**Hepatitis A**

Hepatitis A which is a virus that transmitted by the fecal–oral route causing epidemics that are either waterborne or foodborne, their mode of transmission can be traced by sexual transmission as well as blood transfusion (in cases of blood taking or donating by a viremic individual).

Pathogenesis of hepatitis A:

The virus has an incubation period of 2-6 weeks after infection.

The virus reaches the liver via the portal system after a phasic replication in the GIT thus causing liver cell damage as a consequence of immune response against virus-infected cells and this is associated with the release of liver enzymes, particularly alanine aminotransferase (ALT) and the development of antibodies to the virus which marks the onset of clinical manifestations and then the virus is cleared from the circulation.

Hepatitis viruses share the same pathologic features and clinical manifestations. Generally, viral hepatitis is associated with liver cell damage and mononuclear cell infiltration that varies in extent between one virus and the other. One of the most important factors is age or the magnitude of an immune response that generated against infection, there are certain features that can be utilized to distinguish one hepatitis virus from the other depending on the phases of pathologic changes, ex: hepatitis A can produce mononuclear cell infiltration that has a periportal distribution with acidophilic degeneration and activation of reticulo-epithelial cells of the sinusoids and portal tracts, whereas hepatitis B is characterized by conspicuous parenchymal cell damage.
HAV may cause parenchymal cell damage, but it is considered a characteristic of HBV. HCV is characterized by steatosis of infected cells (fatty infiltration of hepatocytes) but this also can be seen in HAV infection, cholestasis is a characteristic of HEV. However, HAV can cause cholestatic changes.

So, pathology can be similar in the different types of viruses but each of these viruses has unique features with respect to pathologic changes as mentioned before. All hepatitis viruses can be associated with widespread pathologic damage of the liver, confluent hepatic damage can be seen in all types of hepatitis, far more common in acute hepatitis D (in the cases of coinfection between B & D) and more common for HEV among pregnant women.

Confluent hepatic damage can lead to fulminant hepatitis (the highly fatal condition, it leads to the death of more than 75% of cases), it is seen in cases where we have a severe immune response in the infection. So, it is more common among adults (usually, it is not seen among children).

Clinically, hepatitis viruses are similar with respect to the clinical cause in that they are characterized by having 4 phases:

1- Incubation period: A part of the disease in all viruses that varies from 2 weeks up to 6 months depending on the virus.

2- Prodrome: Usually, precedes the icteric phase. It lasts for few days but sometimes extending to 2 weeks depending on the virus. It is associated with non-specific manifestation of a viral infection but they may involve the liver, thus causing right upper abdominal quadrant's clinical manifestations; pain and tenderness "if the liver is involved".

3- Icterus: It is associated with jaundice "yellowish discoloration of the skin and mucous membranes". After a period of time that varies, the icteric phase is followed by either Convalescence in viruses with no establishment of cholesity or establishment of chronicity in cases where chronic liver disease results or it is followed by death.
4- Convalescence: associated with either in the cases where we have no chronicity that leads to the development of an immune-response which lasts for the life of the individual.

So, HAV has an incubation period of 2-6 weeks (average 30 days), followed by prodromal phase or preicteric phase that lasts 2-7 days. Clinical manifestations include: headache, fever, malaise, loss of appetite and right upper quadrant pain or tenderness and then other symptoms start to appear or to replace these preicteric manifestations being marked by development or appearance of antibodies, usually preceded by the mounting of cellular immune response against virus infected cells.

