6- Viral Hepatitis

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Objectives

- Discuss the structure, properties, epidemiology, clinical presentation, laboratory diagnosis, and treatment of:

1. Hepatitis A (HAV)
2. Hepatitis B (HBV)
3. Hepatitis C (HCV)
4. Hepatitis D (HDV)
5. Hepatitis E (HEV)

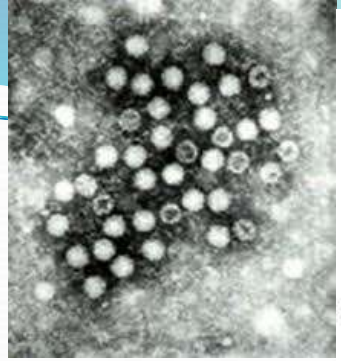
Introduction

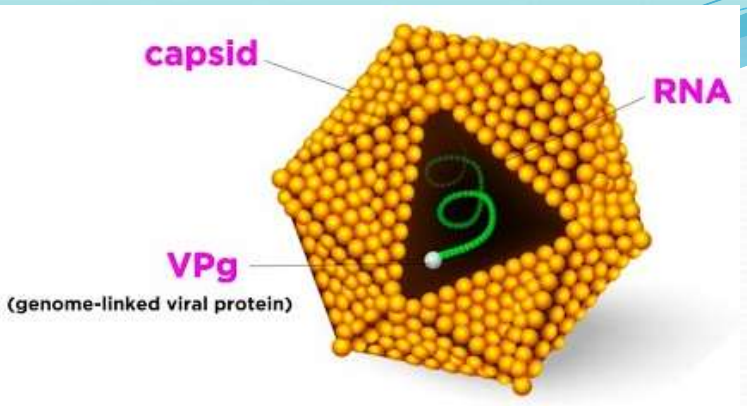
- Hepatitis: inflammation of liver; presence of inflammatory cells in organ tissue
- The causes of hepatitis are varied and include viruses, bacteria, and protozoa, as well as drugs and toxins (eg, isoniazid, carbon tetrachloride, and ethanol).
- Acute hepatitis: symptoms last less than 6 months
- Viral Hepatitis: is inflammation of the liver induced by viral infections
- The clinical symptoms and course of acute viral hepatitis can be similar, regardless of etiology, and determination of a specific cause depends on laboratory tests.

- Hepatitis may be caused by at least five different viruses (A, B, C, D, E) Other viruses, such as Epstein–Barr virus and cytomegalovirus, can also cause inflammation of the liver, but hepatitis is not the primary disease caused by them.

Hepatitis A

- HAV is a picornavirus,. It replicates in the liver, is excreted in bile and is then excreted in the faeces of infected persons for about 2 weeks before the onset of clinical illness and for up to 7 days after.
- Hepatitis A virus is spread by the fecal–oral route, and outbreaks may be associated with contaminated food or water.
- Humans appear to be the major natural hosts of hepatitis A virus.
- The major mode of spread of hepatitis A is fecal–oral. transmission
- HAV particles can be demonstrated in the faeces by electron microscopy.





Structure

- 27- to 32-nm spherical particle
- linear single-stranded RNA
- Terminal viral protein (VP)
- Icosahedral Cubic symmetry
- Nonenveloped
- Only one serotype is known
- HAV is stable to treatment with 20% ether, acid (pH 1.0 for 2 hours), and heat (60°C for 1 hour)
- Heating food to above 85°C (185°F) for 1 minute and disinfecting surfaces with sodium hypochlorite are necessary to inactivate HAV

Epidemiology

- Hepatitis A is the most common type of viral hepatitis occurring world-wide, often in epidemics.
- The disease is commonly seen in children and young adults.
- Spread of infection is mainly by the faeco-oral route and arises from the ingestion of contaminated food or water .
- Overcrowding and poor sanitation facilitate spread.
- There is no carrier state.
- More than 90% of the adult population in many developing countries shows evidence of previous hepatitis A infection. Travelers from developed countries who enter endemic areas are particularly susceptible.
- Patients are most contagious in the 1 to 2 weeks prior to the onset of clinical disease.

