Lecture 9

Hepatitis A & E

Microbiology team 430

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HEPATITIS

Viral hepatitis:

- As part of generalized infection –systemic infection including hepatitis- (caused by: CMV, EBV, Yellow fever virus).
- Infect primarily the liver due to:
  - Fecal-borne hepatitis (A & E). "fecal-oral route"
  - Blood-borne hepatitis (B, C & D).

CMV: Cytomegalovirus
EBV: Epstein Barr Virus

FECAL-BORNE HEPATITS

Hepatitis A Virus (HAV)	Hepatitis E Virus (HEV)
- **Genus**: *Hepatovirus* - ***Family:*** *Picornaviridae*	- ***Genus***: *Hepevirus* - ***Family:*** *Hepeviridae*
Nonenveloped, Icosahedral, ss,+ sense RNA, One serotype.	

HEPATITIS A VIRUS (HAV)

- Short incubation period hepatitis.(in contrast to other viral hepatitis)
- Infectious hepatitis.
- Epidemic hepatitis.

❖ ***Epidemiology***:

- **Distribution:** A worldwide, endemic in tropical countries.
- **Transmission:**
  - Fecal-oral route (due to Contaminated food &water) [major route].
  - Sexual contact (homosexual men).
  - Blood transfusion (v.rarely).
- **Age group:**
  - In developing countries "3rd world countries": children (due to poor hygiene).
  - In developed countries "1st world countires": young adults.

❖ ***Pathogenesis:***

Enter through the *mouth* → reaches the *gut* → *affect epithelial cells* → *invade to the blood causing viremia* → disseminates to *liver* → multiply in *hepatocytes* → activation of immune system → producing *cell mediated immunity (CMI)* → Damage of virus-infected hepatocyte → causing an increase ↑in liver enzymes (ALT ,AST & Bilirubin).

❖ ***Manifestations:***

- Hepatitis:
  - Commonly Asymptomatic
  - Symptoms increase with age
  - Incubation period (IP): 2-6 Ws (viruses present in the feces 1-2 weeks before the symptoms appear)
  - Pre-icteric [Pre-Jaundiced] phase: (prodrome or early symptoms): non-specific symptoms (fever, fatique, nausea, Vomiting & right upper quadrant pain (RUQP).
  - Icteric phase: dark urine, pale stool, jaundice

These three stages – except IP- are the typical presentation of all types of hepatitis, they differ only in IP.

- So patients with [Hepatitis A] are commonly present Asymptomatic or with anicteric infection (mild infection without jaundice) → common in children.
- Or they could be Symptomatic (with jaundice, the risk will increase with age).

❖ ***Prognosis:***

- Self-limited disease.
- Fulminant hepatitis (sudden sever damage to the liver) → rare.
- Mortality rate ~ 0.1 - 0.3%
- No chronicity or malignancy changes.

❖ ***Lab Diagnosis:***

- Serology:
  - Anti-HAV IgM → marked for Current infection.
  - Anti-HAV IgG → marked for immunity (either by vaccine or previous infection).

❖ ***Management:***

- Treatment: Supportive therapy.
- Prevention:
  - Sanitation & hygiene measures.
  - Vaccine:
    - Inactivated (killed).
    - Given IM at (6 -12 Months).
    - >1 Y of age.
    - **Side effect:** mild local reaction.
    - **Indication:**
      - Patients at high risk of infection.
      - Patients at high risk of severe disease.
  - HIg (human immunoglobulin) → passive immunization:
    - Given before or within 2 Weeks of exposure.
    - Indication: 1) travellers. 2) Unvaccinated, exposed patients.
  - A combination vaccine (HAV &HBV).

For children < 1 year → HIg is used.
For people from 1 -40 yrs → Vaccine is given
For old people > 40 yrs → both (vaccine & HIg) are given

HEPATITIS E VIRUS

- **Family**: Hepevirus ,Hepeviridae

❖ ***Epidemiology:***

- outbreak of waterborne & sporadic cases of VH
- **Age group:** young adults.
- **Transmission** (4 routes)**:**
  - Waterborne (most common, due to fecal rout & contaminated water).
  - Zoonotic foodborne. (Meat from an infected animal).
  - Bloodborne (fecal born route).
  - Perinatal.

❖ ***Clinical features:***

- Similar to HAV infection except:
  - Longer IP =4-8 Ws.
  - Fulminant disease.
  - Mortality rate is 10 times > HAV (higher).

~ 1-3% [20%in pregnancy]. (Because the immunity is decreased in pregnancy).

❖ ***Lab Diagnosis:*** ELISA → Anti-HEV IgM.

