Lecture – 10

Viral hepatitis (B, C, D, and G)

Microbiology Team - 430

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Hepatitis: Is inflammation of the liver

Viral Hepatitis

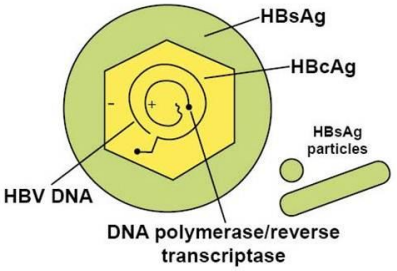
- Hepatitis feature of many diseases usually as a part of a generalized infection (systemic infections) e.g. cytomegalovirus, yellow fever, Epstein-Barr virus.
- However, some viruses primarily target the liver to cause viral hepatitis.
- Viral Hepatitis presents a similar clinical picture. Whatever the causative viruses.
- Laboratory tests can differentiate between different viruses.
- We have to determine the causative virus to know how to treat and what's the prognosis.

Viral hepatitis is divided into two large groups, based on the mode of transmission:

Enterically Transmitted	*ParenterallyTransmitted*
water born hepatitis	*blood born hepatitis*
hepatitis A and E viruses.	hepatitis B, C, D & G viruses

Hepatitis B viruses

- Family of *hepadna-viridae.*
- The complete virus particle is 42-nm in diameter.
- It consists of an outer envelope containing hepatitis B surface antigen (HBsAg).
- And internal core (nucleocapsid) composed of hepatitis B core antigen (HBcAg).
- The viral genome is small partially circular ds-DNA.
- There are eight known genotypes (A – H).
- Genotype D is the dominant in Saudi patients.
- The virus contains the reverse transcriptase and polymerase enzymes.



- **The serum of infected individual contains three types of hepatitis B particles:**
  - Large number of small spherical free HBsAg particles.
  - Some of these HBsAg particles are linked together to form filaments.
  - The complete HBV particles (Dane particles) → Has 2 Antigens,HBsAg and HBcAg .

Transmission of HBV:

1-Parentally (By blood):	2- Sexually (unprotected sex):	3- Perinatally (from mother to baby):	4- Verticaltransmission.
• Direct exposure to infected blood or body fluids (e.g. receiving blood from infected donor). • Using contaminated or not adequately sterilized tools in surgical or cosmetic practice (dental, tattooing, body piercing). • Sharing contaminated needles, razors, or tooth brushes.	• The virus is present in blood, semen and vaginal secretions.	• Infected mothers can transmit HBV to their babies mostly during delivery. • Breastfeeding is also way of perinatal transmission.	• Through placenta from mother to fetus.

➢ High risk groups INCULDES:

- Intravenously drug users.
- Hemodialysis patients.
- Patients receiving clotting factors.
- Individuals with multiple sexual partners.
- Health care workers with frequent blood contact.
- Individuals who exposed to tattooing, body piercing or cupping

Hepatitis B markers:

Types	Description
HBV DNA	Marker of infection.
Hepatitis B surface antigen (HBsAg)	Marker of infection.
Hepatitis B e antigen (HBeAg)	Marker of active virus replication, the patient is highly infectious; the virus is present in all body fluids.
Antibody to hepatitis B e antigen (Anti-HBe)	Marker of low infectivity, the patient is less infectious.
Antibody to hepatitis B core (Anti-HBc) IGg	It indicates exposure to natural hepatitis B infection not vaccine.
Antibody to hepatitis B core (Anti-HBcAg) IgM	confirmed recent infection (acute infection)
Antibody to hepatitis B surface antigen (Anti-HBs)	Marker of immunity.

- If the patient have [Hepatitis B e Antigen][HBeAg], he then must have [Hepatitis B surface antigen] [HBsAg]

The clinical outcome of HBV infection:

About 90 % of infected adults will develop acute hepatitis B infection, they'll become immunized and recover completely (self-limiting).	< 9 % of the infected adult, 90% of infected infants and 20% of infected children may progress to chronic hepatitis B.	1 % may develop fulminant hepatitis B, characterized by massive liver necrosis, liver failure and death

Lab diagnosis of hepatitis B infection:

- Hepatitis B infection is diagnosed by detection of Hepatitis B Surface Antigen[HBsAg] in the blood.(SEROLOGY)
  - ➢ Positive results must be repeated in duplicate.
  - ➢ Repeatedly reactive results must be confirmed by neutralization test.

> Neutralization test → protection testAAtest to determine the antimicrobialactivity of a serum.

- Additional lab investigations:
  1- Liver function tests (LFT)→ ALT
  2- Ultrasound of the liver.
  3- Liver biopsy to determine the severity of the diseases.(In case of chronic hepatitis)

In the acute phase:

- *BEST diagnostic way → serology*
- Acute viral hepatitis usually lasts for several weeks or< 6 months

Serological profile of acute HBV infection:

• Hepatitis B DNA→is the 1st marker that appears in circulation, 3-4 weeks after infection. • HBsAg→ is the 2nd marker that appears in the blood and persists for < 6 monthsthen disappears. • HBeAg→ is the 3rd maker that appears in circulation and disappears before HBsAg.	• Anti-HBcAb→is the 1st antibody that appears in the blood and usually persists for several years. • Anti-HBe→with the disappearance of HBeAg, it appears and usually persists for several weeks to several months. • Anti-HBs Ab→ is the last marker that appears in the blood, It appears few weeks after disappearance of HBsAg and persists for several years, it indicates immunity to hepatitis B infection.

