بسم الله الرحمن الرحيم

Last lecture we complete talking about DNA viruses and we start talking about hepatitis viruses .

In this sheet we will cover hepatitis viruses in detail ,and we will talk about some other RNA viruses .

Notes about the previous lecture :

*hepatitis viruses are RNA viruses except for HBV , they are 6 viruses (A,B.C.D.E.G) .each one belongs to certain family (viridae).

*in the table :

-insidious: slow but very harmful .

-HBV, HCV :have the longest incubation periods (IP)

-s:sexual , p:parenteral , fo : fecal oral .

-HAV : transits by FO and P (not s)

-carrier state :means that the virus remains in the body and can't be cleared , still replicating there .

****

Hepatitis viruses :

**hepatitis A virus (HAV):

it is a naked (+) sense ssRNA virus ,with icosahedral symmetry . it is related to enteroviruses ,formally known as enterovirus so it was classified with them . it was known as enterovirus 72 ,nowadays it is a hepatovirus of the picornaviridae family .

there is one stable serotype only; 4 genotype exist (in practice most of them are group 1) . it is difficult to be grown in cell culture ,but it can be grown in it (in comparison to HBV

that can't be grown in a cell culture).

-cause diseases in children and young adults:

In children :the symptoms are mild or asymptomatic.

In the adults : the symptoms are more severe and the jaundice is more .

-HAV invade/enter to the human body through fecal oral (FO) route , multiply in the intestinal epithelia, goes to the blood causing viraemia, after that it goes to one bed later, goes to the hepatocytes and replicate there .then it is released in the bile and in the feces.

-refer to the graph in the slides:

These are the serological markers,(in hepatitis viruses these serological markers could help us in diagnosis and knowing which stage of infection the patient is in).

For HAV : we notice that we have short IP (incubation period), after that the symptoms start to appear this is associated with increase in the liver enzymes(ALT),at the same time we start to see production of IgM and IgG antibodies for hepatitis A .

-for the presentation we have 2 stages :the preicteric (predromal)and the icteric.

The icteric or the icterus is the jaundice(so we have jaundice and prejaundice).

Prejaundice ,there is fatigue, joint and abdominal pain , vomiting, lack of appetite and enlargement of the liver.

icteric phase ,we have jaundice which can be seen in the skin, sclera ,mucous membranes .and it is associated with elevated bilirubin level. This elevation is translated as bilirubinuria (it is excreted in the urine, and gives dark color to the urine and pale or clay colored stool).

-treatment :There is no specific treatment for HAV ,we have an immunoglobulin from which from which the patient can benefit ,especially immunocompromised patients.

The treatment is supported with adequate nutrition and rest . (nowadays there is a common behavior in dealing with hepatitis patients ,we give them sweets ,rest…but what is the idea behind this, we don't know!! You can search for it ☺)

You can give passive immunization ,active immunization or the vaccine (formalin killed HAV ,it is 100% protective and given in 2 doses with 6-12 months apart).

**hepatitis B virus (HBV):

It is the only DNA virus ,it is a partial dsDNA virus .replication involves a reverse transcriptase (we took it ,replication NO.7).it is endemic in the human population ,and hyperendemic in many parts of the world. there are 8 genotypes. not yet possible to grow it in a cell culture.

-refer to the slides to see the 2 forms of HBV :

Once HBV replicates in the body ,it is going to produce these 2 forms :

a)it is the mature progeny virus ,which has the genome and surface antigens.

b)we have 2 forms ,one is the filamentous and the spherical form ,which contains the HB surface antigen only, it doesn't have the genome .

the production of these 2 forms (b)during replication of HB is more than the production of the progeny virus which have the nucleocapsid .

these are the structures from which HB benefits and become a complete virus .

*in HBV we have : HB surface antigen (HB s antigen)

HB e antigen

HB core antigen

(they are important because we will benefit from them in knowing the stage of the illness and in serology -serological markers-)

in acute infection we have HB s antigen and HB e antigen ,at the same time the HB core antibody (IgM anti HB core) is seen also in the acute stage.

