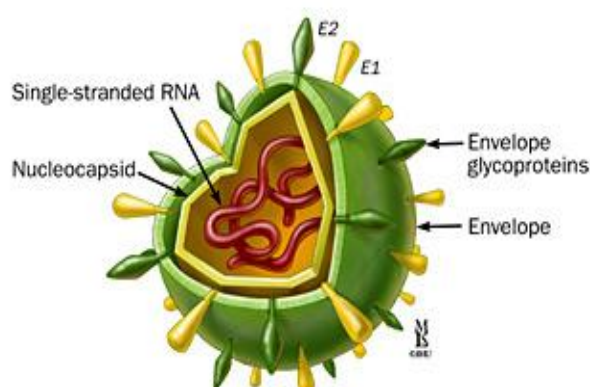


Virology 5

Hepatitis C virus :

- *spherical icosahedral positive sense single stranded RNA virus
- *its belong to *Hepacivirus* genus of the Flaviviridae family.
- *An enveloped virus
- *The morphological structure is still under investigation and research .
- * Hepatitis c virus is classified into a total of 11 genotypes , genotype 1 and 4 are the most severe and resistant to infection and they have poor prognosis and response to interferon therapy .
- *Genotypes 1 and 2 present in 90% of the hepatitis c virus infection in the U.S and 70% of them are caused by the genotype 1 .



Structure of the virus :

We have envelope and within the envelope we have 2 embedded glycoproteins E1 and E2 and we have nucleocapsid and inside there is the single strand +ve sense RNA

Viral genome:

As we said hepatitis c virus has a positive sense single stranded RNA genome. The genome consists of a single or one open reading frame and when we say one open reading frame that the mRNA is translated to produce single segment , and in the case of hepatitis c the segment will be translated into a polyprotein which is further cleaved by proteases into individual proteins .

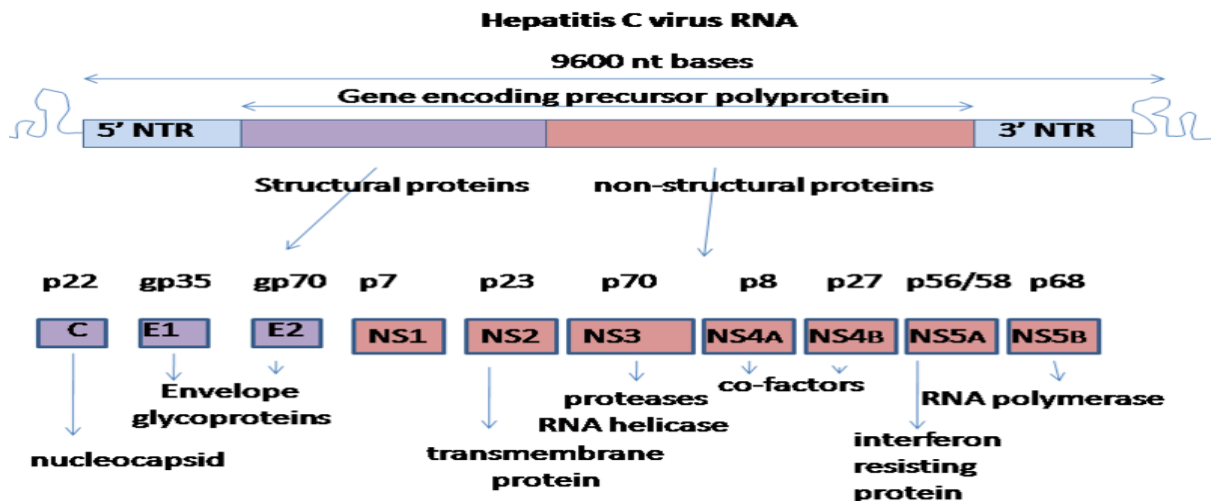
Note: in hepatitis B virus it has 4 open reading frames .

