الجهاز الهضمي

علم الأمراض

رقم المحاضرة : 4.5

الكتّاب : علاء خضر

المدقق :

الدكتور :

1. Autoimmune Hepatitis

- Chronic hepatitis with immunologic abnormalities

-Histologic features are similar to chronic viral hepatitis

-Indolent or severe course

-Dramatic response to immunosuppressive therapy

Today, we are going to discuss about autoimmune hepatitis , Nonalcoholic Fatty Liver Disease and Hemochromatosis.
Autoimmune hepatitis is a chronic hepatitis and it is slowly progressive one, it is characterized as the immunological abnormality.

It has similar histological features with chronic viral hepatitis; it is important to distinguish and differentiate between them because their treatment differs.

- It can be indolent (mild or no pain) or severe course. Also, it is one of causes of cirrhosis.

- The immunosuppressive therapy can help declining the severity of autoimmune hepatitis and it responds dramatically with the therapy. However, autoimmune hepatitis is not cured with immunosuppressive therapy!!

Features:

1-Female predominance (70%)

2-Negative serology for viral Ags (antigens)

3-↑high serum Ig (immunoglobin) (>2.5 g/dl)

4-High titers of autoantibodies (80% of cases)

Note that in most cases not all cases

5-The presence of other autoimmune diseases as RA, thyroiditis, sjogern syndrome, UC (ulcerative collitis) in 60% of the cases.

The type of autoantibodies

1-Antismooth myuscle abs(antibodies)

- **anti actin**
- **anti troponin**
- **anti tropomyosin**

- Most common autoantibodies that get affected.
- These antibodies attack proteins inside our smooth muscles such as: Troponin, Tropomyosin, and Actin.

2-liver/kidney microsomal Abs

- **anti cytochrome P-450 components**
- **anti UDP-glucuronosyl transferases**

- Antibodies against enzymes (transferases of hepatocytes, P-450 enzyme system, etc)

3-Anti – soluble liver / pancreas antigen

Outcome

Mild to severe chronic hepatitis

Full remission is unusual

Risk of cirrhosis is 5% which is the main cause of death

- **What is the outcome of autoimmune hepatitis:**
  1. **chronic hepatitis usually (mild to severe but it is prolonged)**
  2. **it is not fully cured always.**
  3. **5% of patients develop cirrhosis; which is main cause of death.**

2. Nonalcoholic Fatty Liver Disease

Types:

1. Steatosis (Fatty liver)
2. Steatohepatitis
   - hepatocyte destruction
   - parenchymal inflammation
   - progressive pericellular fibrosis

- Now our next disease is about nonalcoholic fatty liver disease NAFLD.
- It is important nowadays, because any cause apart from alcoholism, especially metabolic causes, will result in NAFLD.
- Although alcohol is the most common cause of fatty change, the fatty infiltration/change here is not related to alcoholism, therefore it's categorized as Non-alcoholic fatty change of liver disease.
- We have 2 types:
- 1. Steatosis: simply fat infiltration of the liver.
- 2. steatohepatitis: Note the -itis, it is associated hepatocyte destruction, parenchymal inflammation and progressive paracellular fibrosis. It is more SEVERE.
- -NOTE: Primarily fatty change is a reversible process, but once there is fibrosis, we will conclude it led to chronicity of this disease.

Predisposing factors :

- Extra: You can use the following formula to calculate your body mass index (BMI).
- BMI= mass in kg / (height in meters)2

1-Type 2 DM (Diabetes mellitus)
2-Obesity : body mass index BMI
> 30 kg /m2 in caucasians
> 25 kg /m2 in Asians
3-Dyslipidemia (↑ TG, ↑LDL, ↓HDL)

What is dyslipidemia? Abnormality in fat profiling and is manifested as increased serum (triglyceride + LDL) which is harmful, and a decrease in the useful fat which is HDL.

Pathogenesis

.**Metabolic syndrome**

- Insulin resistance
- Obesity
- Dyslipidemia

Fat accumulation in the liver can be due to a metabolic syndrome such as: Insulin Resistance, Obesity, and Dyslipidemia.

