (IF)

2. IgM -AB - ELISA, IF: (most used)

3. RT-PCR to examine Arbovirus RNA

Prevention:

- Vector Control:
  - Elimination of vector breading sites
  - Using insecticides
  - Avoidance contact with vectors (repellants, net)
- Vaccines:
  - Tick-borne encephalitis vaccine
  - Japanese encephalitis vaccine

summary

- Infection is more common during summer in children, and low hygiene is a risk factor.
- They spread mainly by oral-fecal route.
- 90-95% of poliovirus infections are asymptomatic with no illness, only 1-2% of infections manifest as major diseases (Aseptic meningitis or Paralytic poliomyelitis) & about 4-8% are minor illness with no CNS involvements.
- Pathogenesis of poliovirus is from blood or peripheral nerves then it enters the CNS and damage the AHCs which might lead to paralysis.
- Lab diagnosis of enteroviruses include:
  - Isolation of virus (stool sample is taken).
  - Enteroviruses RNA detected by RT-PCR
  - Serology (limited value – not very useful).
  - CSF analysis.

summary

	HSV encephalitis	Rabies encephalitis	Arboviruses encephalitis
	ds DNA enveloped	Ss RNA enveloped (bullet shape)	Ss RNA enveloped - e.g. West Nile virus
Reservoir	Human	Dogs, cats and bats (transmitted by bite)	Wild birds and mammals (mosquitoes are vectors)
Diagnosis	MRI - CSF analysis (lymphocytosis, ↑protein) - PCR	IF (detection of virus antigen) - RT.PCR (rabies RNA in saliva) - Histopathology (negri bodies) - Virus cultivation	Isolation (Gold standard) - IF and ELISA (IgM antibodies) - PCR
Treatment/ prevention	Acyclovir	**prevention** Human anti-rabies immunoglobulin -Human Diploid Cell Vaccine	Tick-borne encephalitis vaccine - Japanese encephalitis vaccine

Questions

1. A 7 year old male child came to the hospital with inability to move and limited sensation , he has a history of fever headache and nausea .The lab PCR results came with positive Non enveloped , icosahedral , ss (+) RNA , what is the most likely causative agent

a. Poliovirus
b. Arboviruses
c. HSV(Herpes simplex virus -1)

2. The most common type of meningitis is?

A Viral
B- Fungal
C- Bacterial
D- Parasitic

3. What is the only viral infection of the CNS that can be treated through drugs?

A- Rabis encephalitis
B- HSV encephalitis
C- Arboviral encephalitis
D- Meningitis caused by Coxsackievruses A

Qs	Answer
1	A
2	A
3	B

For any problems and suggestions please contact:

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Thank you