In the Chronic phase:

- Best diagnostic ways → serology , Liver function tests (LFT) and Liver biopsy→ to determine the severity of the diseases
- Chronic hepatitis B is defined by the presence of HBsAg or HBV-DNA in the blood for > 6 months.

Chronic hepatitis B has three phases:

1- The replicative phase:	*2- Inflammatory phase:*	*3- Inactive phase:*
• The patient is positive for HBsAg, HBeAg and HBV-DNA. • High viral load (VL)> 10^5 copies/ml. • ALT is normal or nearly normal. • Liver biopsy shows minimal damage.	• HBsAg positive for > 6 months, HBeAg positive and Decline in HBV-DNA in the blood. • VL is > 10^5 copies/ml. • ALT is elevated. • The immune system attacks hepatocytes harboring the virus →Liver biopsy shows damage to hepatocytes.	• HBsAg positive. • Negative for HBeAg. • Positive for anti-HBe, HBV-DNA. • VL < 10^5 copies/ml. • Normal ALT

Clinical presentation:

Acute HBV	Chronic HBV
• Acute viral hepatitis usually lasts for several weeks or < 6 months. • Most acute hepatitis B are asymptomatic or anicteric. 1- *Anicteric phase (non- jaundice):* Low grade fever, anorexia, malaise, nausea, vomiting and pain at the right upper quadrant of the abdomen. 2- *Icteric phase (jaundice):* This is characterized by jaundice, dark urine and pale stool. 3- *Convalescent phase.(recovery)*	• Chronic hepatitis B is defined by the presence of HBsAg or HBV-DNA in the blood for > 6 months. • The majority of patients with chronic hepatitis B asymptomatic or have mild fatigue only • Symptoms include right upper quadrant abdominal pain, enlarged liver& spleen. Jaundice may or may not be developed, fatigue.

Complication:

Cirrhosis	Hepatocellular carcinoma (HCC)
❖ Is a chronic diffuse liver disease. ❖ Characterized by fibrosis and nodular formation. ❖ Results from liver cell necrosis and the collapse of hepatic lobules. ❖ Symptomsincludes: ascites, coagulopathy (bleeding disorder), portal hypertension, hepatic encephalopathy, vomiting blood, weakness, weight loss.	❖ One of the most common cancers in the world. Also, one of the most deadly cancers if not treated. ❖ Hepatitis B and C viruses are the leading cause of chronic liver diseases. ❖ Symptoms include: abdominal pain, abdominal swelling, weight loss, anorexia, vomiting, and jaundice. ❖ Physical examination reveals hepatomegaly, splenomegaly and ascites. ❖ Prognosis: very poor if not treated by transplantation. ❖ Diagnosis: alpha-fetoprotein and CT scans ❖ Treatment: surgical resection and liver transplant.

- The patient should have chronic hepatitis to develop HCC and Cirrhosis.

Prevention and Control:

- Pre-exposure prophylaxis:
  - Active vaccination given to all newborn, childrenor adults.

  Recombinant hepatitis B vaccine: It is prepared by cloning HBsAg in yeast cells
    - ✓ The vaccine is given in 3 IM injections at 0-1-6 months.
- Post exposure prophylaxis:

  Persons exposed to needle prick or infant born to +veHBsAg mother should immediately receive both: Active vaccine and hepatitis B specific immunoglobulin.

Treatment:

- α –interferon is used in treating of chronic hepatitis B (resistant).
- Lamivudine
- Adefovir
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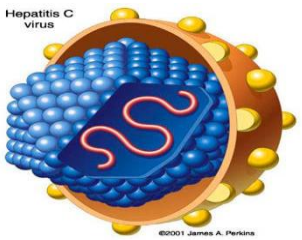
Hepatitis C virus



HETEROGENOUS: rabidly changes its antigens.That's why there is no vaccine.

- Family: *flaviviridae. Genus: hepacivirus*
- The virus is small, 60 – 80 nm in diameter.
- Consists of an outer envelope, icosahedral core and linear positive polarity ss-RNA gemone.
- HCV is extremelyHETEROGENOUS, and has a high mutation rate.
- There are 6 major genotypes (1 – 6);genotype 4 is the dominant in Saudi patients.
- Its severity is higher than Hepatitis B virus.
- Incubation period = 2-7 weeks (shorter than HBV)
- Viral replication occur in the hepatocyte and possible in peripheral blood mononuclear cells.
- Clinical picture → same as Hepatitis B

Transmission of HCV:

- **Parenterally (mainly).**
- **Sexually.**
- **From mother to child, perinatally.**

Hepatitis C markers:

1. ***Hepatitis C virus – RNA.*** ❖ ***Is the first marker that appears in the serum, it appears as early as 2-3 weeks after exposure;It is a marker of infection.***	2. ***Hepatitis C core antigen.*** ❖ ***The second marker that appears in the serum , usually 3 -4 weeks after exposure .it is a marker of infection***	3. ***IgG Antibody to hepatitis C.*** ***Antibodies to hepatitis C virus is the last marker that appears in the serum, usually appear 50 days after exposure(long window period).***

The clinical outcome of HCV infection:

• ***About 20 % to 40% of the infected individuals will develop self-limiting acute hepatitis C and recover completely.***	• ***About 80 % of the infected will progress to chronic hepatitis C.***	• ***Less than 1 % will develop fulminant*** *(late stage)* ***hepatitis C, liver failure and death.***

The chronic hepatitis C patients may present as "Carrier state" with normal liver enzymes or typical chronic active hepatitis → Cirrhosis → death.

Lab diagnosis of hepatitis C infection: By detection of both:

- **Antibody to HCV in the blood by ELISA.**
- **HCV-RNA in the blood using PCR.**
- **Liver biopsy**
- **Liver function test → ALT**

Treatment of hepatitis C infection & vaccine

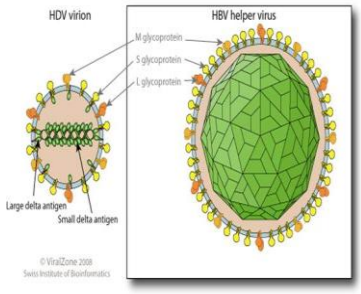
Treatment is limited to those positive for HCV-RNA, HCV-Ab, elevated ALT and moderate liver injury based on liver biopsy.

- *The currently used treatment is the combined therapy, using* **pegylated alpha** interferon and **ribavirin.**

Hepatitis C vaccine:

- **At the present time, there is no vaccine available to hepatitis C**

Hepatitis D virus (delta virus):



- **It is a defective virus that cannot replicates by its own.**
- **It requires a helper virus →The helper virus is HBV.**
- **HBV provides the free HBsAgparticles to be used as an envelope.**
- **HDV is small 30-40 nm in diameter.**
- **Composed of smallss-RNA genome, surrounded bydelta antigen that formsthe nucleocapsid.**
- **Diagnosis by detection of Anti-HDV antibodies**

Types of HDV infections:

1- Co-infection:

- **The patient is infected with HBV and HDV at the same time leading to severe acute hepatitis.**
- **Prognosis: recovery is usual.**

2- Super infection:

- **In this case, delta virus infects those who are already having chronic hepatitis B leading to severe chronic hepatitis.**

Hepatitis G virus

- **Hepatitis G virus or GB-virus was discovered in 1995.**
- **Family: flaviviridae , genus hepacivirus**
- **Enveloped, ss-RNA with positive polarity.**
- **Parenterally, sexual and from mother to child transmission have been reported**
- **Cause mild acute and chronic hepatitis Gcases.**
- **Usually occurs as co-infection with HCV, HBV and HIV.**

Summary:

- A, E, C, D, G viruses →have the same genetic material (ss-RNA) expect hepatitis B viruses (ds-DNA).
- Hepatitis C viruses transmitted mainlyparentally.
- HBV, Genotype D is the most dominant in Saudi patients.
- HBV DNA and Hepatitis B surface antigen (HBsAg) → marker of infections
- Antibody to hepatitis B surface antigen (Anti-HBs) →marker of immunity
- Hepatitis B infection is diagnosed by detection of HBsAg in the blood.(SEROLOGY)
- Most acute hepatitis B, C are asymptomatic or anicteric.
- Chronic hepatitis B infection is defined by the presence of HBV-DNA or HBsAg in the blood for > 6 months
- Chronic hepatitis is limited to hepatitis B, C, D and may be G viruses.
- The majority of patients with chronic hepatitis B and C are asymptomatic or has mild fatigue only.
- Hepatitis D viruses are adefective virus, that cannot replicates by its own.So they need helper virus like HBV to replicate.
- Hepatitis D viruses ,Diagnosis by detection of Anti-HDV antibodies
- HCV is extremely HETEROGENOUS, and has a high mutation rate.
- About 90 % of infected adults will develop acute hepatitis B infection and recover completely (self-limiting).
- *About 80 % of the infected will progress to chronic hepatitis C.*
- α –interferon is used in treating of chronic hepatitis B
- *The currently used treatment for HCV is the combined therapy, using*pegylated alpha interferon and ribavirin.
- there is no vaccine available to hepatitis C.
- Persons exposed to needle prick or infant born to +veHBsAg mother should immediately receive both: Active vaccine and hepatitis B specific immunoglobulin.
- *Lab diagnosis of hepatitis C infection ,* By detection of both :
  - ✓ HCV-RNA in the blood using PCR.
  - ✓ Antibody to HCV in the blood by ELISA.
- Chronic cases of HBV and HCV may complicated to **cirrhosis and hepatocellular carcinoma .**