And then we have the icteric phase, manifestations include: bilirubinuria which is darkening of the urine because of the increase in the concentration of bilirubin, sometimes the stool becomes pale and jaundice develops involving the skin and mucous membranes. The first and earliest manifestations which are the most evident manifestations of icteric phase are observed on the sclera of the eye, then at this time with the development of jaundice fever resolves and the patient's clinical condition starts to improve. So, most patients feel better after development of jaundice which means clearance of the virus and the sensation of liver cell damage (clearance of the virus means that the virus is no more present in the circulation of the individual), at this point primarily, the resolution of infection is taking place and that's why hepatitis retains to normal after few days from the onset of jaundice and there might be manifestations related to the liver, at this stage (icteric phase), less than 1% of those with hepatitis A will develop fulminant hepatitis as a consequence of confluent hepatic damage while dissemination of pathology in the liver and this occurs in the first 6-8 weeks of acute hepatitis "the percentage is different in other types of hepatitis viruses".

In those with fulminant hepatitis, ascites develops with bleeding abnormality (bleeding diathesis) and decerebrate rigidity of the brain and this leads to death in 70-90% of cases.
Fulminant hepatitis is highly dangerous because it is associated with high mortality which varies depending on age, but those who develop fulminant hepatitis above the age of 45 are unlikely to survive, and there are markers of a bad prognosis in such individuals which are: persistent vomiting, shrinkage of the liver’s size. Normally, in hepatitis we have hepatomegaly (enlargement of liver because of hypertrophy) whereas in those who develop fulminant hepatitis we have shrinkage in the size of liver (A bad prognosis). Also, disturbed behavior indicating Hepatic encephalopathy because of the lack of liver function, tremor of the outstretched hands and increasing drowsiness. While examination of those individuals we can notice a poor cerebral function and this is classically demonstrated by the inability of those patients to copy or draw a five-pointed star while being able to copy or draw a square (this condition is called: constructional apraxia and it is pointing to a bad prognosis).

Hepatitis A can develop into cholestatic hepatitis and this is associated with decrease of alkaline phosphatase and prolonged or deepening of jaundice and severe purities, usually, resolves within weeks after developing of cholestatic hepatitis.

Resolution of uncomplicated hepatitis A is slow but patient recovery is complete, however, few patients 3-20% can develop a relapsing hepatitis within the first 15 weeks of hepatitis A (after improvement, the clinical manifestations reappear in these individuals), relapsing hepatitis can develop one, two or three times in those individuals (more than one relapse can take place).

In general, hepatitis A is mild in children (it is not associated with relapses or fulminant hepatitis), whereas it is more severe in adults and it is associated with relapses, fulminant hepatitis and cholestatic hepatitis but in all cases of Hepatitis A that do not prove fatal, will resolve (no chronicity is established in hepatitis A), it is either acute hepatitis followed by full recovery or acute hepatitis that leads to death.

Depending on the socioeconomic status of the country, hepatitis A is either seen during early childhood or at a later age.
Epidemiology of hepatitis A is changing, in the developing countries where most people live in conditions with poor hygiene and sanitation, the disease is acquired early in life, it is very benign followed by lifelong immunity and usually there are sporadic cases of infection (no major epidemics). While improvement of sanitation and personal hygiene protect some of those individuals getting the disease early in life, so they remain susceptible until adulthood, in this case they are likely to develop severe disease that is usually epidemic and it would be fatal.

The shift is complete in developed countries where cases are not seen during childhood, all individuals are susceptible but there is no virus circulating in the community. So, they do not have a trouble, except if they travel to an endemic area, and that's why they should be protected by vaccination.

Since 1997, a vaccine was produced for hepatitis A and children receive it in the developed countries for the reason that hepatitis A is considered a threat in those individuals because adults are susceptible. The vaccine is not widely utilized in the developing countries, so, the epidemiology of hepatitis A varies from one country to another. Because two thirds of cases occur in children and 70% of death occurs in those above the age of 49; hepatitis A is not a major issue in the developing countries unlike developed countries and as conditions improve one should think of preventive methods for hepatitis A to adopt vaccines for example.

So, clinically HAV is mild especially among children, there is loss of appetite with nausea, cigarette aversion in adults who smoke, abdominal discomfort, fever (usually mild), jaundice develops during the icteric phase, fulminant hepatitis can be dangerous for adults and there is no chronic infection.