Mechanism of fatty accumulation

1. Impaired oxidation of fatty acids
2. Increased synthesis & uptake of FFA
3. Decreased hepatic sec. of VLDL

. ↑TNF , IL6 , chemokine →liver inflammation & damage

❑ Any mechanism that is associated with an increase in the fatty acids in circulation can result in deposition of fat in the liver. These mechanisms include:

- Impaired oxidation of fatty acids.
- Increased synthesis and uptake of free fatty acids.
- Decreased hepatic secretion of VLDL (very low-density lipoproteins).

* Remember that VLDL is the carrier of fatty acids to target organs so they can utilize them. *

- Activation and release of TNF, IL-6, and other chemokines (possibly due to direct or indirect effects of lipid) cause liver inflammation and damage.

In conclusion, the presence of any anti-inflammatory process associated with an increase in inflammatory mediators helps in fatty accumulation, but not alcoholism.

Don't forget that fatty infiltration is reversible in the early stage of the disease, but later on it can be irreversible and associated with viral hepatitis.

Clinically

-NAFLD is the most common cause of incidental ↑increase in transaminases (indication of hepatocellular damage)

-Most pts. are asymptomatic.

-Non-specific symptoms

Fatigue, malaise, RUQ discomfort

-Severe symptoms

-Liver Bx is required for dx.

-NAFLD m.b a significant contributer to cryptogenic cirrhosis

- ❑ NAFLD is the most common cause of incidental ↑increase in transaminases. Transaminases are produced by the liver and they're one of the components of liver function test, their increase indicates hepatocytes damage.
- ❑ We should suspect of NAFLD, if the patient is obese and has High Transaminases.
- ❑ Most patients are asymptomatic (NAFLD following diabetes)
- ❑ Non-specific symptoms:
  - Fatigue, malaise, RUQ (right upper quadrant) discomfort.
  - Severe symptoms (when its advanced)
- ❑ Liver biopsy is required for diagnosis to confirm the diagnosis and evaluate the degree of chronicity and fibrosis.
- ❑ NAFLD may be a significant contributor to cryptogenic cirrhosis which is cirrhosis found in patients with no predisposing conditions.

3. Hemochromatosis

- Excessive accumalation of body iron (liver & pancreas)

-1ry or 2ry (genetic or acquired)

It is a metabolic disease , most common metabolic disease that affects the liver, characterized by excessive accumulation of body iron (liver & pancreas) and can be primary or secondary (genetic or acquired).
The Classical form in liver and pancreas but it can occur in any part of the body ex. skin ...etc

In general terms, Both primary and secondary iron accumulation is called hemochromatosis but clinically we call the primary (genetic)---> hemochromatosis and the secondary (acquired) ---> siderosis .

Causes of acquired hemosidrosis :

1-multiple transfusions

2-ineffective erythropoiesis (thalassemia)

3-increased iron intake (Bantu sidrosis)

4-chronic liver disease

Causes of acquired hemosiderosis or genetic :

1-multiple transfusions: Repeated blood transfusions can lead to accumulation of RBCs, and these red blood cells contain iron, and over time, this excess iron can accumulate in various organs and tissues, resulting in hemosiderosis.

2-ineffective erythropoiesis (thalassemia) : these thalassemia patients are on chronic blood transfusion; their system will be overloaded with iron + ineffective erythropoiesis (which is damage of the RBCs in bone marrow, before releasing in the circulation). These patients have their red cells' life span is short so they rapture, and iron accumulates in the body.

3-increased iron intake (Bantu sidrosis): who are the bantu?

They are African tribes who are used to preparing their food/beverages in iron containers, so their body gets overloaded with iron. Extra

4-chronic liver disease.

-**Features:**

1- Micronodular cirrhosis (all patients)

2- D.M (75 – 80%)

3- skin prigmentation (75-80%)

4- cardiomegaly , joints disease, testicular atrophy

5- Symptoms appear 5^{th} – 6^{th} decades not before age 40

6- Men : Female ratio 5 – 7 : 1

7- Genetic hemochromatosis (4 variants):

The most common form is auto. recessive disease of adult onset caused by mutation in the HFE gene on chr.6

Features:

1- Micronodular cirrhosis (all patients): usually these patients come late to the clinic; because iron take years to accumulate and cause damage.