In hepatitis c we have 3 structural proteins and 5 nonstructural proteins

Structural proteins are :

- *the core and the capsid protein
- *E1 and E2 envelope glycoproteins and within the E2 structural protein we have 2 hypervariable regions and those hypervariable regions have high mutation rate and as a result high antigenicity or multiple genotypes.

Non structural proteins : we have NS2 , NS3 , NS4 , NS5 in addition to NS1 or P7 which is the ion channel , and the NS5 is the RNA dependent RNA polymerase.



*Like the other RNA viruses the RNA dependent RNA polymerase lacks proof reading so there is a high rate of mutation in HCV and HCV considered one of the viruses that replicates very fast so in 24 hours 10^{12} new virions are being produced and since RNA dependent RNA polymerase lack proof reading so the mutations are going to be very high and this will lead to formation of what we called **quasi species** which is the pool or the total amount of mutated virions .

Replication cycle of HCV :

*Starts by binding of the glycoproteins into receptor on target cells it can infect B , T lymphocytes , monocyte, but the primary target is the Hepatocytes.

* CD81 , CLDN1 , SR-B1 in addition to LDL(which is thought to chaperon the hepatitis C virus to the hepatocytes) , they are all and in addition to some other receptors on the hepatocytes are thought to play a role in internalization of HCV into the hepatocytes after that it enters in the form of receptor mediated endocytosis .

*Drop in the PH will lead to fusion between the viral and the endocytic vesicles and release of the nucleocapsid , this step is followed by uncoating and release of the +sense RNA .

***For translation:** +sense RNA goes to the ribosomes and gives us polyprotein and this polyprotein is further cleaved into individual proteins .

***For replication of the genome :** we have a negative sense intermediate which has a template for the replication of the genome which is going to be the genome for the newly produced viruses .

After that assembly occurs and the virus is released from the body infected cells .
refer to the picture in the slide ☺

*Transmission of HCV :

*the main route for transmission is parenteral through blood products , IV drug use , contaminated needles .

*Vertical transmission is possible also (vertical transmission : is an infection caused by bacteria, viruses or, in rare cases, parasites transmitted directly from the mother to an embryo, fetus or baby during pregnancy or childbirth)

*role of sexual transmission is questionable and they think that HCV transmitted in homosexual but it's not the main route for transmission.

*20% of hepatitis c cases the cause is unknown; might be due to denial of patients the usage of IV drugs .

***HCV pathogenesis :**

*Liver damage in hepatitis C virus occur as a result of the immune system whether the innate or the adaptive immune systems .

*The adaptive is divided into humeral and cellular.

And all of these are union in destruction of the liver by formation of fibrosis, cirrhosis and eventually hepatocellular carcinoma .

*Innate immunity :

1)activation of cytokines and INF which play a role in protection against the virus but the virus evades and cause liver damage .

2) Natural killer cells lead to fragmentation of nuclei of infected cells and induces apoptosis

*For the humoral immunity : we have highly antigenic location in E1 and E2 (remember these are the enveloped glycoproteins and there is high mutation rate due to the lack of proof reading in RNA dependent RNA polymerase) E1 and E2 are most important in neutralize antibodies against HCV and once there is mutation in the glycoproteins (especially in glycoprotein E2) the preformed antibodies will not be protective against the new species or the new antigens in the mutated glycoproteins and this will lead to persistent of the infection

*In addition to this antigenic variation it will lead to high variable antibody production , these antibodies are not able to neutralize these new viruses but it would rather bind to the antigen and this will form antigen-antibody complexes , these complexes will deposit in the liver or in extrahepatic location (kidney, small blood vessels) and they will activate a complement and cause damage to all these organs

*CD4 T cells secrete proinflammatory cytokines and leads to hepatocyte death in addition to CD8 which recognize MHC1 on viral infected cell and lead to cell death

*other factors which increase the severity of HCV infection : alcohol , smoking ,and co-infection with other Hepatitis viruses and HIV .