❖ ***Management:***

- **Treatment:** Not specific.
- **Prevention:**
  - Sanitation & hygiene measures.
  - No HIg.
  - No vaccine.

In the diagnosis of hepatitis we aim for detection of Ag, Ab in the sample (commonly blood) due to immunoassay tests (generally).

Herpes-viridae

- Epstein- Barr virus (EBV).
- Cytomegalovirus (CMV).
- **Description:** dsDNA, Icosahedral & Enveloped Virus.

Epstein – Barr Virus (EBV)

- It is lymphotropic .
- It has oncogenic properties: (progress into malignancies).
  - Burkitt's lymphoma
  - Nasopharyngeal carcinoma

Latent EBV presents in lymphocytes, that's why it is called "lymphotropic"

❖ *Epidemiology:*

- **Distribution:** worldwide
- **Transmission:**
  - Saliva [kissing disease]
  - Blood [rarely]
- **Age:** Depending on Socio-economic status (SE):
  - Low SE class → early childhood.
  - High SE class → adolescence.

❖ *Clinical Features:*

1- Immunocompetent host:	*2- Immunocompromised host* :
○ Asymptomatic. ○ Infectious mononucleosis [glandular fever]. ▪ Mainly in teenagers & young adults ▪ IP = 4-7 weeks ▪ Fever, pharyngitis, malaise, LAP, hepatosplenomegaly & abnormal LFT ± hepatitis. (Non specific symptoms). ○ Complications: ▪ (acute air way obstruction, splenic rupture, CNS infection) ▪ Chronic EBV infection.	• Lymphoproliferative disease (LD). • Oral hairy leukoplakia (OHL).

❖ *Diagnosis (Dx):*

- **Hematology:** shows ↑ WBC, lymphocytosis, (Atypical lymphocytes).
- **Serology:**
  - Non-specific Antibody test → Heterophile findings: positive Heterophile Abs [they're –ve in CMV], OR Paul-Bunnell or Mono-spot test
  - EBV-specific AB test: IgM Abs to EBV capsid antigen

❖ *Management:*

- **Treatment:** Antiviral drug are *not effective* in *Infectious mononucleosis* [IMN]
- **Prevention:** No vaccine.

Because, it results from CMI not replication of the virus.

Cytomegalovirus CMV

❖ ***Special features:***

- Its replication cycle is longer.
- Infected cell enlarged with multinucleated. [cyto=cell, megalo=big]
- Resistant to acyclovir (acyclovir used in treatment of herps type 1 &2).
- Latent in monocyte, lymphocyte & other.

❖ ***Epidemiology:***

- **Distribution:** worldwide.
- **Transmission:**
  - Early in life: due to Transplacental transmission, Birth canal and Breast milk.
  - Young children: saliva (most common).
  - Later in life: sexual contact.
  - Blood transfusion & organ transplant.

❖ ***Clinical features:***

- **Acquired Infections:**
  - Immunocompetent host:
    - Asymptomatic.
    - Self-limited illness:
      - Hepatitis.
      - Infectious mononucleosis like syndrome [Heterophile AB is –ve]
  - Immunocompromised host:
    - Encephalitis, Retinitis, Pneumonia.
    - Hepatitis, Esophagitis, Colitis.
- **Congenital Infections:** (if the infant got the infection during pregnancy).

❖ ***Lab Diagnosis:***

- **Histology:** Intranuclear inclusion bodies [Owl's eye].
- **Culture: (most used)**
  - In human fibroblast.
  - CPE (cytopathological effect).
  - Shell Vial Assay.
- **Serology:**
  - Antibody (AB) → (IgM: indicates current infection and IgG indicates immunity due to previous exposure only).
- Antigen (Ag) →CMV pp65 Ag by IFA (best for immunocompromised patients)
- **PCR.**

❖ ***Management:***

- **Treatment:**
  - ***Ganciclovir:*** effective in treating severe CMV infection.
  - ***Foscarnet:*** the 2_{nd} drug of choice. (if the virus is resistant to Ganciclovir)
- **Prevention:**
  - Screening:
    - Organ donors.
    - Organ recipients.
    - Blood donors.
  - Leukocyte-depleted blood. (Blood without leukocyte).
  - Prophylaxis: Ganciclovir, CMVIG (CMV immunoglobulin - passive immunization).
  - No vaccine.

Arthropod –borne Viruses (Arboviruses)
Yellow Fever virus

- Family: Flaviviridae
- Asymptomatic to Jaundice + Fever ± hemorrhage ± renal failure

❖ ***Epidemiology:***

- Tropical Africa & South America
- Jungle Yellow Fever → affects monkeys.
- Urban Yellow Fever → affects human.

