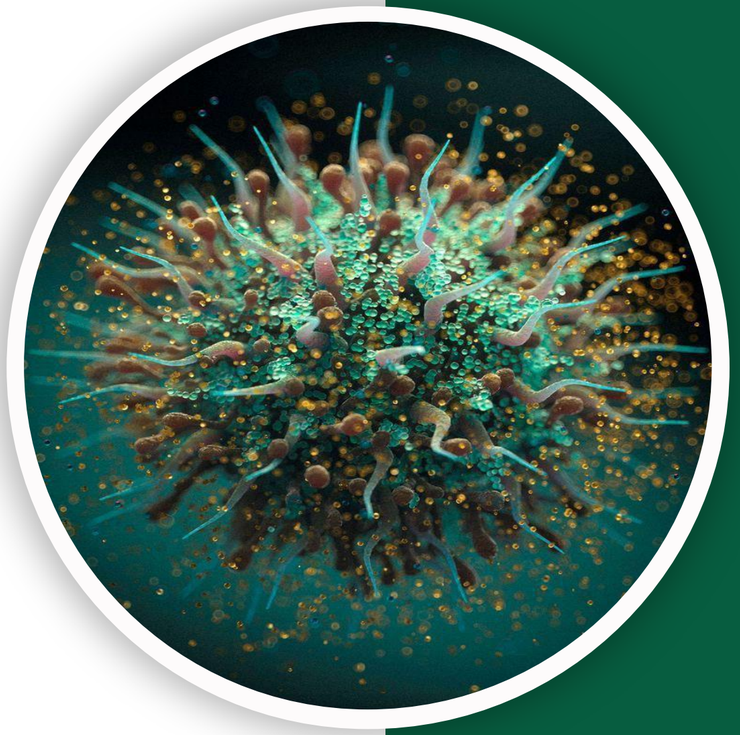
بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

GIS Pathology | FINAL 4

Autoimmune Hepatitis, Hemochromatosis, Willon Disease



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Autoimmune Hepatitis

- Autoimmune hepatitis is very important to consider because its liver changes can **look very similar to viral hepatitis or drug-induced liver injury.**

- The problem is **not only in making the differential diagnosis**, but also in **choosing the correct treatment**. Because if we treat a patient as having autoimmune hepatitis when actually they have viral hepatitis, we might aggravate the condition.

- That is why **differentiating is very important, and vice versa.**

- If viral hepatitis **is treated as autoimmune hepatitis with suppressive drugs,** this **may worsen the disease and lead to complications.**

- **Chronic hepatitis with immunologic abnormalities.**
- **Histologic features are similar to chronic viral hepatitis.**
- **Indolent or severe course.**
- **Dramatic response to immunosuppressive therapy.**

Autoimmune Hepatitis

- It is important to recognize autoimmune hepatitis as a condition because it is not uncommon. After excluding viral hepatitis, autoimmune hepatitis should be considered as a cause of chronic hepatitis, and **it is associated with the development of fibrosis.**

- **Histologic features are similar to chronic viral hepatitis.**
- slowly progressive (gradually developing) **Indolent or severe course.**
- **Dramatic response to immunosuppressive therapy.**
- Patients usually have the disease for the rest of their lives. The importance of recognizing
  and diagnosing autoimmune hepatitis is that it shows a dramatic response to immunosuppressive therapy, because the underlying mechanism is an autoimmune attack. This is beneficial for the patient, as the response to treatment can be very significant. However, patients may still experience bouts of disease activation, so lifelong follow-up is necessary.
- Remission may occur complete remission of the disease process is unexpected.

Features:

1) Female predominance (70%).

This does not mean that males are not affected, but the disease is less frequent in them.

2) Negative serology for viral Ags.

Which means negative serology for evidence of viral infection, and that's why serological testing is important.
Fortunately, with modern virology tests, we can detect hepatitis B and hepatitis C, which are common causes associated with chronic hepatitis.

3) ↑serum Ig (>2.5 g/dl)

increased level of serum immunoglobulins, indicating the presence of autoantibodies.

Features:

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

Some patients may have negative antibodies, which can create difficulty in diagnosis, since there are no completely specific serological findings.

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

For this reason, it is important to ask patients about other manifestations or any known autoimmune disease.

The type of autoantibodies

1 Antismooth muscle abs (most common) :

anti actin

anti troponin

anti tropomyosin

2 liver/kidney microsomal Abs:

anti cytochrome P-450 components

anti UDP-glucuronosyl transferases

3 Anti – soluble liver / pancreas antigen

✓ These antibodies are directed against different cellular components, leading to cell damage.

