Medical Virology for 2nd Year M.D. Students

Hepatitis Viruses (2)

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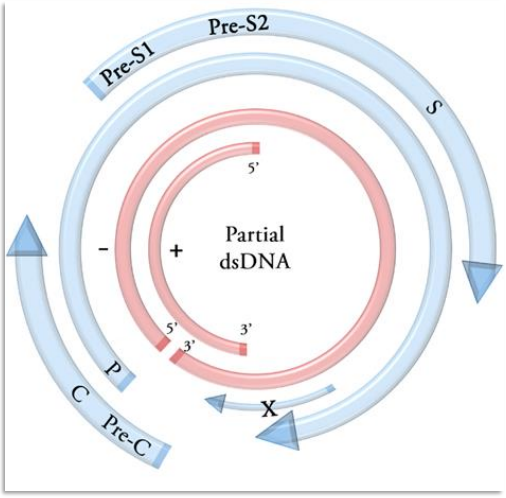
Hepatitis B virus (HBV)

- HBV is a DNA virus with a peculiar genome that is a circular partially double-stranded DNA of about 3.3 kb.
- HBV is the only human virus that belongs to the family *Hepadnaviridae*.
- HBV is characterized by the circulation of three EM morphologically recognized structures: The 42-nm virion particles, the 22-nm spherical particles and the 22-nm tubular particles that are up to 200 nm in length.
- The 22-nm particles, that are non-infectious, are produced in excess compared to the virions which might be a viral decoy mechanism to trick the immune system.

HBV Genome



The genomic structure of HBV with the blue arrows indicating the four open reading frames (S: surface, X: trans-activator of transcription, C: core and P: polymerase). The genomic DNA is shown in pink

Hepatitis B virus (HBV)

- HBV replication is unique in the way that its replication occurs through an RNA intermediate (the pregenomic RNA) from the minus DNA strand.
- The polymerase of HBV has the following activities in four domains: terminal protein at the amino end that has a role in initiation of DNA synthesis, a spacer domain that is not critical in function, RT and RNase H.
- The core protein (HBcAg) form the capsid and exists as a dimer.
- Translation of the preCore region results in the production of the soluble form of core protein (HBeAg) with its presence in serum marking higher transmissibility.

Hepatitis B virus (HBV)

- The surface proteins embedded in the envelope are small (S), medium (M) and large (L). The most abundant is the S protein that is the product of S while translation of both PreS2 and S results in the production of M protein and translation of PreS1, PreS2 and S all together results in L protein production.
- The pre-S1 domain of the L protein binds to the hepatic receptor of HBV namely sodium taurocholate co-transporting polypeptide (NTCP).
- HBV is currently classified into at least eight genotypes designated with capital letters (A-H).

Natural History of HBV

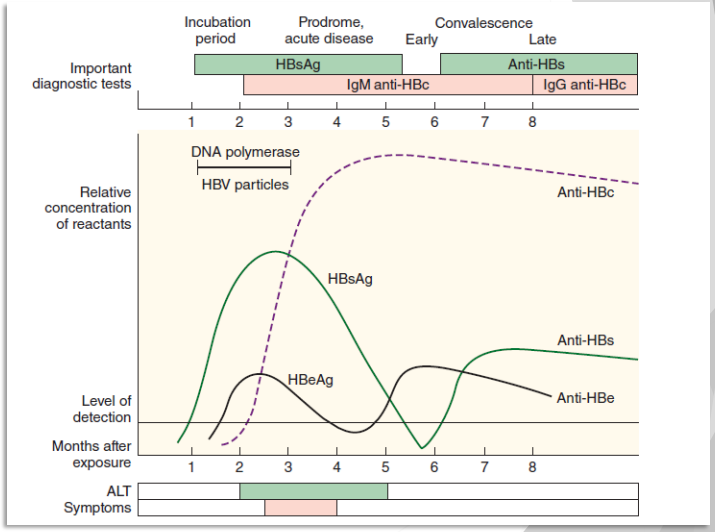
- **The percutaneous transmission is the major route for HBV infection**. Other major routes of transmission include sexual spread and MTCT.
- In areas with high endemicity (sero-prevalence ≥8%, e.g. Southeast Asia), MTCT represents a frequent mode of spread with its subsequent high prevalence of chronicity.
- HBV can cause both acute and chronic infections, with age as one of determinants of chronicity. Fulminant hepatitis can follow acute infection.
- In adults, the majority clear the infection and a minority develops chronic infection during which, hepatocyte damage occurs as a result of T cell mediated immune attack on hepatocytes expressing HBV antigens on the context of their HLA molecules.

Diagnosis, Treatment and Prevention of Hepatitis B

- After HBV infection, the first markers of the disease is viral DNA in the liver and plasma together with circulating HBsAg. High levels of viremia is followed by rise in the level of markers of hepatocyte damage (mainly ALT) and the appearance of clinical features (fever, malaise and jaundice).
- HBsAg becomes undetectable 1–2 months after the appearance of jaundice.
- **The persistence of HBsAg beyond 6 months marks HBV chronicity.**
- HBcAb appears within the first two weeks after the appearance of HBsAg and preceding HBsAb.

Diagnosis, Treatment and Prevention of Hepatitis B

- The window between decline of HBsAg and rise HBsAb is associated with HBcAb as the only serologic evidence of infection.
- Clearance is associated with the appearance of HBsAb.
- NAT is also available for screening blood/blood products.



Diagnosis, Treatment and Prevention of Hepatitis B

- Multiple options are available for treatment of chronic hepatitis B including **IFNs** and several **nucleotide and nucleoside analogs** with the goal of reducing the viral load to an undetectable level and to reach HBsAg clearance.