If we consider the different age groups of those exposed to hepatitis A, jaundice is seen in less than 6% in those below the age of 6 years but this increases by more than 5 folds in those between the age of 6-14 years old (40-50%), and the majority of individuals having jaundice are above the age of 14 (meaning that they develop severe disease with iris of fulminant hepatitis).
Most individuals in countries with improved sanitation are in the group >14 because they were not infected early in life.

Rare complications of hepatitis A include: fulminant, cholestatic and relapsing hepatitis and again there is no chronic manifestations.

Mortality is age dependant, more specifically, it increases with age because of the increase in severity of the disease (3 per thousand in those < 5 years old, 1.6 per 1000 between the age of 5-29, it doubles after the age of 30-49 and it increases by several folds above 49 of age. Most cases of hepatitis A take place in the developing countries in first years of life (most cases are registered in childhood), but most deaths are observed among adults (death is not common during childhood).

Diagnosis of Hepatitis A:

Generally, hepatitis can be diagnosed clinically but not the specific virus that causes the disease (HAV, HBV or HCV…etc).

Specific diagnosis requires the isolation of the virus, demonstration of the genome of the virus (PCR) or demonstration of the virus in the circulation (serology tests).

Virus isolation in the cases of hepatitis A is difficult; HAV can grow for a while in liver cell but it does not maintain for a long period of time and that's why it is not regarded as the recommended method of diagnosis.

However, the genome of the virus can be demonstrated by PCR examination of saliva, feces or blood to demonstrate the presence of the virus.

Serology is a useful diagnosis and acute hepatitis A is associated with production of IgM antibodies that last for 4-6 months and then they are replaced by IgG antibodies. So, the detection of IgM indicates either an ongoing or a recent infection, whereas the detection of IgG in the absence of IgM indicates immunity and past infection.
Hepatitis A is responsible for the majority of cases of hepatitis; 40-60% of cases are due to hepatitis A. Hepatitis A disease is endemic throughout the world but it is hyperendemic in the developing countries. Epidemics may take place and usually they are common source epidemics (common source epidemic occurs when a group of people is exposed to a single common source of infection such as the contamination of food or water), for example: the epidemics of hepatitis A that took place in Shanghai-China as a consequence of consumption of contaminated sea food oyster, 300,000 cases were reported in two months.

The map (slide 28) shows the prevalence of hepatitis A worldwide, the red color indicates highest prevalence followed by blue, green, yellow and finally the pale where they don't have the virus.

Africa and Asia and some parts of Latin America are the regions of the world with hyperendemicity of hepatitis A and this is related to the low socioeconomical conditions in these regions.

Transmission can take place by more than one mode: fecal-oral, close personal contact, sexual transmission as well as blood, contamination of food and water. The virus is most abundant in feces followed by serum and saliva.

The transmission of the virus depends on endemicity, in countries that are hyperendemic there are no epidemics (the spread of the disease is usually sporadic) but in most countries we have epidemicity because of relative improvement in sanitation and hygiene worldwide and that's why infection in highly endemic regions is acquired during early childhood (most infections are asymptomatic) by person to person transmission and the disease rate is low to high.

In countries with moderate endemicity, the disease rate is high and it is acquired also by person to person outbreaks, while in regions of low endemicity the transmission or disease rate is low but adults are infected and they are at risk of developing severe infections which are highly fatal, they do not acquire the disease in their countries unless they travel to an endemic country.
(Endemic is a disease that exists permanently in a particular region or population whereas epidemic is an outbreak of disease that attacks many people at about the same time and may spread through one or several communities).

Treatment of hepatitis A infection is symptomatic meaning that the medical therapy of the disease only affects its symptoms, not its cause, but there are preventive methods to prevent acquisition of the infection including personal hygiene (i.e.: hand washing), sanitation (i.e.: clean water sources), vaccination for pre-exposure prevention and giving immunoglobulins for pre and post-exposure prevention.

