الجهاز الهضمي

علم الأمراض

رقم المحاضرة : ٥

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Color code:
SLIDES IN BLACK
What the doctor said in RED
What is important in purple
What is additional and for further understanding in BLUE

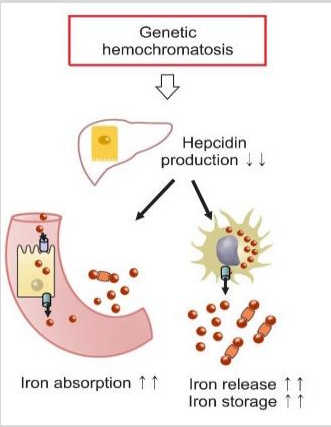
The lecture topics

1) **Metabolic liver diseases :**

- Hemochromatosis (Fe)
- Wilson disease (Cu)
- Alpha-1-Antitrypsin disorder

We talk about **Hemochromatosis** (the important summary): that is **Autosmal recessive** disease because of inherited mutation in the gene that is responsible of hormone production = **Hepcidin hormone** to control iron absorption… the gene is **HFE gene**

Additional image:



-Two mutation can occur in HFE gene:

1 Mutation at 845 nucleotide → tyrosine substitution for cystine at AA 282 (C282 Y)

C282Y mutation is the most common HFE mutation.

2 aspartate substitution for histidine at AA 63 (H63D)

10% of pts. have other gene mutations

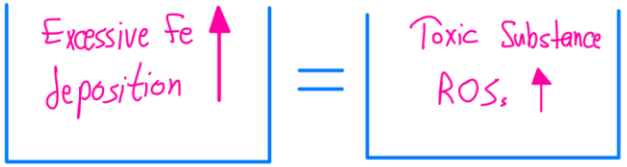
-Carrier rate for C282Y is 1/70

-Homozygosity(two identical mutated allele)is 1/200

-80% of pts. are homozygous for (C282Y) mutation & have the highest incidence of iron accumulation

-10% of pts. are either homozygous for H63D mutation or compound heterozygous for C282Y/H63D mutation

Why are these informations important ?
If we try to screen for Hemochromatosis disease , we should look for common mutation of HFE gene.However, the absence of common mutation doesn't mean there is no disease but that mean there are other less common mutation.



Excessive Fe deposition → toxicity of the tissues. Mechanism of liver injury include the following :

1. **Lipid peroxidation via iron catalysed free free radical reactions**
2. **Stimulation of collagen formation by activation of hepatic Stellate cells**
3. **DNA damage by reactive oxygen species.**

These notes from the book

Morphological changes:

1 Deposition of hemosiderin in diffferent orgens

Liver

Pancreas

Myocardium

Pituitary

Adrenal

Thyroid & parathyroid

Joints

Skin

2 Cirrhosis

3 Pancreatic fibrosis

Hemochromatosis is multisystemic disease which means that the doctor has to check other organs as:

Pancreas (for D.M)

Myocardium (for fibrosis)

Adrenal gland (for Endocrine problems)

Joints (for joint patient as pseudogout)

Skin (for spots or pigmentation because of hemosiderin deposition.

Hemochromatosis can lead to complications in various organs, including the testes. In males, hemochromatosis can lead to testicular dysfunction, which may manifest as hypogonadism (reduced testosterone production) and infertility. Excess iron deposition in the testes can damage the testicular tissue.

-No inflammation

-Fibrosis

-Cirrhosis

-Synovitis

If the patient has joint problem,will have synovitis. Synovitis is swelling (inflammation) in the synovial membrane that lines some of your joints.

-Polyarthritis(pseudogout)

-Pigmentation of liver

-fibrosis of pancreas & myocardium

-Atrophy of testes

Clinical presentation

M:F 5 – 7 :1 5 – 6 the decades

Hepatomegaly

Abdominal pain

Skin pigmentation

D.M

Cardiac dysfunction

Atypical arthritis

Hypogonadism

$erum Fe ferritin

HCC 200x in the risk

Symptoms usually appear earlier in men than in women the menstrual bleeding limits the accumulation of iron until menopause.

Because of increase oxygen reactive species

Additional (help you to remember 😁)

1. "Hypo": This prefix means "below" or "under."
2. "Gonad": This refers to the reproductive organs, specifically the testes in males and the ovaries in females.
3. "Ism": This suffix is used to denote a condition or state.