2. DM: Due to destruction of islets cells; The excess iron deposition in the pancreas can impair insulin production and lead to insulin resistance

3. skin pigmentation : doesn't need explanation I believe 😊 but if you insist. It is Due to iron deposition in subcutaneous tissue

4. Cardiomegaly (an enlarged heart) , joints disease, testicular atrophy (comes to you because of their infertility).

5. 5^{th} – 6^{th} decades not before age 40 (middle aged): we expect the manifestations of hemochromatosis

to show early in life because it is inherited. However, it takes a long time for the iron to accumulate. Thus, the manifestations do not appear before the age of 40.

6. Men : Female ratio 5 – 7 : 1 : menstrual bleeding in women limits the accumulation of iron until menopause. While in men it appears earlier.

7- Genetic hemochromatosis: It has 4 variants and The most common form is autosomal recessive disease of adult onset caused by mutation in the HFE gene on chromosome 6.

Pathogenesis

1-1ry defect in intestinal absorption of dietary iron.

2-Total body iron 2-6gm in adults 0.5gm in liver mostly in hepatocytes

3-In disease >50gm Fe accumulated → 1/3 in liver

4-In hereditary hemochromatosis there is a defect in regulation of intestinal absorption of dietary iron leading to net iron accumulation of 0.5 – 1 gm/yr

In order to understand the process, we should know the mechanism of iron metabolism in the body:

- Iron doesn't have anyway to be excreted in the body; that's why our body controls amounts of iron absorbed. And the amount of iron absorbed should be equivalent to what the body needs.

1. Since our primary site of absorption of iron is intestine (duodenum). In these patients, the mutation results in loss of control over the absorption process of iron, so excessive absorption occurs. As we said before it takes years to accumulate and develop iron overload.

2+3. Total body iron is 2-6g in adults in which 0.5g presents in the liver mostly in hepatocytes. In hemochromatosis, more than 50g Fe accumulate of which one-third presents in the liver + other organs.

4. In hereditary hemochromatosis there is a defect in regulation of intestinal absorption of dietary iron leading to net iron accumulation of 0.5 – 1 g/yr. The gene responsible is HFE gene located on chr.6 close to HLA gene complex.

Manifestations + liver problems start to appear when the iron load is more than 20 grams.