Clinical Manifestations

- Incubation period of 10 to 50 days
- Followed by the onset of fever; anorexia; nausea; pain in the right upper abdominal quadrant;
- Within several days, jaundice. Dark urine and clay-colored stools may be noticed by the patient 1 to 5 days before the onset of clinical jaundice.
- The liver is enlarged and tender
- Recovery occurs in days to weeks. Almost all cases (99%) of hepatitis A are self-limiting. Chronic hepatitis such as that seen with hepatitis B is very rare.
- Many persons who have serologic evidence of acute hepatitis A infection are asymptomatic or only mildly ill, without jaundice.

Diagnosis

- Liver biochemistry: A raised serum AST or ALT, which can sometimes be very high, precedes the jaundice. In the icteric stage the serum bilirubin reflects the level of jaundice.
- Haematological tests There is leucopenia with a relative lymphocytosis.
- The erythrocyte sedimentation rate (ESR) is raised.
- Viral markers: antibodies to HAV IgG antibodies are common in the general population over the age of 50 years, but an anti-HAV IgM means an acute infection.
- Immune electron microscopic identification of the virus in fecal specimens and isolation of the virus in cell cultures remain research tools.

Treatment and Prevention

- There is no specific treatment for patients with acute hepatitis A. Supportive measures include adequate nutrition and rest.
- Avoidance of exposure to contaminated food or water are important measures to reduce the risk of hepatitis A infection.
- Passive immunization with Immune serum globulin (ISG), is protective if given before or during the incubation period of the disease.
- Active immunization with formalin-killed vaccines induce antibody titers similar to those of wild-virus infection and are almost 100% protective.

Hepatitis B

- The viral genome consists of partially double-stranded DNA with a short, single stranded piece. It comprises 3200 nucleotides, making it the smallest DNA virus known.
- The main components of the virus include the core - hepatitis B core antigen (HBcAg) and the pre-core- hepatitis B e antigen (HBeAg), and the envelope of the virus contains the hepatitis B surface antigen (HBsAg)
- Hep B is usually an asymptomatic or limited illness with fever and jaundice for days to weeks. It becomes chronic in up to 10% of patients and may lead to cirrhosis or hepatocellular carcinoma.

Epidemiology

- The hepatitis B virus is present world-wide with an estimated 300 million carriers. 2 billion people have markers of infection
- 400 million have chronic infection.
- Spread of this virus is either by the intravenous route (e.g. by transfusion of infected blood or blood products, or by contaminated needles used by drug addicts, tattooists or acupuncturists), or by close personal contact, such as during sexual intercourse, particularly in male homosexuals.
- The virus can be found in semen and saliva.
- Vertical transmission from mother to child during parturition or soon after birth is the usual means of transmission world-wide.
- Needle stick injuries, has resulted in a higher risk of hepatitis B in medical personnel.

Clinical Manifestations

- The incubation period may be as brief as 7 days or as long as 160 days (mean, approximately 10 weeks).
- Acute hepatitis B is usually manifested by the gradual onset of fatigue, loss of appetite, nausea and pain, and fullness in the right upper abdominal quadrant. Early in the course of disease, pain and swelling of the joints and occasional frank arthritis may occur. Some patients develop a rash.
- With increasing involvement of the liver, there is increasing cholestasis and, hence, clay-colored stools, darkening of the urine, and jaundice. Symptoms may persist for several months before finally resolving.

- Fulminant hepatitis, leading to extensive liver necrosis and death, develops in less than 1%.
- Development of chronic hepatitis occurs in approximately 10% of all patients with hepatitis B infection, hepatocellular carcinoma, in up to 25% of patients.

Diagnosis

Serology:

- **HBsAg** - used as a general marker of infection.
- **HBsAb** - used to document recovery and/or immunity to HBV infection.
- **anti-HBc IgM** - marker of acute infection.
- **anti-HBcIgG** - past or chronic infection.
- **HBeAg** - indicates active replication of virus and therefore infectiveness.
- **Anti-Hbe** - virus no longer replicating. However, the patient can still be positive for HBsAg which is made by integrated HBV.
- **HBV-DNA** - indicates active replication of virus, more accurate than HBeAg especially in cases of escape mutants. Used mainly for monitoring response to therapy.