❑ Outcomes:

- **Mild to severe chronic hepatitis.**
- **Full remission is unusual.**
- **Risk of cirrhosis is 5% which is the main cause of death.**

Nonalcoholic Fatty Liver Disease

- **Non-alcoholic fatty liver disease (NAFLD)** represents another significant form of liver disease.

- While **fatty infiltration** of the liver was once thought to be **reversible** and **unrelated to cirrhosis**, we now understand that it can progress and must be carefully assessed in patients with predisposing conditions.

- The term **"non-alcoholic" distinguishes** this condition **from alcohol-related fatty liver disease.**

- Despite fatty infiltration being commonly associated with alcohol use, NAFLD is **driven by underlying metabolic abnormalities** rather than alcohol consumption.

Nonalcoholic Fatty Liver Disease

Types:

1. **Steatosis (Fatty liver) :** mild form, **there is only fatty infiltration of the liver.**

2. **Steatohepatitis:** fatty infiltration associated with **inflammation and inflammatory infiltrates**. This represents a **more damaging condition** because **inflammatory cells release different chemical mediators** that can **initiate fibrosis.**

    - **hepatocyte destruction.**
    - **parenchymal inflammation.**
    - **progressive pericellular fibrosis.**

Predisposing factors :

- The patients most liable to develop non-alcoholic fatty liver disease are those with metabolic disorders.

1) **Type 2 DM :** have increased insulin resistance. Because of this insulin resistance, they cannot properly utilize glucose, which contributes to the development of diabetes and fatty liver disease.

2) **Obesity : body mass index**
   - **30 kg /m2 in caucasians**
   - **25 kg /m2 in Asians**

3) **Dyslipidemia (↑ TG, ↑LDL, ↓HDL)**

Triglycerides = TG
low-density lipoprotein = LDL
high-density lipoprotein = HDL

Pathogenesis

Metabolic syndrome

Patients usually present with this metabolic syndrome, and whether they are diagnosed with it or are being followed for another reason, we should always consider the possibility of liver involvement. If liver problems are present in these patients, they are most likely related to fatty infiltration of the liver

- **Insulin resistance :** interferes with lipid metabolism. This leads to an excess of free fatty acids in the circulation and their infiltration into the liver.
- **Obesity**
- **Dyslipidemia**

Mechanism of fatty accumulation

1. **Impaired oxidation of fatty acids.**

2. **Increased synthesis & uptake of FFA.**

3. **Decreased hepatic sec. of VLDL** which normally transport fatty acids from the liver into the circulation for utilization.

- In these patients, metabolic abnormalities also **redirect glucose metabolism toward fat synthesis**, resulting in **increased storage of free fatty acids**. All these conditions **lead to fat accumulation in the liver.** In non-alcoholic steatohepatitis, fatty accumulation is associated **with inflammation, tissue damage, and release of different chemical mediators (⬆ TNF, IL6, Chemokine → liver inflammation & damage)** that **further aggravate liver injury**. Therefore, **these patients are liable to liver damage** and **commonly present with abnormal liver function tests.**

Clinically

- NAFLD is the most common cause of incidental ↑ in transaminases.
- 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

Clinically

- Transaminases are enzymes synthesized and released by hepatocytes and are an important component of liver function tests.

- Liver function tests are a group of investigations that measure bilirubin, liver enzymes, and proteins such as albumin, which reflects the functional capacity of the liver. Disturbance in these tests indicates abnormal liver function. One common finding is elevated transaminases, which indicates hepatocellular damage. When hepatocytes are damaged, these enzymes are released into the circulation. Therefore, **increased transaminases suggest liver cell injury, and non-alcoholic fatty liver disease is one of the most common causes of this nonspecific elevation**

- If a patient has elevated transaminases for any reason, we should think about a possible liver problem. In patients with risk factors such as obesity, diabetes mellitus, or elevated blood lipids, non-alcoholic fatty liver disease should be considered as a common cause. Nowadays, obesity and dyslipidemia are very common, so this condition is frequently encountered.

- Patients may live a normal life and remain asymptomatic.

Clinically

- Patients may have manifestations related to diabetes or metabolic abnormalities. Regarding the liver, symptoms are usually absent or minimal.

- If symptoms are present, they are nonspecific, such as fatigue, malaise, or discomfort in the right upper quadrant. These findings become more significant in patients with risk factors like diabetes mellitus. **Therefore, diabetic patients should be followed up with liver function tests to assess glucose control and detect possible liver complications.** Sometimes the symptoms may become severe if the process is chronic.

- In severe cases, steatohepatitis can progress to liver fibrosis and eventually lead to the consequences of chronic liver damage.

Clinically

- ***For diagnosis***, a liver biopsy may be needed to confirm that the increased transaminases are caused by fatty infiltration of the liver, to evaluate the extent of liver damage, and to exclude other possible causes.