Jungle Yellow Fever	Urban Yellow Fever
▪ **Vector:** mosquito. ▪ **Reservoir:** Monkeys. ▪ **Accidental host:** humans. ▪ It is a disease of Monkeys.	▪ **Vector:** mosquito. ▪ **Reservoir:** human. ▪ It is a disease of humans.

❖ ***Lab Diagnosis:***

- **Lab. Methods:**
  - Isolation.
  - IgM -AB* - EIISA, IF: (most used).
  - Yellow Fever Virus - RNA by RT-PCR.

❖ ***Management:***

- **Prevention:**
  - ***Vector Control:***
    - Elimination of vector breading sites.
    - Using insecticides.
    - Avoidance contact with vectors (repellants, net).
  - 2-***Vaccines:***
    - Yellow Fever vaccine (Life attenuated vaccine "LAV", one dose /10 yrs).

Summary:

- Primary hepatitis infection is caused by hepatitis viruses A, B, C, D, E, F & G.
- All hepatitis viruses are human viruses except HEV which is zoonatic.
- Fecal borne hepatitis is caused by HAV and HEV.
- HAV infection:
  - It is non-enveloped with ss+ RNA, family is Picornaviridae
  - HAV is transmitted by fecal oral route →invade to the blood casing viremia → enter liver →causes Cell Mediated Immunity → Damage the hepatocytes which increases liver enzymes (ALT,AST, and Billibrubin)
  - IP is 2-6 weeks (short – in comparison with other viral hepatitis).
  - Diagnosis by serology →Anti HAV IgM indicates current infection and IgG indicates immunity (either by previous infection or vaccine).
  - HAV is self limiting and it is prevented by vaccine (killed) given IM or HIG.
  - Vaccine is given to pt with high risk to get infection or sever disease, while HIG is given for travelers & unvaccinated exposed pts.
- HEV infection:
  - It is a waterborne disease.
  - In comparison with HAV, HEV has longer IP 4-8 weeks, higher mortality rates, causes fulminant disease and there's no vaccine.
  - HEV Diagnosis by ELISA → Anti HEV IgM.
- Systemic infection including hepatitis is caused by CMV, EBV and Yellow fever virus (Arbovirus).
- EBV and CMV are enveloped with ds DNA, family: Herpes-Viridae.
- EBV infection:
  - It is a lymphotropic virus that can progress to malignancies: Burkitt's lymphoma and Nasopharengeal carcinoma.
  - EBV is most likely to be transmitted by saliva (kissing disease).
  - EBV diagnosis by CBC (↑ WBCs, lymphocytosis) and serology (specific ABs as IgM, non-specific ABs as heterophile +ve).
  - EBV infection in teenagers and young adults presents as Infectious mononucleosis (glandular fever) "find heterophile + ABs" but antiviral drugs are NOT useful in treatment.
- CMV infection:
  - CMV infection causes hepatitis and Infectious mononucleosis like syndrome "find heterophile -ve ABs".
  - CMV diagnosis is by histology (Intranuclear inclusion bodies "Owl's eye"), Serology (IgM in current infection and IgG in previous infection) and IFA (CMV pp65 Ag).
  - Treatment of CMV is by Ganciclovir.
- Yellow fever infection:
  - Yellow fever virus is an Arbovirus causing yellow fever infection Transmitted by mosquitoes (zoonatic infection).
  - Epidemiology : tropical Africa & south America
  - Diagnosis by ELISA and IF → IgM-Ab.
  - Yellow fever prevented by live attenuated vaccine.

Markers are very IMPORTANT

	HAV	HEV	EBV	CMV	Yellow fever
Description	Nonenveloped, Icosahedral, ssRNA		Enveloped, Icosahedral, dsDNA.		
Distribution	Worldwide, endemic in tropical area.	Outbreak in sporadic & water-born	Worldwide	Worldwide	Tropical Africa & south America
Transmission	Fecal oral rout	Fecal oral (waterborne)	Saliva & blood	Saliva (most commonly)	mosquito
Diagnosis	Detection of Anti HAV IgM by serology	Detection of anti-HE-IgM by ELISA	CBC→ ↑WBC (lymphocytosis) Serology → find heterophile +ve ABs	Histology → Intranuclear inclusion bodies [Owl's –eye]. serology → IgM Ab heterophile -ve Abs IFA → CMV pp65 Ag	ELISA and IF → IgM-Ab
Treatment	Supportive	Supportive	Supportive	*Ganciclovir Foscarnet*	Supportive
prevention	HIG, vaccine (killed)	No IG, no vaccine	No vaccine	*Screening, no vaccine*	Vaccine (LAV)

Good Luck ☺