There are certain considerations that are important in taking decisions regarding vaccination. Generally, many cases occur in community-wide outbreaks of hepatitis A, no risk factors identified for 40-50% of cases, highest attack rate is seen in 5-14 years old children and children serve as reservoir of infection.

There are certain groups of people who are at increased risk of infection including: travelers to developing countries, homosexual men, illegal drug users and persons with chronic liver disease.

Hepatitis A vaccine which was made in 1997 is composed of an inactivated virus, it is usually given in 2 doses, the vaccine is highly efficacious, the efficacy ranges from 70-90% protection after a single dose and 100% protection is achieved after the second dose in children, adolescents and adults. The efficacy of preventing the disease is 94-100% of children after taking one dose.

Antibodies persist for years after infection, disease is prevented for 5-6 years follow-up. Mathematical models that relate concentration of antibodies to decay suggest that antibodies persist for 20 years or more.

Cellular immunity which is not measured by mathematical models is also important in prolonged protection.

Hepatitis A vaccine is licensed for the individuals above the age of 1 year.
It is safe for children without maternal antibodies because they can interfere with the vaccine and they persist for 1 year or more and that's why the vaccine is not given for those below the age of 1.

Those who should receive the vaccine are specific groups of people including: international travelers, persons who have clotting factor disorders and persons with chronic liver disease…etc.

As mentioned before, the vaccine is given in 2 doses for children and adults. For those above 18 years old, the dose is 1 ml and contains 1440 units and the 2\textsuperscript{nd} dose is given 6-12 months later.

For individuals of the age 2-18 years old, the dose is 0.5 ml containing 360 units (1/4 of the adult dose) and the 2\textsuperscript{nd} dose is given 6-12 months later.

There are mild side effects; local reactions that have been demonstrated as a result of utilizing hepatitis A vaccines.

There are 2 types of hepatitis A vaccine:

- Havrix, produced by Glaxosmithkline.
- VAQTA, produced by Merck.

The efficacy ranges from 94-100\% in studies that were carried in some developed countries, US and Thailand.

The efficacy can reach 94\% for the 1\textsuperscript{st} vaccine and 100\% for the 2\textsuperscript{nd} one. N indicates the number of vaccinated individuals.

The most common side effects include local reactions such as: soreness in 50\% of vaccinated individuals, headache in 15\% and malaise in 7\% but there are no threatening side effects.

Safety in pregnancy is not determined, although the virus is inactivated and should not cause problems.

Contraindications are associated with allergic vaccine component and there are no special precautions for immunocompromised or HIV-infected individuals, they can take the vaccine without developing severe reactions.
Factors that can interfere with the immunogenicity (the ability to provoke an immune response in the body) of hepatitis A vaccine:

Decreased antibody concentration:

- Concurrent administration of IG (immunoglobulins)
- Presence of antibodies either from natural (maternal antibodies) or artificial source (injection)
- Age
- Chronic liver disease, they may not respond optimally

Decreased seroconversion, (meaning: the development of detectable specific antibodies to microorganisms in the blood serum as a result of infection or immunization), had been shown in:

- HIV infection (remember that HIV infection is not considered a contraindication for vaccination, although the rate of antibodies detected may be less).
- Liver transplantation.

Prevention can be achieved by administration of immunoglobulins and they can be given either pre-exposure to travelers to intermediate and high endemic areas or post-exposure (within 14 days because minimum incubation period is 2 weeks, so they should be given before).

Post-exposure includes:

- Routine: household and other intimate contacts.
- Selected situations: institutions (day care centers) and common source exposure.
**Hepatitis B**

A second important cause of liver disease, hepatitis B has been known for hundreds of years but the discovery of the agent causing hepatitis B was made in 1965 by Dr. Baruch Blumberg at Fox Chase Cancer Center, who discovered an antigen in the blood of an Australian aborigine and the antigen was named as Australia antigen, it was later found to be hepatitis B surface antigen. This antigen was the first vaccine to protect against hepatitis B in 1982 that was the first anti-cancer vaccine and because of this discovery Blumberg was given Nobel Prize in 1976.