- More than one cause may be present in the same patient. Liver biopsy may show fatty infiltration or steatohepatitis, which confirms the diagnosis. Previously, fatty infiltration progressing to cirrhosis was classified as cryptogenic cirrhosis because the underlying cause was unknown. However, it is now recognized that many of these cases are related to metabolic abnormalities and fatty infiltration of the liver rather than common causes such as alcoholism or viral hepatitis

Hemochromatosis

- **Excessive accumalation of body iron (liver & pancreas)**
- **1ry or 2ry (genetic or acquired)**

Acquired iron overload is commonly related to blood disorders

- Normally the only way of controlling the iron concentration in our body is by **controlling the absorption, there is no excretory pathway for iron in our bodies.**
- Any excess iron getting absorbed to the circulation **will get deposited in different tissues (liver, skin, pancreas, etc.).**
- **That's why the only way of controlling the iron is by controlling the absorption.**
- Iron is being absorbed normally **in the duodenum & proximal jejunum.**

Usually, the term hemochromatosis refers to the hereditary form, while the acquired form is more commonly referred to as hemosiderosis.

Causes of acquired hemosidrosis (more common than the hereditary) :

when iron overload is suspected, acquired conditions should be considered first.

1. Multiple transfusions; Patients who require multiple transfusions because of hematological diseases gradually develop iron overload, since each transfused blood unit contains iron that becomes deposited and stored in the body. There is no effective excretory pathway for iron, so most of the iron entering the body remains stored if it is not utilized.
2. ineffective erythropoiesis (thalassemia); Which is one of the most common hematological diseases in our region. Thalassemic patients often depend on lifelong blood transfusions, which continuously overload their bodies with iron and may lead to iron overload.
3. increased iron intake (Bantu sidrosis); as seen in some African siderosis syndromes.
4. chronic liver disease; may be associated with a mild increase in iron load; however, it is usually not severe and mainly indicates chronicity and hepatocyte damage.

Hemochromatosis is not very common; however, it is one of the most important metabolic diseases affecting the liver.

Features:

1.Micronodular cirrhosis (all patients).

These patients commonly develop micronodular cirrhosis, especially after a certain age. Therefore, hemochromatosis should be considered as a possible underlying cause of cirrhosis

2.D.M (75 – 80%). **Due to pancreatic fibrosis.**

Patients may also develop diabetes mellitus because iron is deposited in the pancreas, particularly in the beta cells of the islets, leading to their damage and impaired insulin production. That is why classical patients with hemochromatosis often become diabetic.

Features:

3.skin prigmentation (75-80%). **Due to deposition of iron.**

The presence of these skin changes raises the possibility that cirrhosis may be associated with hemochromatosis. · Hemochromatosis is characterized by excessive iron accumulation in different organs, especially the liver and skin.

4.cardiomegaly , joints disease, testicular atrophy.

patients should be asked about manifestations of damage in other organs because hemochromatosis is a multisystem disease.

- · Patients may have associated cardiac problems or may be receiving medications for heart disease
- · Therefore, the combination of cirrhosis, skin pigmentation, and evidence of involvement of other organs in a patient within the appropriate age group increases the suspicion of hemochromatosis.
- · The possibility becomes stronger after excluding the more common causes of cirrhosis, particularly alcoholism and viral hepatitis.

Features:

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

- **M:F ratio 5 - 7: 1**
- Females usually present about one decade later than males because iron accumulation is delayed by recurrent blood loss during the childbearing period. · In contrast, males tend to present earlier due to continuous iron accumulation throughout life.

- **Genetic hemochromatosis (4 variants).**

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

- Autosomal recessive disease : **both alleles have to be mutated to establish the disease.**

- Each allele **can have different type of mutation.**

- **Each mutation will result in the substitution of one amino acid into the other.**

Pathogenesis

- **1ry defect in intestinal absorption of dietary iron.**
- **Total body iron 2-6gm in adults 0.5gm in liver mostly in hepatocytes.**
- **In disease >50gm Fe accumulated → 1/3 in liver.**

- Normally in our body there is **2-6 gm of iron stored in different tissues**, mostly in **liver**, others are in **bone marrow and muscle, etc.**
- The symptoms of liver damage or malfunction appear **after of 20 gm accumulated in the stores.**
- The more the iron accumulation → the more the damage → the more symptoms.