Wilson Disease

Now, we will talk about second metabolic disease which is less common than Hemochromatosis , is Wilson disease

-aut. Recessive disorder of Cu metabolism

-mutation in ATP7B gene on chr. 13 which encodes an ATPase metal ion transporter in Golgi region

-> 80 mutations

-Gene freq. 1:200

-Incidence is 1:30000

Pathogenesis

Main source of Cu is from diet

↓

Absorption of ingested Cu (2-5 mg/d)

↓

Complex with albumin

↓

Hepatocellular uptake

↓

Incorporation with α-2-globulin to form Ceruloplasmin

Explain next slide

↓

Sec. into plasma

(90 – 95% of plasma Cu)

↓

Hepatic uptake of ceruloplasmin

↓

Lysosomal degradation

↓

Secretion of free Cu into bile

More one? 👇

- **In Wilson disease absorbed Cu. Fails to enter the circulation in the form of ceruloplamin & the biliary excertion of Cu. is ↓**
- **Defective function of ATP-7B →failure of Cu. excretion into bile & inhibits sec. of ceruloplasmin into the plasma →Cu. accumulation in liver**

Explain the pathogenesis:

Befor talking about pathogenesis, we should mow the normal condition of copper metabolism.

1) Main source of Cu is from diet
2) Apsorbtion of Cu in small intestine
3) Cu forms a complex with albumin
4) Then inter the circulation until reaches the liver
5) In liver: Copper is released from copper-albumin complex to incorporate with alpha2-globulin this formation is called ceruplasmin .
6) Then ceruplasmin is secreted into blood circulation to different organs for utilizing copper for many Biochemical processes and any excess of ceruplasmin back(uptake)to liver .
7) The copper is released from ceruplasmin and incorporated with bile for exc via feces.

Now, what is the problem?

Mutation of ATP7B gene (longe gene) Which results in failure to incorporate copper into ceruplasmin and impaired in copper exc into bile .

The result is accumulation a toxic level of copper in liver and other organs as brain  and eye  .

-↑Cu. Accumulation in the liver reults in:-

1-Production of free radicals toxic substances

2 binding to sulfhydryl groups of cellular proteins

3 displacement of other metals in hepatic metalloenzymes

-By the age of 5yrs. Cu. Spills over to circulation causing hemolysis & involvement of other organs as brain & cornea also kidneys, bones joints & parathyroid glands

-Urinary exc. Of cu. ↑

In the liver, we have different changes because of copper accumulation .

If the patient is young , he/she might have any of these liver morphology

Morphology

Liver

1- Fatty change

2- Acute hepatitis

3-chronic hepatitis

4-cirrhosis (late diagnosis)

5-massive hepatic necrosis

(rhodanine stain or orcein stain)

Unlike iron, copper doesn't have specific stain to find it…also the electron microscope can't differentiate iron from copper, really we depend on clinical manifestations and other tests for diagnosis

Brain (very important organ in Wilson disease) :

Toxic injury to basal ganglia esp. the putamen causing atrophy of ganglia & cavitation (cavities because of dead cells)

The patient might have neurological and psychological manifestations .
Such as: behavioural changes, dementia and chorea.

Eye:

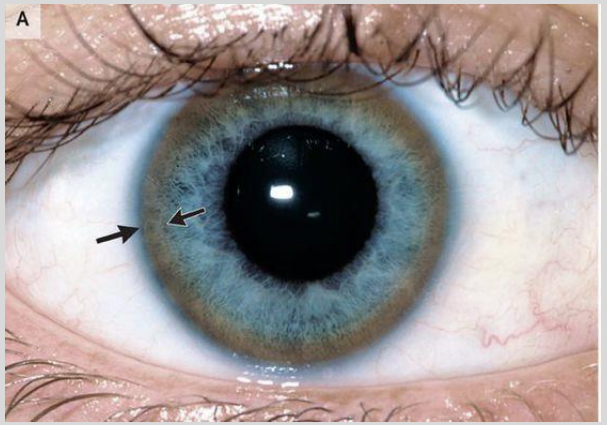
We need ophthalmoscopy for kayser-fleischer rings examination.

kayser- fleischer rings

green – brown depositis of Cu. in descemet membrane in the limbus of the cornea

Wilson disease also is Known as(hepatolenticular degenceration)

Also we might notice this manifestation by physical examination :



Age ↑ clinical manifestation appearance ↑

- **Clinically**

-Presentation > 6 yrs of age

-Most common presentation is acute on chronic hepatitis

-Neuropsychiatric presentation can occur :

Especially for children at school age

behavioral changes

Frank psychosis

Parkinson disease- like syndrome

disease for elder people

Diagnose

- **DX**

1- ↓ in serum ceruloplasmin level

2- ↑ in urinary exc. Of Cu.

3- ↑ hepatic content of copper

> 250 mg/gm dry wt.

1) Because no incorporation of copper with alpha2 globulin
2) Because no excretion through small and large intestine … another way is urinary excretion
3) Because of no formation of ceruplasmin , the copper cannot leave the liver and be released to circulation

α-1-Antitrypsin Defeciency

-- Aut. Recessive disorder

- freq. 1:7000 in N. american white population

- α-1-antiryrpsin is an enzyme which is a protease inhibtor, examples of proteases include elastase, cathepsinG , proteinase 3 which are released from neutrophils at the site of inflammation (destructive enzymes which act on different components of ECM, walls of blood vessles or airways).