HB e antigen is associated with active replication of the virus (it's presence in the serum means that the virus is replicating in the body).

If you can detect anti HB antibody ,it means that the virus is no longer replicating.

Anti HB s antigen means previous infection or previous exposure either from infection or through vaccination .

HBV (Dane particle) is an enveloped virus ,core antigen is located in the centre ,e antigen is linked or related to the core (an indicator of transmissibility)

It is a minor component of the core (antigenically distinct from the core antigen –so they are 2 separate antigens but the e antigen is a minor component of the core antigen-)

The spherical and filamentous (22nm) forms don't have the DNA so they are not infectious, although their numbers more than the progeny virus itself.

-we have about 350 million carriers of HBV worldwide, the carrier rate can exceed 10 %(10-15 %of infected persons can become carriers).

15-20% of chronically infected patients will die from chronic liver diseases (as we said chronicity is associated with damage to the liver which will lead to cirrhosis ,transformation of the liver ,leading to hepatocellular carcinoma. both of cirrhosis and hepatocellular carcinoma require liver transplant, if the patient doesn't receive liver transplant he will eventually die).

-pathogenesis and immunity:

virus enters hepatocytes by the blood , immune response by cytotoxic T cells to viral antigens expressed in hepatocytes cell surface is responsible for clinical syndrome.

During the replication of the virus in the hepatocytes ,the immune system especially cytotoxic T cells play a role in the lysis of viral infected cells . the liver has the ability to regenerate ,so the harm that you can see in the form of in increase the level of liver enzymes can be due to the infection itself or due to the immune system attacking the hepatocytes and destroying them in order to contain the viral infection.

At the same time, not all the hepatocytes are infected, so not all the liver is infected at the same time.

20-25 % of hepatocytes are infected at the same time only.

So again , the infected cells are targeted by cytotoxic T cells ,it is lysed ,the liver has the ability to regenerate itself(this cycle of infection, lysis, regeneration also responsible of liver transformation leading to hepatocellular carcinoma).

10 % become chronic carriers ,higher risk of hepatocellular carcinoma is seen in chronic carriers especially those who are e antigen positive.

*HB s antibody indicates lifelong immunity, HB e antibody indicates low transmissiblity (e antigen: active replication. e antibody :no longer replication/no longer transmissible or infectious).

-refer to the slides to see the serology diagram of HBV:

HB s antigen with HB e in the acute stage. Followed by IgM of anti hepatitis B core , and we have anti HB e antigen (in this stage no active replication-the patient is in the recovery stage-anti HB s antigen means recovery as well).

We can see what is called window period ,you can neither see HB s antigen nor anti HB s antibody (in fact there is HB s antigen and antibody ,but at this stage the antigens are neutralized by the antibodies –that’s why during the window period you can't detect the antigens or the antibodies).

There is a conflict between the antigens and the antibodies until the body can overcome the production of the virus. at this stage the antibodies start to appear again (which means the patient has been exposed or previous infection). Anti HB core IgM is a marker of acute infection, while Anti HB core IgG for chronic infection.

The DNA of the virus can be detected using PCR ,and it indicates active replication of the virus.

-treatment: We can use interferon , lamivudine , adefovir and entecavir.

-prevention: we have vaccine(it should be given to those who are at higher risk to get the infection such as health care workers).we have also HB immunoglobulins.

(Q: you are doctors, working with patients, suppose that you deal with a patient that was infected with HB ,you are not aware and you get a needle sting while working with him !!what you will do ??

We have 2 conditions :vaccinated or not vaccinated .

If not vaccinated ,you should give immunoglobulins immediately and start the vaccine.

If vaccinated ,immunoglobulins are given immediately and you should measure the titer of the vaccine if it is protective no need to give vaccine .if it is lower than the protective level you should give the booster dose then re-measure it again to see if becomes protective or not.)