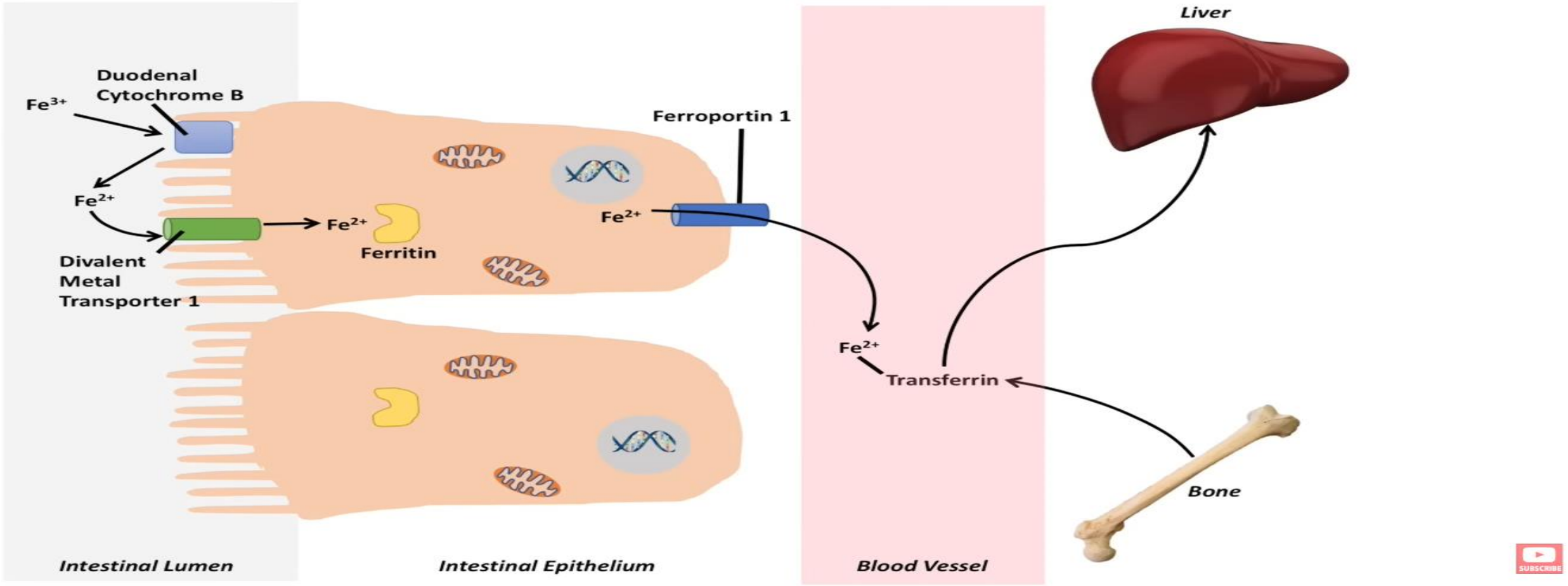
Pathogenesis

The gene responsible is HFE gene located on chr.6 close to HLA gene complex

-HFE gene regulates the level of hepcidin hormone synthesized in liver

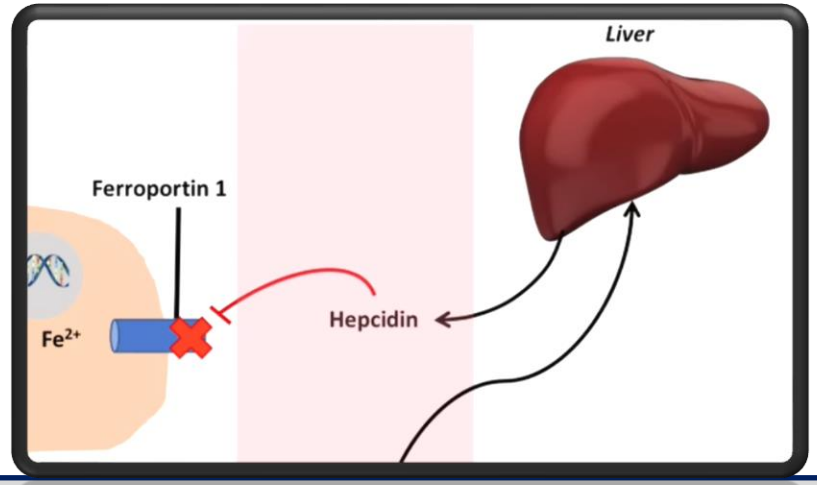
-Hepcidin → (-) Fe. absorption from intestine

-HFE gene deletion causes iron overload



Normal iron absorption in our body: Iron Absorption, Transport, Metabolism and Regulation - Biochemistry Lesson – YouTube

This is extra explanation, but the doctor said it was revision to the normal process so that we can understand the pathogenesis.



Hepcidin normally acts as a key negative regulator of intestinal iron uptake.

- **HFE gene regulates the level of hepcidin hormone synthesized in liver. This Hepcidin decreases iron absorption from intestine. So, HFE gene deletion causes iron overload.**
- **Hepcidin's Function: Hepcidin regulates iron absorption from the gut and iron release from cells, thereby maintaining iron balance in the body. When iron stores are high, hepcidin production is increased, This reduces iron absorption. Thus, preventing excessive iron accumulation.**
- **Furthermore, Hepcidin synthetic process depends on the iron demand of the body when there is blood loss the hepcidin level decreases allowing more iron to be absorbed and reach the circulation.**

❑ **In hereditary hemochromatosis, as mentioned earlier, mutations in genes like HFE can result in decreased hepcidin production or impaired function, leading to excessive iron absorption and iron overload.**

THE END

Thanks for reaching here, Smile. 🤞😄