Haemochromatosis & Wilsons Disease

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Haemochromatosis

What is haemochromatosis

- Dysregulation of iron absorption.
- Due to mutation in HFE gene at chromosome 6.
- Most common gene is C282Y.
- Normal body iron store 3- 4 g.
- Daily iron absorption and excretion 1 mg /d in males and 1.5mg/d in females.
- In hemochromatosis : iron absorption increases to 4 mg/day with the same excretion rate

- -Hereditory haemochromatosis(HH).
- -acquired haemochromatosis.

- (HH): genetic defect in iron metabolism
- -excess iron absorbed from the gut
- -symptoms due to pathologic deposition of iron in body tissue= iron overload.

Clinical Manifestations

- Classic triad :

- liver cirrhosis (hepatic damage)
- diabetes (II) (pancreatic damage)
- bronzing of skin (hyperpigmentation).

Traditional triad means too late diagnosis

- Damage may be only partially reversible
- Goal is to detect the disease BEFORE organ damage occurs.

Reversible Manifestations

- Heart: cardiomyopathy, conduction disturbances
- Liver: abdominal pain, elevated LFTs, hepatomegaly (95%)
- Skin: bronzing (melanin deposition), gray pigmentation (iron deposition)
- Infection (*Vibrio vulnificus, Listeria monocytogenes, Pasteurella pseudotuberculosis)*

Irreversible Manisfestations

- Liver: cirrhosis, hepatocellular carcinoma (most common cause of death)
- Pituitary gland: gonadotropin insufficiency leading to secondary hypogonadism
- Pancreas: diabetes mellitus (30-60%)
- Thyroid: hypothyroidism
- Genitalia: primary hypogonadism
- Joints: arthropathy in MCPs (20-70%), pseudogout

When to consider the diagnosis?

In asymptomatic patients with:

- Unexplained elevation of liver enzymes or asymptomatic hepatomegaly.
- Abnormal serum iron maekers on routine blood work.
- Lethargy/ fatigue /loss of libido.
- First degree relatives of aconfirmed HH case.

Diagnosis

- Combination of criteria
  - Clinical
  - Laboratory
  - Pathologic
- Elevated serum transferrin saturation >45%(earliest abnormality) and an elevated serum ferritin
- Caution serum ferritin = 300 ->1000.
- TIBC : normal or slightly elevated.
- S. Iron : elevated.
- Confirmation = ‘gold standard” = liver biopsy (also defines extent of disease)

Treatment

Aim of treatment

Reserved for evidence of iron overload/complications.

- Avoid iron supplements, red meat
- Avoid alcohol and tobacco
- Avoid handling of raw seafood

- Phlebotomy
- Removal of (500) ml of blood Removes (250) mg iron.
- Do weekly or twice aweek until serum ferritin levels <50U g/L.
- Long term maintenance about once every 3 months.

- Desferrioxamine (oral & parenteral).
- Removes 10 -20 mg iron /d.
- Less effective than phlebotomy.
- More costles.
- Help in sever anemia where phlebotomy cant be done.

Prognosis

- 5 years survival rate increases from 33 – 89 % with phlebotomy.
- Major causes of death are;
- Cardiac failure.
- Hepatic failure.
- Hepatocellular carcinoma.
- Portal hypertension.

what is the value of genetic testing?

- To confirm diagnosis
- Sequential screening of family members
- -family member with identical mutations can be offered:
- screening plan to monitor for iron overload.(normal life expectancy if diagnosed before DM or cirrhosis).
- treatment plan to prevent further organ damage,morbidity & mortality.(prolonged survival with serial phlebotomy.
- environmental modification : diet , alcohol, viral hepatitis A/B Immunization .

Wilson Disease

Overview

- Autosomal recessive
- Genetic defect: ATP7B
  - Encodes metal-transporting ATPase
  - Reduced hepatic excretion of copper
  - Copper not incorporated into ceruloplasmin
- Systemic accumulation of copper
  - Liver, brain, kidneys, cornea, heart, pancreas, and joints

Wilson Disease

Hepatic Manifestations

- Asymptomatic hepatomegaly
- Persistently abnormal AST and ALT
- Fatty liver
- Cirrhosis

- Acute hepatitis
  - Similar to viral or autoimmune etiologies
- Acute liver failure
  - Coomb's negative hemolytic anemia
  - Acute renal failure