As mentioned before, it is believed that hepatitis B causes diseases for hundreds of years and it is associated with human beings for more than 1000 years but we do not have evidence for this statement. However, we have conclusive evidence that confirms the presence of the virus for more than 500 years. A naturally mummified body of a Korean child was found intact containing a large liver in the right upper quadrant which was shown to harbor the virus; depending on biopsies were taken from this modified body demonstrating the presence of the DNA of hepatitis B virus and it was genotype C (there are 8 genotypes of HBV).

The liver showed no pathology because it is known that HBV does not cause disease in children (infection is usually asymptomatic or subclinical). Hepatitis B is considered hyperendemic in the Far East where some villages have prevalence of 100% (very high prevalence, high prevalence rate is >10%). So, if 10% of the population has chronic liver disease, this means that 100% of them were infected at one point of time because the rate of chronicity is 10% on average.
HBV is a spherical enveloped virus with an icosahedral capsid. The envelop is incorporated with an antigen known as hepatitis B surface antigen (HBsAg), the core which is icosahedral is composed of hepatitis B core antigen (HBcAg) and the core antigen is associated with E antigen (HBeAg) which is produced from the overlapping sequence, but the E antigen does not incorporate into the virus, it is shed in the circulation of the infected individual.

The core is composed of partial dsDNA which is completed immediately after entry into the cell. The first step is the completion of double strandedness then the genome is transcribed into several RNA molecules by cellular transcriptases, 32 thousand nucleotides making up the largest mRNA which codes for the DNA polymerase, the core antigen and also it acts as a tribute to introduce the genome or DNA of the virus and actually several mRNA molecules are present, one of them is very small (700 nucleotides) that codes for the HBsAg, in addition to the fact that the 700 mRNA is an oncogene that transforms the infected cell.

Hepatitis B viruses are unusual among all viruses in that they are: partial dsDNA viruses, utilize reverse transcriptase to generate DNA molecule from RNA, and the other two most important facts that they are unusually resistant to environmental conditions (although it is an enveloped virus), they require 41:39 and they exist in 3 forms.

Forms of HBV:

Complete particle or Dane particle, spherical particle (22 nm in diameter of HBsAg) and filamentous particle (with a diameter of 22 nm but the length varies).

The only infectious form is the double shelled particle or Dane particle. However the other 2 forms of HBV (spherical and filamentous) are highly immunogenic and they are present in extremely high concentration.
They play an important role in the pathogenesis of the infection; because they act to shield and protect the virus from being neutralized in infected individuals because they adsorb antibodies that detect the virus (Dane particle).

Slide 6: An electron micrograph of the serum of an infected individual showing the Dane particle, filamentous form and the spherical form.

Hepatitis B is a parenteral virus because the most efficient route of transmission is the parenteral route by injection either as a consequence of blood, blood products transfusion or drug addiction (illegal drug users who share needles), the presence of just 0.003 ml is sufficient to infect an individual (one particle can cause hepatitis) so, this route of transmission is extremely infectious.

The less efficient route of infectivity is across mucous membranes (in cases of sexual contact, the dose should very high in order to be infected as compared to parenteral route).

The virus is present in the bloodstream of the pregnant mother but it is not transplacentally transmitted to the fetus, neonates who are at risk of developing lifelong infection are infected as a consequence of exposure to blood (the bleeding that takes place during delivery and this is the source of infection for those individuals). Once infected, neonates develop chronic infection in 70-90% of cases (it is usually asymptomatic), the chronic infection can be prevented by vaccination at birth (vaccination results in 70% prevention), but if vaccination is combined with administration of immunoglobulins then the protection of neonates may increase to 90%, otherwise, they will develop cancer within the first few years of life because chronic liver disease leads to cancer.