-The gene pi. Is located on chr. 14

-At least 75 forms of gene mutation are present

-The most common genotype for encoding the protein is pi.MM present in 90% of individuals (normal)

-PiZZ genotype →↓ level of α-1-antitrypsin in blood (only 10% of normal) are at high risk of developing clinical disease

A less frequent inherited condition.
The presentation may not be clear, so it's usually diagnosed by the exclusion of other diseases.

Proteases have an important function at sites of inflammation where they inactivate and kill pathogens. However, these enzymes may introduce damage to the normal cells of the host, so an inhibition over them after inflammation subsides is required and that's primarily indicated by proteases inhibitors like alpha-1 antitrypsin.

Alpha-1 antitrypsin deficiency leads primarily to the development of pulmonary emphysema because the activity of destructive proteases is not inhibited, resulting in excessive damage of lung parenchyma and wall of vessels.

So what are the effects of this condition on the liver? Alpha-1 antitrypsin is synthesized in the liver, in this condition, it will also causes liver disease as a consequence of hepatocellular accumulation of the misfolded Alpha-1 antitrypsin protein .

Remember that the excessive deposition of any substance within hepatocytes will eventually results in damage.

pathogenesis

-The mutant polypeptide (PiZ) is abnormally folded & polymerizes causing its retention in the ER of hepatocytes

-Although gh all individual with Pizz genotype accumulate α-1-AT-Z protein only 10% of them develop clinical liver disease .The pathogenesis is not primarily restricted to the liver. This is due to lages in ER protein degradation pathway

Since it's a recessive disorder, loss of the 2 normal alleles is required to develop the disease (homozygous).
While carriers who carry the heterozygous genotype of PiMZ have intermediate levels of misfolded proteins.

This disorder must be accounted during differential diagnosis as it may be found incidentally in patients with liver cirrhosis.

-The accumulated α-1-AT-Z is not toxic but the autophagocytic response stimulated within the hepatocytes appear to be the cause of liver injury by autophagocytosis of the mitochondria

-8-10% of patients develop significant liver damage

Morphology

-Intracytoplasmic globular inclusions in hepatocytes (within the cytoplasm) which are acidophilic in H&E. sections

-The inclusions are PAS-+ve & diastase resistant

-Neonatal hepatitis cholestasis & fibrosis Chronic hepatitis

Cirrhosis Fatty change

Mallory bodies (they're similar in appearance, but not as large as mallory bodies)

- Clinical features

-neonatal hepatitis (very severe) with cholestatic jaundice appears in 10 – 20% of newborns with the disease

-Attacks of hepatitis in adolescance

-chronic hepatitis & cirrhosis

-HCC in 2- 3 % of Pizz adults + cirrhosis

Cells are full of collagen, PAS stain may not be sufficient to show alpha-1 antitrypsin protein, so we use PAS with diastase stain. Diastase stain releases collagen from cells by degradation, so any remaining globules in the cytoplasm are considered to be alpha-1 antitrypsin.

Neonatal hepatitis is a very severe category of diverse diseases that affects newborns , which includes alpha1 antitrypsin deficiency. Patients may present years afterward with acute hepatitis,jaundice (very important and may also be associated with hemolytic anemia), cirrhosis, fatty change and many other severe manifestations.

Unfortunately, these changes may not be apparent in a degree sufficient to be diagnosed quickly or may have normal results of liver tests, so as we mentioned before, it has to be on differential diagnosis list.

Very important

Reye's Syndrome

- Microvesicular Fatty change (infiltration) in liver & causing liver failure and Encephalopathy

A serious condition

-< 4 yr.

-3 – 5 d after viral illness

-↑liver & abn. LFT Vomiting lethargy. 25% may go into coma

A very severe insidious condition that has no specific treatment, only supportive treatment.

Liable patients are young and patients' history shows having a viral illness days before.

Liver function tests will show abnormal results, liver is enlarged as well.

Symptoms may include vomitting,unconsciousness and may exacerbate to coma and death.

Pathogenesis

-Derangement of mitochondrial function along or in combination with viral infection & salicylate (like aspirin)

-Microvesicular steatosis (can be seen under the microscope)

-Brain edema which leads to neurological manifestations and encephalopathy.

-Absent inflammation (the problem is due to failure of function not an injury to hepatocytes)

-Sk. Muscles, heart, kidneys – fatty change (high risk is mostly associated with the liver, liver failure)

The pathogenesis used to be thought of as follows , during viral illnesses, fever develops and patiens administer aspirin as an antibiotic which leads to the development of Rey’s syndrome . However, it was demonstrated later on that other causes lead to this syndrome including abnormal mitochondrial functions.

(قُلْ هَلْ يَسْتَوِي الَّذِينَ يَعْلَمُونَ وَالَّذِينَ لا يَعْلَمُونَ)

تمّ بحمدِ الله

السلام عليكم رابط الفيدباك اذا في مجال تعطونا رايكم وشكرا

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