Wilson Disease

Fulminant Hepatic Failure

- Coombs-negative hemolytic anemia
- Coagulopathy unresponsive to vitamin K
- Rapid progression to renal failure
- Modest rise in AST/ALT (< 2000 IU/L)
- Normal or markedly subnormal alkaline phosphatase (< 40 IU/L)
- Alkaline Phosphatase:bilirubin ratio is < 2
- Female to male ratio: 2:1
- Serum ceruloplasmin usually decreased
- Serum and urine copper increased
- K-F rings may be absent in 50% of patients
- Underlying cirrhosis is typically present
- Viral infections or drug effects may precipitate fulminant WD

Wilson Disease

Neuropsychiatric Manifestations

- Movement disorders
  - Tremors
  - Involuntary movements
- Drooling
- Dysarthria
- Dystonia
- Pseudobulbar palsy
- Seizures
- Migraine headaches
- Insomnia
- Depression
- Personality changes
- Psychosis
- Typically presents later than liver disease

Wilson Disease

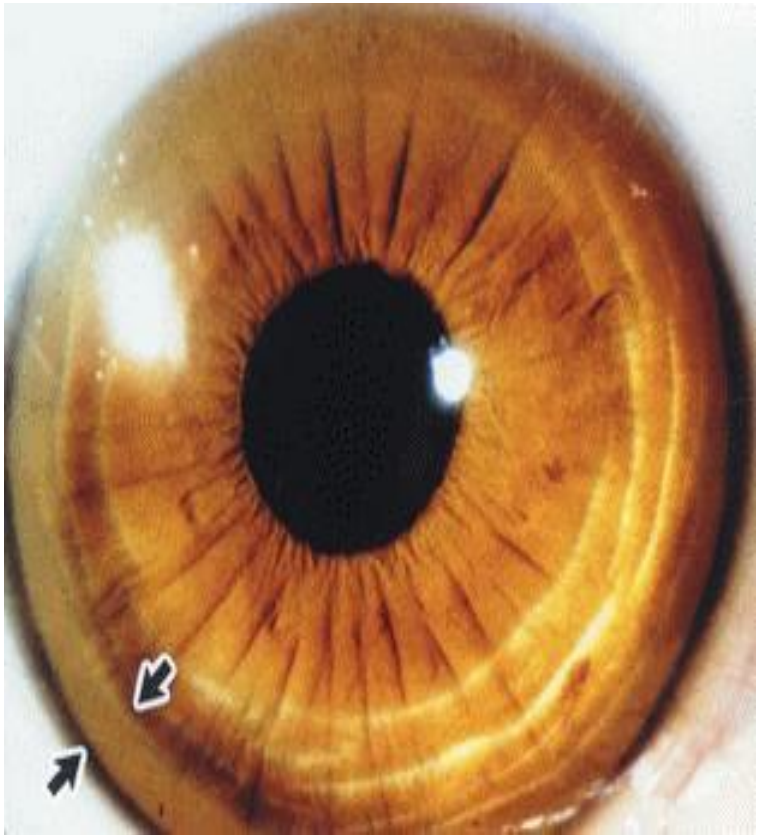
Extrahepatic Manifestations

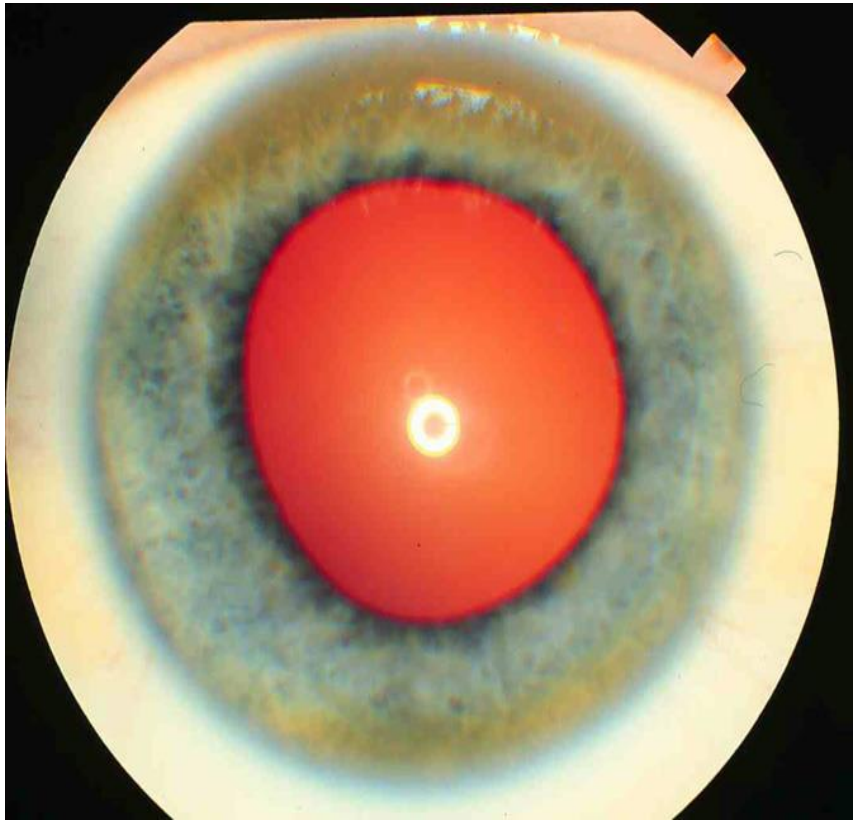
- Proximal RTA
  - Fanconi's syndrome
- Distal RTA
  - Nephrolithiasis
- Skeletal
  - Osteoporosis
  - Arthritis
- Cardiac
  - Cardiomyopathy
  - Dysrhythmias
- Gastrointestinal
  - Pancreatitis
- Endocrine
  - Hypoparathyroidism
  - Menstrual irregularities
  - Infertility