- The laboratory diagnosis of acute hepatitis B is best made by demonstrating the IgM antibody to hepatitis B core antigen in serum.
- Almost all patients who develop jaundice are anti-HBc IgM positive at the time of clinical presentation. HBsAg may also be detected in serum.
- Past infection with hepatitis B is best determined by detecting IgG anti-HBc, anti-HBs, or both.
- Liver Chemistry tests
  - AST, ALT, ALP, and total Bilirubin are elevated
- HBV Viral DNA: Most accurate marker of viral DNA and detected by PCR
- Liver Biopsy: to determine grade(Inflammation) and stage(Fibrosis) in chronic Hepatitis

Treatment

- There is no specific treatment for acute hepatitis B. A high-calorie diet is desirable.
- Corticosteroid therapy has no value in uncomplicated acute viral hepatitis,
- For chronic hepatitis, interferon alpha provides long-term benefit in (~33%) of patients.
- Lamivudine (3TC), a potent inhibitor of HIV is also active versus hepatitis B virus both in vitro and in initial clinical trials, but resistance to this agent develops in about 25% of patients after 12 months of therapy.
- Adefovir, a nucleotide analog of adenosine monophosphate, is newly approved for the treatment of chronic hepatitis B.

Prevention

- Safe practices and avoidance of needle stick injuries or injection drug use are approaches to diminishing the risk of hepatitis B infection.
- Vaccination - highly effective recombinant vaccines are now available. Vaccine can be given to those who are at increased risk of HBV infection such as health care workers. It is also given routinely to neonates in many countries.
- Hepatitis B Immunoglobulin - HBIG may be used to protect persons who are exposed to hepatitis B. It is particular efficacious within 48 hours of the incident. It may also be given to neonates who are at increased risk of contracting hepatitis
- Other measures - screening of blood donors, blood and body fluid precautions.

Hepatitis D – Delta Hepatitis

- Delta hepatitis is caused by the hepatitis D virus. This small single-stranded RNA virus requires the presence of hepatitis B surface antigens for its transmission and is thus found only in persons with acute or chronic hepatitis B infection.
- Delta hepatitis is most prevalent in groups at high risk of hepatitis B. Injection drug users, and as many as 50% of such individuals may have IgG antibody to the delta virus antigen. Other risks include dialysis. Non parenteral and vertical transmission can also occur.

Clinical Manifestations

Two major types of delta infection have been noted:

- Simultaneous delta and hepatitis B infection: Simultaneous infection with both delta and hepatitis B results in clinical hepatitis that is indistinguishable from acute hepatitis A or B; however, fulminant hepatitis is much more common than with hepatitis B virus alone.
- Delta superinfection in those with chronic hepatitis B. Persons with chronic hepatitis B who acquire infection with hepatitis D suffer relapses of jaundice and have a high likelihood of developing chronic cirrhosis.

Diagnosis

- Diagnosis is made most commonly by demonstrating IgM or IgG antibodies, or both, to the delta antigen in serum.
- IgM antibodies appear within 3 weeks of infection and persist for several weeks.
- IgG antibodies persist for years.

Treatment and Prevention

- Response to treatment with interferon alpha in patients with delta hepatitis (and hepatitis B) is less than in those with hepatitis B alone.
- Recommended doses are higher and may produce sustained improvement in only 15–25% of patients.
- Because the capsid of delta hepatitis is HBsAg, measures aimed at limiting the transmission of hepatitis B to prevent the transmission of delta hepatitis.
- Individuals infected with hepatitis B or D should not donate blood, organ, tissues, or semen.
- Methods of reducing transmission include decreased use of contaminated needles and syringes by injection drug users and use of needle safety devices by health care workers.

Hepatitis C

- Hepatitis C virus is an RNA virus in the flavivirus. It has a very simple genome, consisting of just three structural and five nonstructural genes.
- Hepatitis C is an insidious disease in that it does not usually cause a clinically evident acute illness. Instead, its first manifestation (in 25% of those infected) may be the presence of smoldering chronic hepatitis that may ultimately lead to liver failure. Its transmission is less well understood than for hepatitis A, B, and D.
- Hepatitis C was the major cause of post-transfusion hepatitis until a serologic test for screening blood donors was developed.

- The transmission of hepatitis C by blood is well documented: indeed, until screening blood for transfusions was introduced, it caused the great majority of cases of post-transfusion hepatitis.
- Hepatitis C may be sexually transmitted but to a much lesser degree than hepatitis B.
- Needle sharing accounts for up to 40% of cases. In the United States, 3.5 million people (1.8%) have antibody to hepatitis C.
- Screening of donor blood for antibody has reduced post-transfusion hepatitis by 80–90%.
- Other individuals considered at risk for hepatitis C are chronic hemodialysis patients and spouses.