*infants: there are several options depending on the status of the mother.

If the mother is HB s antigen negative ,then you should give the vaccine at birth,1-2 months,6-18 months.

If the mother is HB s antigen positive ,vaccine and HB immunoglobulins are given within 12 hours of birth,1-2months then 6 months.

In the national vaccination program that we have in Jordan, HB vaccine is given 2-4-6 months. but in western world ,newborn receives within

couple of hours of birth HB vaccine and gets vitamin k (to prevent bleeding).

*in adults :as medical students, you should take the first dose today, one month later the booster dose ,then six months or more you take the second booster dose.

**hepatitis D virus(HDV ,or the delta agent):

It consists of particle 35 nm diameter ,consisting of the delta antigen surrounding by outer coat of HB s antigen.

The genome of the virus is very small consisting of ssRNA ,although it is RNA virus but it replicates in the nucleus using the cellular machinery .

The genome /RNA is from the virus and HB s antigen is required for HDV to replicate .so it comes as co infection or super infection .

It shows similarities with viroids in the plants.

**hepatitis C virus (HCV):

Spherical , icosahedral , positive sense ssRNA virus . we have the nucleocapsid ,the envelop, the glycoproteins (E1 and E2).

In E2 we have a hypervariable region ,it is associated with very high rate of mutations .

HCV is one of the fastest replicating viruses, you can have up to 1 billion progeny virus in 24 hours.

It has RNA dependent RNA polymerase (which lacks proof reading, so it is going to introduce many mutations during the replication of a single virus).

So at the end of the day (after24 h),after getting one billion progeny virus, you can't find a virus that shares the genetic code with other

viruses .so we have huge variation in the genome of HCV , that’s what we call "quasi species".

-serology :

Chronicity here is seen in 85% of patients ,in comparison with 10-15%in HBV.

An important thing about the serology of HCV ,you might not get a seroconversion against the virus up to 4-6 months.

Also HC infection most of the time is not associated with acute illness , it goes or passes unnoticed(asymptomatic),and the patient is diagnosed when he becomes a carrier.

Refer to the graph in the slides:

We have the IP ,then you see the symptoms (associated with increase in the liver enzymes .but you see that the level of the enzymes are going up and down ,why?? Due to regeneration –cytotoxic T cells kill the infected cells ,regeneration, improvement of the liver enzymes-).

-diagnosis :we can detect RNA by PCR (reverse transcribe RNA) . RNA can be used as a marker for improvement with antiviral treatment (when you start with antiviral treatment you measure the viral load –amount of RNA in a specific volume of the serum ,after that you start giving antiviral drugs ,and to see how effective is the antiviral drug is working you should see a decline in the titer of the virus) .

-treatment: pregerated interferon and ribavirin .

*like HB we have cirrhosis ,hepatocellular carcinoma which need transplant.

In HC we see another phenomena ,we have quasi species which have variation(due to the hypervariable region in E2 glycoprotein). the body responds to the presence of these glycoproteins by producing antibodies, so we will have multiple antigen-antibody complexes due to the variation. these complexes might precipitate in extrahepatic

locations such as the joints , skin , kidneys causing arthritis , skin problems , glomerulonephritis respectively .

**hepatitis E virus (HEV) :

It is a calici like virus ,it is unenveloped, (+) sense ssRNA genome .it is very labile and sensitive, was cultured recently. Again ,we have IP ,we see elevation in the liver enzymes and the production of IgM and IgG which give lifelong immunity. There is no vaccine.

**hepatitis G virus (HGV):

Belongs to flaviviridae family .

Transmission: by parenteral transmission.

*we said that HDV is completely associated with HBV(no HD infection without the presence of HB infection).here they find that 10-20% of patients infected with HCV also infected with HGV.

Prevalence is higher In HC infected persons.

Other RNA viruses:

We have already talked about some RNA viruses (hepatitis A,C,D,G,E)

Check the slides to see divisions of RNA viruses .