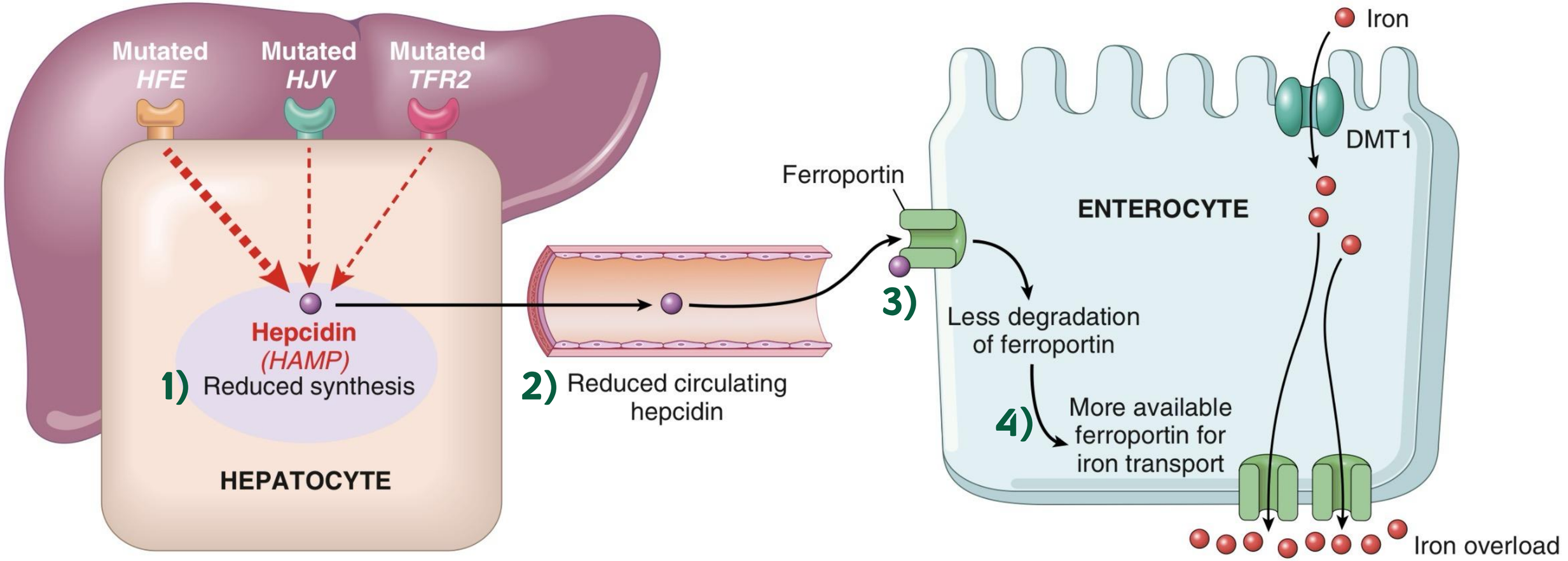
Pathogenesis

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

Hepcidin:

- **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.**
  - Hepcidin function is to **decrease the absorption of iron from the enterocyte to the blood.**
  - Decrease in hepcidine levels will result **in excess iron absorption and as a result increase iron deposition.**
  - The hepcidine level varys allowing **more absorption of iron in cases of iron deficiency (sickle cell anemia, etc).**
  - If the stores of iron are sufficient, the hepcidine level increases to a level that causes **only an amount of iron that is equivalent to the amount of iron lost daily.**
    By this, in normal conditions **the iron is kept within normal non-toxic levels.**
- **HFE gene deletion causes iron overload.**

Pathogenesis:



Extra image.

❑ **Two mutation can occur in HFE gene:**

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

2) Aspartate substitution **for histidine** at AA 63 (H63D).

10% of pts. have other gene mutations.

Epidemiology:

- **Carrier rate for C282Y is 1/70.**
- **Homozygosity 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.**

❖ Carrier : having mutation in one allele, which make them predisposed for establishing the second allele mutation and the development of the disease.

Why accumulation of iron causes damage?

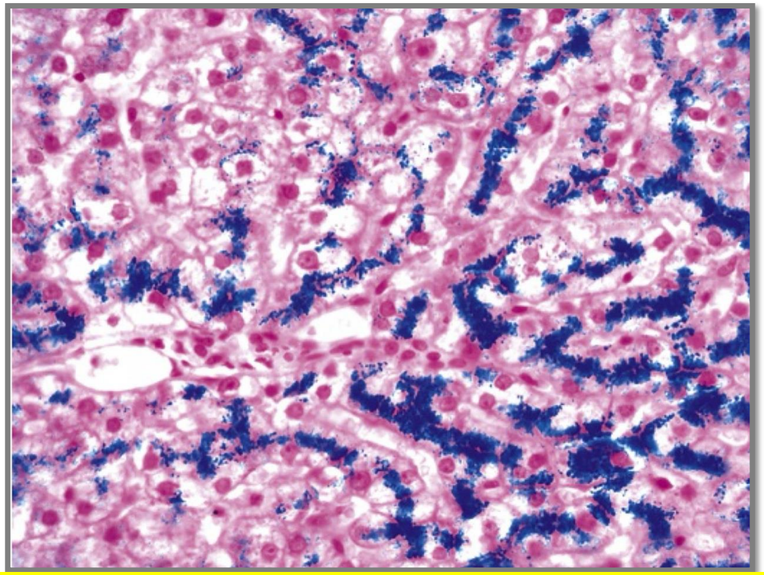
- **Excessive Fe deposition → toxicity of the tissues, how?**
  - ✓ Fenton's reaction : (Fe → Fe+2 + 2e-), Free radicals cause liver damage, By:

1. **Lipid peroxidation**
2. **Stimulation of collagen formation**
3. **DNA damage**

Morphological Changes:

1) Deposition of hemosiderin in diffferent orgens (can be detected using different stains (Prussian blue)).

- Liver — Causes cirrhosis.
- Pancreas — Fibrosis, and damage not only to the endocrine portion (Beta cell) which causes diabetes but also, to the exocrine portion of the pancreas and that's why they have pancreatic fibrosis.
- Myocardium
- **Endocrine:**
  - Pituitary Adrenal
  - Thyroid & parathyroid Joints
- Skin — Bronze Pigmentation.
- Joints : Arthritis



Extra image : Shows iron deposition in liver hepatocyte (appears blue / Prussian blue stain was used).

2) Cirrhosis

3) Pancreatic fibrosis → Which results in Diabetes Mellitus

Morphological Changes:

- **No inflammation.**
- **Fibrosis.**
- **Cirrhosis.**
- **Synovitis.**
- **Polyarthritis (pseudogout).**
  - Polyarthritis that doesn't fit any other type of arthritis.
- **Pigmentation of liver.**
  - Change in liver color should make us think about diseases that causes of liver color change, hemochromatosis is one of them.
- **fibrosis of pancreas & myocardium.**
- **Atrophy of testes.**

Clinical presentation

- M:F 5 – 7 :1 5 – 6 the decades, **Middle age or older**
- Hepatomegaly
- Abdominal pain
- Skin pigmentation
- D.M
- Cardiac dysfunction
- Atypical arthritis
- Hypogonadism
- Increases serum Fe ferritin
- HCC 200x increase the risk.

✓ So, If we suspect hemochromatosis : we should ask them about other symptoms related to other organs that may be affected (not only the liver which is the first to be affected is affected).

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.

Wilson Disease

- The problem in Wilson's disease is the **increased deposition of copper in our body**, primarily in the **liver**. It is caused by mutation in the gene, **ATP7B gene.**
- This gene is responsible for **encoding an enzyme ATPase enzyme**, which is a **metal ion** transporter **present in Golgi apparatus**.
- This is associated with the **increased iron deposition in the body**.
- Genetically, mutation can be of many types, **more than 80 types of mutation** seen in these patients. The gene **can be long**, so **mutation can occur at different sites leading to different mutations that lead to the same outcome.**
- The frequency is less frequent than that of hemochromatosis, **one in 200 carriers, while incidence are one in 30000 in the population.**
- Willson Disease is common in certain areas. It is **not common in Jordan.**

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 **(Apoceruloplasmin)** to form Ceruloplasmin.

↓

Sec. into plasma (90 – 95% of plasma Cu).

↓

Hepatic uptake of ceruloplasmin.