Clinical Manifestations

- The incubation period of hepatitis C averages 6–12 weeks.
- The infection is usually asymptomatic or mild and anicteric but results in a chronic carrier state in up to 85% of adults of patients.
- The average time from infection to the development of chronic hepatitis is 10–18 yrs.
- Cirrhosis and hepatocellular carcinoma are late sequelae of chronic hepatitis.

Diagnosis

- Antigens of hepatitis C are not detectable in blood, so diagnostic tests attempt to demonstrate antibody.
- Unfortunately, the antibody responses in acute disease remain negative for 1 to 3 weeks after clinical onset and may never become positive in up to 20% of patients with acute, resolving disease.
- Current tests measure antibodies to multiple hepatitis C antigens by either enzyme immunoassay or immunoblot
- Even with these newer assays, IgG antibody to hepatitis C may not develop for up to 4 months, making the serodiagnosis of acute hepatitis C difficult.
- Quantitative assays of hepatitis C RNA may be used for diagnosis, estimating prognosis, predicting interferon responsiveness, and monitoring therapy, but there is not a very good correlation between viral load and histology.

Treatment and Prevention

- Combination therapy with interferon alpha and ribavirin is the current treatment of choice for patients with evidence of hepatitis due to hepatitis C.
- Corticosteroids are not beneficial.
- Avoidance of injection drug use and screening of blood products are important preventive measures.
- It is not clear whether prophylactic ISG protects against hepatitis C. In addition, it is questionable whether a vaccine will be effective; patients may be reinfected by wild-type virus.

Hepatitis E

- Hepatitis E is the cause of another form of hepatitis that is spread by the fecal–oral route and therefore resembles hepatitis A.
- Hepatitis E virus is an RNA virus that is similar to but distinct from caliciviruses. The viral particles in stool are spherical, 27 to 34 nm in size, and unenveloped and exhibit spikes on their surface.
- Like hepatitis A, infection with this virus is frequently subclinical. When symptomatic, it causes only acute disease that may fulminate, especially in pregnant women.

- In endemic, developing areas, it has the highest attack rate in young adults, and infection is usually associated with contaminated drinking water.
- It does not appear to spread from person to person. Most cases have been identified in developing countries with poor sanitation, and recurrent epidemics have been described in these areas.
- The incubation period is approximately 40 days. The diagnosis may be confirmed by demonstrating the presence of specific IgM antibody. No treatment is available.

Hepatitis G

- In 1995, hepatitis G, a newly discovered agent, was identified in sera from two different patients. Hepatitis G is an RNA virus similar to hepatitis C and members of the flavivirus family.
- An antibody assay can detect past, but not present, infection, and detection of acute infection with hepatitis G requires a PCR assay for viral RNA in serum. Up to 2% of volunteer blood donors are seropositive for hepatitis G RNA, which is a blood-borne virus.

- In addition to being closely related to hepatitis C, data suggest that the majority of patients infected by hepatitis C are also infected by hepatitis G. Given this association, it has been difficult to ascertain the contribution of hepatitis G to clinical disease.
- Patients infected with both viruses do not appear to have worse disease than those infected by hepatitis C virus only.
- Currently, there is no useful serologic test and no therapy is established.

Table 1 summary

Comparison of A, B, D (Delta), C, and E Hepatitis

Feature	A	B	D	C[a]	E
Virus type	Single-stranded RNA	Double-stranded DNA	Single-stranded RNA	RNA	RNA
Percent of viral hepatitis	50	41	<1	5	<1
Incubation period (days)	15–45 (mean, 25)	7–160 (mean, 60–90)	28–45	15–160 (mean, 50)	?
Onset	Usually sudden	Usually slow	Variable	Insidious	?
Age preference	Children, young adults	All ages	All ages	All ages	Young adult
Transmission					
Fecal–oral	+++	±	±	−	+++
Sexual	+	++	++	+	+?
Transfusion	−	++	+++	+++	−
Severity	Usually mild	Moderate	Often severe	Mild	Variable
Chronicity (%)	None	10	50–70	>50%	None
Carrier state	None	Yes	Yes	Yes	?
Immune serum globulin protective	Yes	Yes[b]	Yes[c]	Uncertain	?

Abbreviation: Plus and minus signs indicate relative frequencies.

[a] Many individuals with hepatitis C virus are also infected with the hepatitis G virus, which is similar to hepatitis C.

[b] Hyperimmune globulin more protective.

[c] Prevention of hepatitis B prevents hepatitis D.