Wilson Disease

Kayser-Fleischer Ring

- Copper deposited in Decemet's membrane
- Slit lamp required in most patients with suspected Wilson Disease
- 50-62% of patients with liver disease
- 95% of patients with neurologic disease
- Chronic cholestatic diseases associated with K-F rings
- WD= K-F rings + low ceruloplasmi





Wilson Disease

Ceruloplasmin

- Major carrier protein for copper
- Values < 20 mg/dL suggestive of WD
- Values < 5 mg/dL highly suggestive of WD
- Normal values do not exclude the diagnosis
- Low values can be seen in other diseases

Wilson Disease

Serum Copper

- Total serum copper decreased in proportion to fall in ceruloplasmin
- FHF: total serum copper may be normal or increased due to increased free copper
- Non-ceruloplasmin bound copper
  - Untreated patients: > 25 μg/dL (nl: < 15 μg/dL)
  - Cu^{2+} bound to ceruloplasmin: 3.15 μg/mg CP
  - Free Cu^{2+} = total Cu^{2+} (μg/dL) - 3x CP (mg/dL)

Wilson Disease

Urinary Copper

- Helps for diagnosing WD and monitoring therapy
- Reflects amount of non-ceruloplasmin bound copper in circulation
- Diagnostic of WD: > 100 μg/24 Hr.
- Values > 40 μg/24 Hr. warrant investigation
- May be elevated in other liver diseases

Wilson Disease

Liver Biopsy

- Early disease
  - Micro and macrovesicular steatosis
  - Glycogenated nuclei in hepatocytes
  - Focal hepatocellular necrosis or "chronic active hepatitis"
- Fulminant hepatic failure
  - Parenchymal collapse + cirrhosis
- Advanced disease
  - Fibrosis and cirrhosis (macro or micronodular)

Wilson Disease
Treatment Options

- Medical
  - Chelators
    - Penicillamine, trientine
  - Metallothionein inducers
    - Zinc
- Surgical
  - Liver transplantation

Wilson Disease

Chelating Agents

- Initial approach to symptomatic patients and those with active disease
- Penicillamine
  - Largest experience worldwide
  - Worsening of neurologic symptoms reported
- Trientine
  - Viable option as primary therapy
  - Effective for hepatic or neurologic disease

Wilson Disease

Zinc

- Presymptomatic disease
  - Can be used as first line therapy
  - As effective as penicillamine and trientine
- Symptomatic disease
  - Combination therapy with chelating agents probably not better than chelating agents alone
  - Used as maintenance therapy after chelation with either penicillamine or trientine

Wilson Disease
Zinc Monitoring

- 24-hour urinary copper excretion
  - < 75 μg/d on stable dose
- Non-ceruloplasmin bound copper
  - Normalization with effective Rx (< 15 μg/dL)

Wilson Disease

Fulminant Hepatic Failure tt .

- Chelating agents and zinc are not effective therapies for fulminant WD
- Liver Transplantation is the only effective treatment for FHF
  - Bilirubin, AST, and PT are prognostically important
- Preservation of renal function
  - Plasmapheresis and exchange transfusions
  - Hemofiltration or dialysis

Wilson Disease

summary

- Autosomal recessive disorder of copper metabolism
- Patients can be asymptomatic or present with a variety of hepatic and extrahepatic manifestations
- Diagnosis based upon clinical exam, LFTs, ceruloplasmin, serum and urine copper studies, and liver biopsy
- Treatment includes chelators, metallothionein inducers, dietary modification, and liver transplantation
- After proband identified, family members should be screened

Thank you