↓

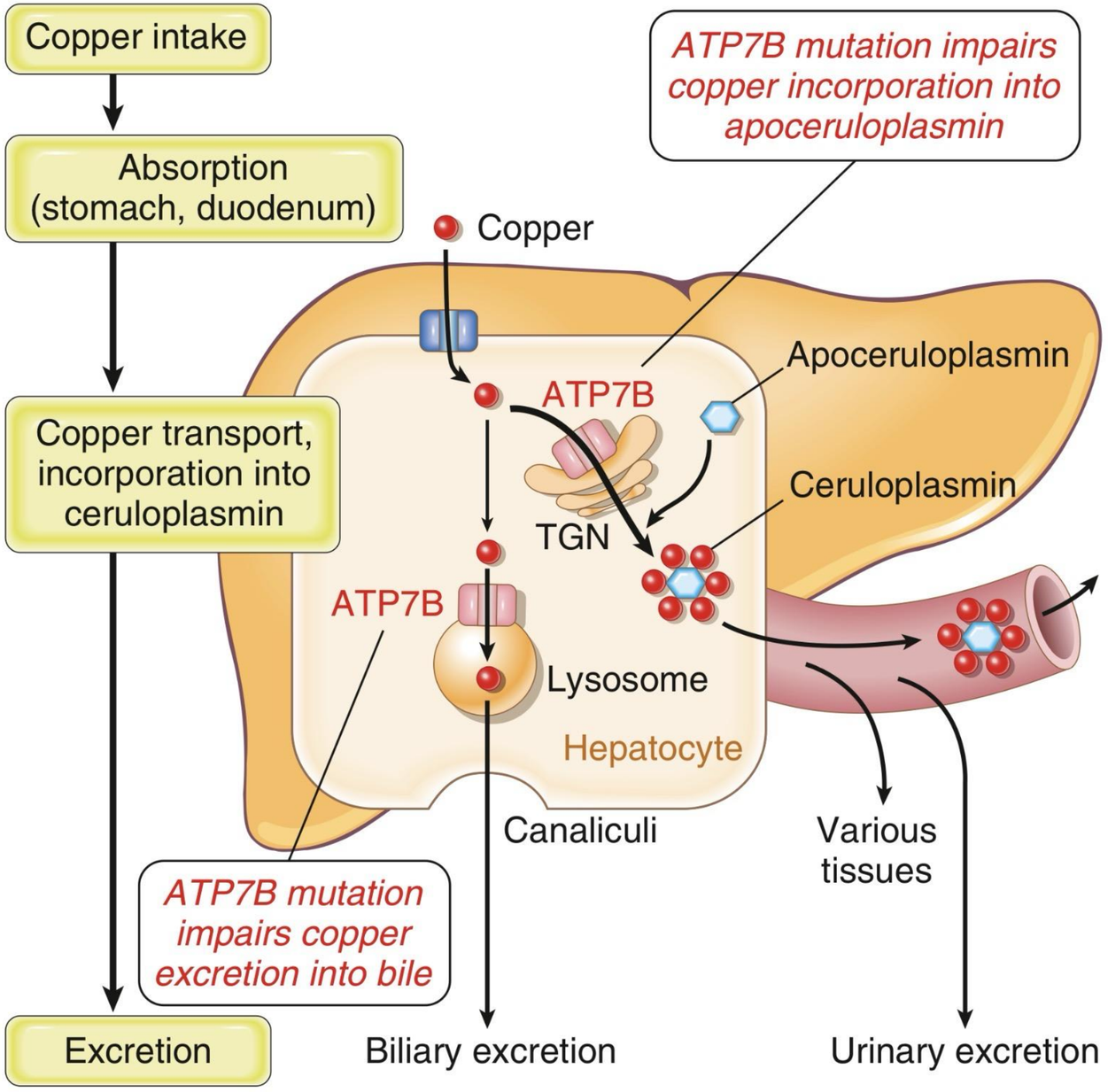
Lysosomal degradation.

↓

Secretion of free Cu into bile.

Extra Book image for better understanding in the next slide.

Pathogenesis



Extra image.

Pathogenesis

❑ ***Normally :***

- At the enterocytes, copper is complexed with albumin. This copper-albumin complex is then secreted into the blood and transported from the enterocytes to the liver.

- In the liver, degradation of this complex occurs, releasing copper, which is then re-complexed with another carrier, alpha2-globulin (A2), synthesized in the circulation, forming a complex called ceruloplasmin. Ceruloplasmin is then re-secreted into the circulation in order to carry copper to different sites of the body where it is utilized.

- After circulation, the complex returns to the liver. In the liver, copper undergoes a second uptake, while ceruloplasmin undergoes lysosomal degradation, again releasing copper. Any excess copper is excreted in the bile. This represents the normal pathway of copper metabolism.

Pathogenesis

❑ ***Willson Disease:***

- In Wilson's disease, the absorbed copper cannot be properly complexed with or released into the circulation. It is not complexed with alpha2-globulin to form ceruloplasmin, and therefore **it remains within the tissues**. As this continues over time, **copper accumulates and produces its damaging effects on the liver.**

- With time, **excess free copper spills into the circulation and appears as free copper in the blood**. This occurs because of a **defect in ATPase**, leading to **accumulation of copper inside the cells** and deposi**tion** of large amounts of copper in tissues.

- Copper accumulation is more or less similar to iron accumulation because copper is also a metallic element. **It can lead to free radical formation, similar to iron**, producing **cellular damage by binding to important cellular components necessary for survival and growth**. In addition, copper **can displace metals** in **metalloenzymes**, producing enzyme inactivation. This results in damage to fragile tissue components. Therefore, copper deposition is associated with tissue injury.

Pathogenesis

- **In Wilson disease absorbed Cu. Fails to enter the circulation in the form of ceruloplamin & the biliary excertion of Cu. is ↓,** Since the ATP7B transporting transmembrane protein is defected, it can't mediated the formation of ceruoplasmin from apoceruplasmin (alpha-2 globulin).

