Lecture – 3

Viral Infections of CNS

Microbiology Team 430

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Virus neurological diseases:

- ***Acute viral infections of the CNS:*** *e.g. Meningitis, paralysis & encephalitis.*
- ***Chronic virus neurological diseases.***
- ***Neurological diseases precipitated by viral infections.***

Meningitis

- **Caused by:**
  - **Infectious agents:** bacteria, viruses, fungi, protozoa.
  - **Non-infectious agents.**

	Viral meningitis	Bacterial meningitis
Called	Aseptic meningitis	Pyogenic meningitis (septic meningitis).
Etiological Agents:	- Most commonly: ***Enteroviruses*** . - Others: Mumps virus. Arboviruses. Herpes viruses (**Type 2**). Human Immunodeficiency Virus. Lymphocytic choriomeningitis virus.	- ***Neisseria meningitides*** - ***Sterptococcus pneumoniae*** - ***Hemophilus influenzae***
Severity	Less sever	More sever
	More common	Less common
Treatment	- No specific treatment (spontaneously relieve). - Symptomatic treatment within a week or two.	Embirical Treatment
Complications	No complications	It may result into: - Brain damage. - Hearing loss. - Learning disability. - Death.
CSF analysis		
Color (Normal is clear)	Clear	Cloudy
Cells/mm^3 (Normal <5)	↑ in cellularity (100 - 1000lymphocytes)	High\ very high (200 – 20000 neutrophills)
Glucose (mg/dl) (Normaly: 45-85)	Normal	Low < 45
Protein (mg/dl) (Normaly:15-45)	Normal / high (50-100)	High > 100

Enteroviruses:

- **Family:** *Picornaviridae*

  Include:
  - Poliovirus (1, 2&3 types).
  - Coxsackieviruses (A&B).
  - Echoviruses.
  - Enteroviruses (68-71).
- **Characters:** Non enveloped, icosahedral, ss "single strand" (+) RNA.

❖ **Epidemiology:**

- Reservoir: Human
- Spread due to:
  - Fecal - oral route (mainly).
  - Inhalation of Infectious aerosols.
- Group age: children > adults. "due to crowded, poor hygiene & sanitation"
- Seasonal distribution: summer & fall.

❖ **Pathogenesis**:

Viruse enters via oral route → GIT → casuing 1ry viremia → target tissue (endothelial system) → causing 2ry viremia → CNS.

Poliomyelitis is a highly infectious viral disease that may attack the CNS and symptoms range from a mild nonparalytic infection to total paralysis.

Pathogenesis of poliovirus:

- Transmitted to CNS by:
  - Blood (septicemia).
  - Peripheral nerves (due to Muscle infection).
- Causing destruction of motor neurons of AHCs (causing paralysis).
- Rarely affects brain stem (bulbar poliomyelitis).
- **It goes through phases:**

Incubation (7 days)	Systemic (5 days)	Neural (5 days)
Non specific symptoms (Fever, Headache, Sore throat, Nausea) / 1-2 weeks.		Headache, Stiffness, Muscle pain, Paralysis

Immunity: IgA & IgG = Lifelong type-specific immunity

IgA & IgG provides lifelong – specific immunity for the body against all types of polio virus.

❖ ***Enteroviral disorders***

- **Infections:** Asymptomatic Infections.
- **Diseases:**

Neurologic Disease	Cardiac and muscular	Skin and mucosa infections	Acute hemorrhagic conjunctivitis	Respiratory tract infections.
-Aseptic meningitis. -Paralysis. -Encephalitis.	-Pleurodynia (epidemic myalgia). - Myocarditis, pericarditis	-Herpangina. -Hand, foot, and mouth disease. –Exanthems.		

❖ **Poliovirus Infections:**

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

❖ **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).

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

☒ All EVs grown except some strains of Cox A viruses.