We have: ssRNA ,(+) and (-)sense. dsRNA(the only one is reoviridae family which is the rotavirus ,it is the number 1 cause of gastroenteritis in infants).

*(+) sense enveloped icosahedral we have :

Flaviviridae, togaviridae(most of these viruses cause what we called zoonotic infections e.g rubella), retroviridae(which is HIV).

*(+)sense enveloped helical :

Coronaviridae (coronavirus causes common cold URT infection).

*(+) sense nonenveloped icosahedral:

Picoronaviridae, caliciviridae., hepatits A .

Also we have Norwalk virus which is associated with gastroenteritis especially among adults in summer camps……

*(-)sense enveloped helical :

Orthomyxoviridae(such as influenza virus) ,paramyxoviridae(RSV, parainfluenza virus),rhabdovirus (rabies virus).

Filo , buny , arena viridae which also cause zoonotic viral infections.

Now let's talk about some of these viruses in detail …

** influenza virus :

-It is an acute RTI that usually occurs in epidemics.

-The viruses receive their names from their special affinity to mucous.

*the immunologic types of the virus:

We have A,B,C.

C is not associated with illness.

Type B,C strictly infect the humans .

A can infect humans, mammals, birds (this is the one that we see reassortment with). Cause swine flu and avian flu.

- it is spherical virus, helical nucleocapsid, one of the segmented viruses (we talked about 2 segmented viruses :influenza and rotavirus),it has 8 segments (except C has 7 segments) while rotavirus has 11 segments.

It is an enveloped virus ,has 2 glycoproteins .glycoproteins are inserted in the envelop and expose the spikes ,HA and NA(H and N) which are haemagglutinin and neuraminidase .there are also certain structural proteins which are specific to different types of influenza .. N2 in Influenza A and NEB in Influenza B .

Each of RNA segments encode for certain viral proteins : seg. 4 encode for HA , seg.6 encode for NA .

-The 2 surface antigens of influenza undergo antigenic variation ,independence of each other ,what did we call this phenomena ??

Antigenic drift (the variation introduced by mutations into the glycoproteins H and N).

Note: reassortment (antigenic shift) for example : human ,swine ,bird influenza can infect a pig cell and the reassortment occurs there. We call it antigenic shift (which is the mixing of the segments into new progeny virus ,which might give more virulent strain).

-we have 4 HA (1,2,3,5).

Actually we have more than 4, but those which are associated with human diseases mostly 3 from HA (1,2,3) and 2 from NA (1,2).

(from this we have for example :H1N1, H5N1. It is based on the glycoproteins).

*(H5N1) after1997 they found that all 8 segments of the bird influenza have jumped and infected the human , and when there is crossing of the species , it is always associated with more virulent infections.

Avian influenza is not transmissible from human to human, so you can break the cycle by destroying the infected birds.

-the virus is inhaled through aerosols or droplets, after that it will replicate in the URT most of the time leading to desquamation of the mucous secretion and ciliated cells , it is a lytic infection (leads to destruction of cells in the URT) which gives us the influenza syndrome .

It could be associated or complicated with LRT infection leading to pneumonia . we can see bacterial super infection (bacterial on top of viral infection), we can see many complication.

-refer to the slide to see the pictures:

The first figure shows normal URT . 3 days post infection we see that all cilia have been disappeared (it is a lytic infection that destroyed all the cilia).

7 days post infection ,they start to grow once again (their growth might take up to from 6-10 weeks) in order to get to the normal or pre-infection state .

-the virus infection itself takes from 7-10 days maximum for complete recovery .but the patient may remain symptomatic up to a longer period of time ,especially coughing. The cilia clear any mucous, foreign bodies or foreign antigens ,so when you lose them due to the infection ,the body compensate by coughing .(so may be suppressing the cough by cough suppressants is not good idea , it is up to you ☺).

- symptoms :cough , fever , headache ,myalgia , rhinitis and ocular symptoms.