*patients may develop cirrhosis in the liver with increased hepatocellular carcinoma ,how could the patient reach to this state : first we have infection which will cause inflammation in the liver and as a result of the immune system we would have necrosis , apoptosis and since it is a chronic process and the liver cells are able to regenerate so patient will have rounds of :damage then regeneration damage regeneration and so on ...and this lead to fibrosis, cirrhosis and hepatocellular carcinoma.

*cirrhosis is seen in 25% of patients of chronic hepatitis

***clinical feature of HCV:**

-Incubation period of HCV is about 2 months

-Clinical illness or symptoms : 70-75% are asymptomatic and 20-30% of whom are symptomatic would have jaundice .

-chronic hepatitis is seen in 70% of the cases and persistence or carriers are seen in 85%

-Immunity : there is no protective antibody .. we have neutralizing antibody if the antibody is effective (because of E1 and E2 glycoproteins as we said before)

***Clinical presentation :**

We have acute infection and chronic infection : 15% are acute and 85% are chronic .

*in acute infection we have nonspecific symptoms such as fatigue, nausea, vomiting joint pain and jaundice .

*the infection resolves spontaneously in 10-50 % of cases of acute infections

The risk will be in the 85% who develop the chronic infection

*if the viral replication persist for more than 6 months then patient will enter the chronic stage .

*in chronic infection the patient might not know that he is infected with HCV for 10 to 20 years and he can know only by laboratory diagnosing which there will be elevation in the liver enzymes .

*chronic infection after several years may cause cirrhosis or liver cancer .

In slide 9 the doctor just read the percentage in HCV infection so please look at them

Laboratory diagnosis :

*in hepatitis C serology test can be used for diagnosis but it's not that efficient or effective as in other hepatitis viruses because from serology we can't tell if the infection is acute or chronic because we don't have specific antibodies to differentiate acute from chronic; also because anti hepatitis C or the antibody titer might take 4 weeks to 4 months to appear so it will not be effective especially in acute infection, also in the case of vertical transmission most infants or neonates

would have maternal antibodies for 1 and half year so serology won't be a good investigation to diagnose hepatitis C .

* HCV-RNA : we can detect that via polymerase chain reaction , can be used for diagnosis but it's used to monitor the effect antiviral therapy .

*HCV-antigen

*HCV genotyping : as we said genotype 1 and 4 are resistant to treatment and has poor prognosis .

*viral Load : can be used to monitor the response of antiviral treatment .

Treatment :

*When we say treatment in HBV and HCV we mean treatment in the chronic phase of the illness so in HBV in the case of acute infection there is no need to give any form of treatment but in HCV theoretically treatment could be given in the acute phase but they prefer to give the body or the immune system the chance in order to recover from the virus but in case of signs of liver damage or chronic state treatment can be used .

*once patient is in the chronic phase clearance of the virus can but very rarely occur without treatment .

*with treatment 40-80% of those with chronic hepatitis c would clear the virus

*Drugs that we can use for hepatitis C treatment :

1)Interferon or pegylated interferon which can be used once weekly

2)Ribavirin

* the combination of Ribavirin and Interferon has better outcome than those individual antiviral drugs

3)Sofosbuvir : which is a new drug has been approved by the FDA , this drug can be used as a combination with Ribavirin as the first interferon free therapy against HCV in case of genotype 2 and 3 its given as a 12 week therapy and given once a day so its 84 tablets , and in genotype 1 and 4 it is used in combination with Ribavirin and Interferon (triple therapy) it's give as a 24 week therapy 168 tablets .

***prevention of HCV :**

Prevention is like other viruses : screening of blood ,tissue donors , high risk behavior modification ,blood and body fluid precautions.

GB virus c :

*It was previously known as hepatitis G now it's known as GB virus c and investigation failed to identify any association between the virus and any clinical illness so it's no longer associated with hepatitis

* it was found with the co-infection with hepatitis c and with HIV

*Transmitted through parenteral ,sexual and vertical transmission