- Observe for CPE (Cyto Pathological Effect).
- Identify the type by Neutralization Test

➢ **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) (Salk, Killed) (route: S/C or I.M)
  - Liveattenuated 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 & Immunocompermized 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	Because we need to cover all 3 types of poliovirus "specific IgA & IgG for each type"
Prevents disease	Yes	Yes	
Induces humoral IgG	Yes	Yes	
Route of administration	Injection	Oral	
Induces intestinal IgA	No	Yes	Presence of intestinal IgA will prevent wide replication of poliovirus, so it will interfere the fecal - oral transmission which stops its transmission to community.
Interrupts transmission	No	Yes	
Affords secondry protection by spread to others	No	Yes	Means that when it is spread to another person it provide protection that called (secondry protection)
Reverts to virulence	No	Yes (Rarely)	

Causes disease in the immuncompermized pt.	No	Yes	So with immunocompermized pt (either children or Adult) 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 , immunocompermized Pt.	That's why Adult & immunocompermized Pt should begiven IPV.

Viral Encephalitis

❖ **Etiological Agents:**
- Enteroviruses.
- Herpes viruses (**Type 1**).
- Rabies virus.
- Arboviruses.
- Others.

Encephalitis is an acute inflammation of the brain.

HSV encephalitis

❖ **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 (Dx):**
- 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).

The only viral infection that is treated by Antiviral therapy

Rabies encephalitis

Is a Fatal acute encephalitis

❖ **Caused by:** *Rabies virus , Rhabdoviridae*
- **Characterized by:** single strand (-) RNA genom, Helical nucleocapsid, Enveloped virus.

❖ **Epidemiology:**
- Reservoir:
  - cats & dogs(most important)
  - Raccoons, Foxes, Wolves & Bats.
- Transmission: (it is a zoonotic disease)
  - 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)

Usually it enters the hippocampus in CNS

— **It goes under 4 phase :**

1-<u>The incubation period</u>: 1-3 m or longer

- Fever, Headache, Malaise, Anorexia, Nausea &Vomiting.
- Abnormal sensation around the wound.

3-<u>Neurological phase</u>:

a) Encephalitis Nervous,↑ lacrimation , ↑salivation, hydrophobia ,convulsion , coma & death .
b) 2-Paralytic illness: Ascending, Death, (associated with Bat bite).

4- <u>Recovery:</u> Extremely rare

❖ **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) :
  Gives 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.

<u>Arthropod –borne Viruses</u>

❖ **Caused by:** Arboviruses > 500 Vs

❖ **Epidemiology:**

- <u>Reservoir:</u> Wild birds & Mammals.
- <u>Vector:</u> Mosquito, ticks& Sandfly.
- <u>Transmission:</u> bite of infected vector.

❖ **Infections:**

➢ Asymptomatic Infections.

➢ Diseases:

- Fever, Rash & arthralgia.
- Hemorrhagic fever with or without hepatitis.
- CNS disease (meningitis & encephalitis).

ArboVs associated with CNS disease:

Viruses	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
- ***Diagnosis***:
  - Lab. Methods :
    - A. Isolation (Gold standard)
      - Samples are taken from: blood, CSF, Viscera.
      - Cell culture: → CPE (Cyto Pathalogical Effect)
        → Identify by Immunoflurecence (IF).
    - B. IgM -AB - ELISA, IF: (most used)
    - C. 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

- Aseptic meningitis is caused by enteroviruses:
  - Enterovirus.
  - Poliovirus.
  - Coxsackivirus.
  - Echovirous.
  - Also caused by HSC type 2
- 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.

Aseptic meningitis CSF analysis

color	Clear
Cells/mm^3	increase100-1000 (mainly lymphocytes)
Protein	Normal/slightly high
Glucose	Normal

- prevention of polio is by taking a vaccine :
- IPV (killed): given IM/S.C
- OPV (live): given orally (contraindication to immune-compromised patients)

- Viral encephalitis is caused by:
  - Enteroviruses
  - Herpes viruses (Type 1)
  - Rabies viruses
  - Arboviruses (e.g. West Nile virus)
- Negri bodies are diagnostic feature of rabies encephalitis.

	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 (by bite)	Wild birds and mammals (mosquitoes are vectors)
Diagnosis	- **MRI** - **CSF analysis** (lymphocytosis,↑ protein) - **PCR**	- **IF** (detection of virus antigen) - **PCR** (rabies RNA in saliva) - **Histopathology** **(negri bodies)** - **Virus cultivation**	- **Isolation** (Gold standard) - **IF and ELISA** (IgM antibodies) - **PCR**
Treatment/ prevention	-Acyclovir	-Human anti-rabies immunoglobulin -Human Diploid Cell Vaccine	-Tick-borne encephalitis vaccine -Japanese encephalitis vaccine

Good Luck ☺