It is more sever in the very young , elderly, immunocompromised or those having preexisting conditions in the lungs or heart .

-complications :

we might see croup (acute laryngotracheobronchitis – infection of larynx, trachea and bronchus) .it is a complication of influenza infection, but you should also link croup with parainfluenza infection.

We have nonpulmonary complications such as myositis, cardiac complications , encephalopathy , liver and CNS complications, Reye syndrome , PNS complications (Guillian-Barre Syndrome)

For Reye syndrome : especially for children , you shouldn't treat fever with aspirin or acetaminophen, because this will lead to Reye syndrome . in this syndrome we can see :fatty changes in the liver , brain edema ,

vomiting , lethargy , coma . (again the risk factors are children treated with aspirin for fever) .

-diagnosis : serology or isolation of the virus in a cell culture .

- treatment and prevention :

*How many drugs we have for influenza ?? 4 .

2 for A type (amantadine and rimantadine , only for A because of M2 protein , work by blocking uncoating) .

2 for A and B together (ciltamavir and zamafavir , which are neuraminidase enzyme inhibitors).

*Do we have vaccine for the influenza ?? yes ,we have 2.

intranasal : benefits from the phenomena of reassortment (we see what are the most pathogenic strains in the previous years. We take the segments of H and N ,put it into live attenuated vector and then give it intranasally .it replicates in the URT ,goes to the blood causing viraemia , the body exposed to H and N antigens then produce antibodies against them).

#shots (IM) : composed of 2 type A strains and one type B strain . it is a killed virus vaccine . so they take either the whole virus or the glycoprotein component of the virus ,and 2 of the most pathogenic A strains and one of the most pathogenic B strain in the previous year .

So the production of the vaccine this year depends on our knowledge in the previous year (vaccines might become non beneficial because of the antigenic drift)

Taking the vaccine doesn't mean that you won't get infected again and it's made in Western side of the world not here (Jordan).

The best time to give the vaccine : as early as July you start giving the vaccine ,but the best time August ,September ,October. No more than October.

** parainfluenza virus :

-it is(-) sense ssRNA virus , enveloped.

-we have 4 serotypes (1,2,3,4).

-we have 2 glycoproteins:

*fusion peptide (F): used for fusion.

*haemagglutinin neuraminidase tetramer(H and N come as one glycoprotein) .

-type 1 is associated with acute croup, pharyngitis , tracheobronchitis.

Type 2 :acute laryngotracheobronchitis.

Type 3 : LRT infection in children .

Type 4 :URT infection . it is the least common one .

-Parainfluenza causes most cases of croup (although croup can come as a complication of influenza virus or even as presentation of infection with other RT viruses such as RSV ,but the first thing should come to our mind is parainfluenza virus).

Other conditions may be caused by it : bronchitis , pneumonia , tracheobronchitis and Corza like illness

-diagnosis : detection of antigen , virus isolation , serology , PCR .

-management :

No vaccine , no antiviral drugs , . it is a self limited mild URT illness .

** respiratory syncytial virus (RSV):

it has the ability to form syncytium or multinucleated giant cell(from this, its name is derived)

it is a ssRNA enveloped virus, belongs to the genus pneumovirus of paramyxovirus family .

considerable strain variation exist causes a sizable epidemic each year ,present worldwide .

peak incidence: 2-5 months age, seen more in winter months .

it is associated with acute bronchiolitis and bronchopneumonia in infants (2-5 months)

reinfection through the life is common but at milder level.

IP 2-8 days .

Ocular, nasal contact of infected secretion are mode of transmission.

We can see cough, runny nose and rhinorrhea.

50 % of primary infections spread to LRT, associated with acute bronchiolitis and bronchopneumonia .we can see hyperinflation and pneumonia in chest X –ray .

Sorry for any mistake ,but I didn't have the slides when I wrote it .

Hope it will be helpful ☺ ☺

Done by : lara Ramadan .