Pathogenesis

- **Defective function of ATP-7B →failure of Cu. excretion into bile & inhibits sec. of ceruloplasmin into the plasma → Cu. accumulation in liver.**

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

1) **Production of free radicals.**

2) **Binding to sulfhydryl groups of cellular proteins.**

3) **Displacement of other metals in hepatic metalloenzymes**

Pathogenesis

- **By the age of 5yrs. Cu. Spills over to circulation causing hemolysis** (because excessive free copper spilling into the circulation **can damage red blood cells, leading to hemolytic anemia**) **& involvement of other organs as brain & cornea also kidneys, bones joints & parathyroid glands.**

- **Urinary exc. Of cu. ↑**

- Although many causes of hemolytic anemia are more common than Wilson's disease, it should still be included in the differential diagnosis.

Morphology

Liver:

1 Fatty change

2 Acute hepatitis

3 chronic hepatitis

4-cirrhosis

5-massive hepatic necrosis

(rhodanine stain or orcein stain)

Willson Disease affecting multiple organs:

- Patients may also present with manifestations involving organs other than the liver, particularly **the brain**. Copper deposition can occur in the cornea, bones, joints, kidneys, and endocrine organs, in addition to the liver. **Increased copper excretion in the urine is commonly seen because of copper spilling into the circulation, and this finding is helpful in diagnosis.**

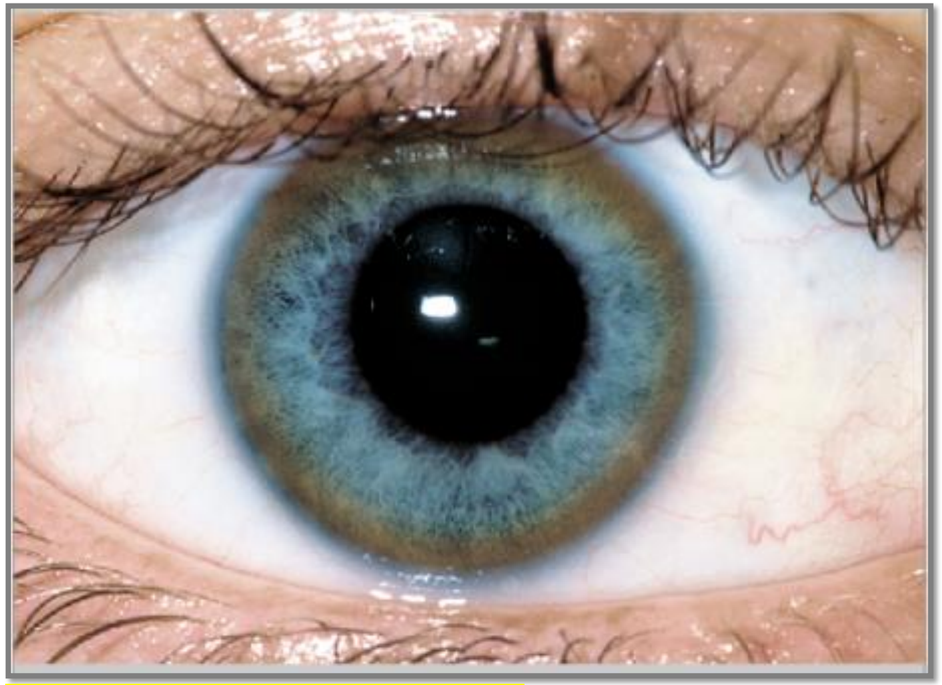
- **Brain:** **Toxic injury to basal ganglia esp. the putamen causing atrophy & cavitation.**

- Atrophy occurs because the cells become damaged and die, and the destruction of these cells leaves cavities within the tissue.

Eye:

kayser- fleischer rings

green – brown depositis of Cu. in descemet membrane in the limbus of the cornea **(hepatolenticular degenceration)**



Extra image : Shows fleischer ring.

Clinically

- **Presentation > 6 yrs of age.**
  - Patients usually present after the age of six. Very young children are less likely to present with the disease because **a significant amount of copper must accumulate before tissue damage becomes clinically apparent**, and this process requires time. Most commonly, the presentation of Wilson's disease begins around the age of 10–12 years or in young adults.

- **Most common presentation is acute on chronic hepatitis**.