Hepatitis B has a long incubation period (6 weeks - 120 days or 4 months), the virus reaches the liver after 3 days of infection and at that period it can be demonstrated to replicate within hepatocytes.
However, manifestations are not apparent at least before 6 weeks, and that depends on dose route of infection and the person. The virus can replicate extrahepatically but with no pathogenicity. The pathology is immune-mediated meaning that all clinical manifestations are due to the host immune response being mounted against the virus which does not cause pathology by itself.

If the immune response is severe, clinical manifestations would be severe as well. However, severe immune response is associated with full recovery, although it can be harmful in the case of fulminant hepatitis.

A weak immune response does not result in the resolution of the infection and this leads to chronic liver disease and that's why in immunocompromised individuals (neonates or HIV-infected persons), chronicity is high. So, viral clearance is the function of the immune response that develops and that's why persistent infection develops in immunocompromised individuals. For unknown reasons, males are twice as females at risk of developing chronic liver disease.

Pathology of hepatitis B varies whether the infection is acute or chronic. In acute hepatitis B, liver cell damage with pathological inflammation that is parenchymal in origin or parenchymal cell damage are present.

Chronicity can develop in hepatitis B, chronic liver disease can be mild or severe. Chronic hepatitis B is Mild persistent hepatitis which is asymptomatic or mild symptoms are seen or it could be in the form of severe active chronic hepatitis. This is the reflection of pathologic changes that take place, pathology could be minimal to mild or moderate to severe and that's why the pathology of chronic hepatitis has been reviewed and reclassified depending on 2 factors:

- necroinflammatory process (an inflammation that is moderate to severe).

- Fibrosis which is (none to severe) and cirrhosis.
Minimal to mild chronic hepatitis is characterized by intact limiting plate and lobular architecture (limiting plate: layer of hepatocytes surrounding each portal triad and separating it from the surrounding sheets of hepatocytes). In minimal to mild, the limiting plate is intact and there is no collapse of the reticular formation of the liver.

In moderate to severe chronic hepatitis, the reticular formation undergoes collapse and the structure of the liver is disorganized as a consequence of extensive erosion of the limiting plate with the formation of active fibrous septa.

Slide 12: Minimal to mild chronic hepatitis is subdivided into: chronic persistent and chronic lobular hepatitis, clinically and pathologically they correlate [In chronic persistent hepatitis (CPH), inflammation is confined to the portal tracts, and necrosis of liver cells is not seen whereas in chronic lobular hepatitis (CLH) there is inflammation of portal tracts, with spotty parenchymal inflammation but no piece-meal necrosis]. Notice that the limiting plate (LP) is normal whereas in moderate to severe chronic hepatitis there is an erosion of the limiting plate with the formation of fibrous septa and it is the pre-stage for the development of fibrosis and cirrhosis in the liver.

The continuing hepatocellular damage accompanied by collapse and fibrosis increase the potential for progression to macronodular cirrhosis.

Chronic hepatitis is differentiated from acute hepatitis by the abundance of plasma cells, also, the HBsAg has integrated into SER of hepatocytes giving them ground glass appearance. So, infiltration of plasma cells and ground glass appearance are characteristics of chronic hepatitis. Chronic hepatitis is associated with more than 100 fold increase in the risk of development of hepatocellular carcinoma (HCC) and more than 80% of cancer cells of the liver will have the DNA of the virus, this DNA is characterized by alterations (deletions, repeats, translocations..etc) and these alterations contribute to the development of cancer.
Cancer of the liver is a result of 2 mechanisms either direct or indirect. The direct mechanism is mediated by the x-protein, the x gene codes for the oncogene which transformed the infected cell.

The indirect mechanism results from the unorganized regeneration of the liver which is associated with mutation and therefore mutation is the 2\textsuperscript{nd} mechanism that leads to HCC. Because there are 2 mechanisms acting at the same time, there is a high chance of developing malignancy in those individuals with chronic hepatitis.

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