- For prevention of HBV infection, an effective vaccine (**recombinant HBsAg**) has been available from mid-1980s, with many countries worldwide implementing universal vaccination of infants.

Hepatitis D virus (HDV)

- HDV is known to be **defective** and require a helper function from HBV for its transmission. **HDV is coated with HBsAg, which is needed for release from the host hepatocyte and for entry in the next round of infection**.
- HDV is unique among human viruses, having an internal nucleocapsid comprising the genome surrounded by the delta antigen and enveloped by an outer protein coat of HBsAg.
- The genome consists of a single-stranded, circular RNA of around 1700 nucleotides, the delta antigen being encoded by antigenomic RNA.

Hepatitis D virus (HDV)

- Two types of infection are described:
  - **Co-infection:** Where a person who is susceptible to HBV is exposed to someone who is co-infected with HBV and delta virus, this results in acute co-infection with both the viruses at the same time.
  - **Super-infection:** When an HBV carrier is exposed to infected blood from co-infected patients then the exposure results in super-infection of the existing HBV infection with delta virus; this may result in development of acute hepatitis (due to delta virus) in an HBV chronic carrier.

Hepatitis D virus (HDV)

- Infection with HDV has a worldwide distribution, but two epidemiologic patterns exist.
- In Mediterranean countries (northern Africa, southern Europe, the Middle East), HDV infection is endemic among those with hepatitis B, and the disease is transmitted predominantly by non-percutaneous means, especially close personal contact.
- In non-endemic areas, such as the United States and northern Europe, HDV infection is confined to persons exposed frequently to blood and blood products, primarily injection drug users and hemophiliacs.

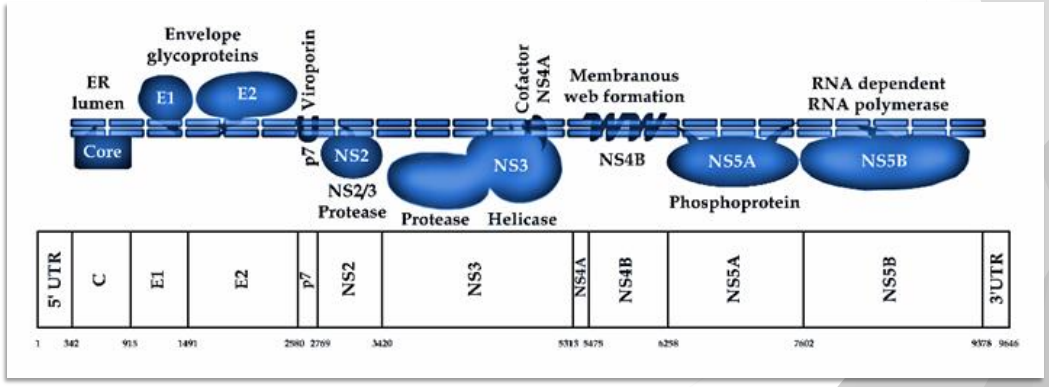
Hepatitis D virus (HDV)

- The presence of HDV infection can be identified by demonstrating intrahepatic HDV antigen or anti-HDV Ab. Circulating HDV antigen, also diagnostic of acute infection, is detectable only briefly, if at all.
- Tests for the presence of HDV RNA are useful for determining the presence of ongoing HDV replication and relative infectivity.
- Delta hepatitis can be prevented by vaccinating HBV-susceptible persons with hepatitis B vaccine

Hepatitis C virus (HCV)

HCV is a member of the genus *Hepacivirus* that belongs to the family *Flaviviridae*.

As a positive-sense single-stranded RNA virus, HCV genome can be viewed as a single ORF which encodes a polyprotein of about 3000 amino acids.



Hepatitis C virus (HCV)

- Hepatitis C is a global health problem with about 70 million people living with chronic HCV infection and 700,000 mortalities by the end of 2015.
- The countries with highest prevalence of sero-positivity to HCV are Egypt and Cameroon with prevalence reported to be more than 10%.
- The major route of HCV transmission worldwide is the exposure to contaminated blood mainly through IDU particularly in the high-income countries.

Hepatitis C virus (HCV)

- After the introduction of effective screening of **blood/blood products** used for transfusion, health-care-related spread of HCV became less common.
- Other lower-risk modes of transmission include **high risk sexual behaviour**, **vertical transmission**, health-care associated infections (percutaneous exposure through **needlestick injuries**, **haemodialysis**, surgeries or dental procedures), intrafamilial spread, tattooing, piercing and acupuncture.
- The per-act risk of infection is mainly related to the volume of inoculum together with the viral load of the source of infection, with transfusion as an efficient route.

Hepatitis C virus (HCV)

- Chronicity that is characterized by **high viral load** (usually associated with HIV-1 co-infection), **follows acute infection in 50–85% of the cases**.
- The hepatocyte tropism is related to HCV identified cellular receptors namely **CD81, claudin, occludin and scavenger receptor class b type I**.
- The serologic assays confirm the history of HCV past infection, nevertheless, **the diagnosis of ongoing infection relies on nucleic acid testing which is also used to monitor response to treatment**.

Hepatitis C virus (HCV)

- Based on the scientific evidence of genotype correlation with outcome of treatment, particularly for IFN-based therapies, **the identification of HCV genotype is considered to have a significant predictive value for treatment success**.
- The novel therapeutic options of HCV in the form of **direct-acting antivirals (DAAs)**, have resulted in rising hope among clinicians and patients for better response, less side effects and shorter duration of therapy.
- Due to **absence of an effective vaccine to HCV infection so far**, prevention of transmission relies on identifying individuals at risk and consulting on behavioural changes to decrease the likelihood of forward transmission.