- **Neuropsychiatric presentation can occur behavioral change.**
  - **Frank psychosis.**
  - **Parkinson disease- like syndrome.**

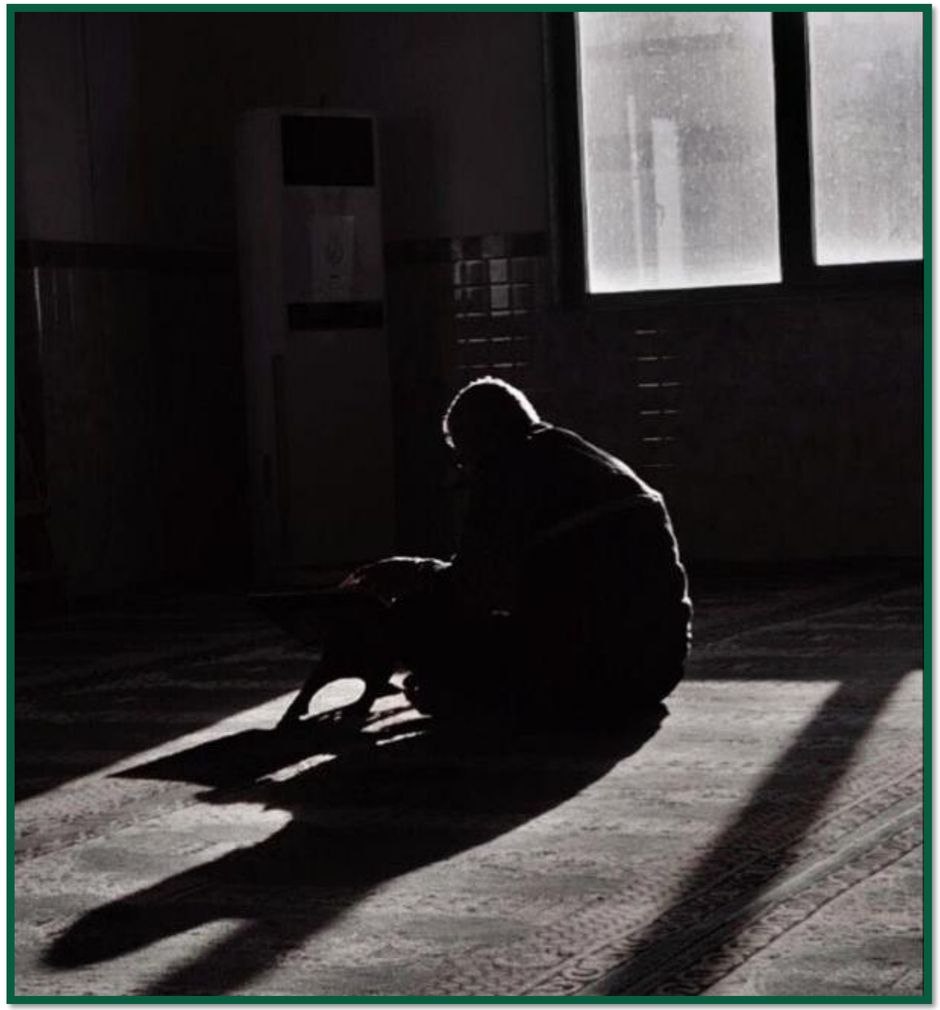
Diagnosis

- Diagnosis can be difficult because the amount of deposited copper may initially be minimal and not detectable under the light microscope, even in a biopsy specimen.

- **However, the diagnosis can be done by examining these changes :**

1) ↓ in serum ceruloplasmin level
2) ↑ in urinary exc. Of Cu.
3) ↑ hepatic content of copper > 250 mg/gm dry wt.

رسالة من الفريق العلمي:



بين النور والظلام ...بين العلم والجهل، وبين رغبة القرب من الله وحقيقة البعد عنه ...هناك يقبع خالد...

يعيش، ولكنّه لا يعيش .**يعلم أنّ حاله ما هو إلا نتيجة تراكم ذنوبه، ويعلم أنّ الحل هو التوبة،**
ويعلم أنّ ما يفصل بينه وبين الإنسان الذي يريد أن يكونه ...**أن يعود كما كان.**

هل خالد **راضٍ عن نفسه؟** لقد قال لي بملء لسانه :**لا.**
أهو **جاهل بالطريق؟** لقد قال بملء لسانه :**لا.**
لعلّه **خائفٌ منه؟** لعلّه لا يدري، ولكن **ما الخوف من طريقٍ نهايته جنّة النعيم؟**

رسالتي إلى خالد:
اعلم أنّك تعلم أنّه لا راحة لك في طريقك هذا، وان راحته عذابٌ، وأنّ الراحة الأبدية **ليست إلا في طريقٍ سلكتَه سلفا، فألفته ثم التفتَّ عنه، واستجبتَ لصوت الوساوس القادم من الطريق المزيّن بالزهور، وطمأنتَ نفسك بقولك :إنّ الله غفورٌ رحيم.**

يا خالد ...يا أخي ...يا أنا...
رحمة الله ليست حجّة لفعل الذنوب فكيف بسعيِّكَ إليها...

تُبْ.

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			