

Metabolic Liver Diseases

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Hemochromatosis: Clinical Symptoms

- Classical Triad: 1) hepatomegaly/cirrhosis, 2) diabetes mellitus and 3) bronze skin
- Others symptoms: cardiomyopathy, arthropathy and hypogonadism
- Symptoms result from abnormal iron deposition in hepatocytes, pancreatic β -cells, keratinocytes, myocytes, joints and pituitary
- *Patients often asymptomatic with indolent development of cirrhosis*

Three “Classical” Inherited Disorders of Metabolism Affecting the Liver

- Hereditary hemochromatosis
- Wilson disease
- Alpha-1-antitrypsin deficiency

Molecular Pathogenesis

- HFE protein normally expressed in crypt enterocytes of the duodenum
- HFE protein associates with transferrin receptor, which is responsible for cellular uptake of transferrin-bound iron
- Various mechanisms proposed as to how mutation in HFE protein leads to increased iron uptake from intestine

Hereditary Hemochromatosis

- Autosomal recessive inheritance
- Abnormal iron storage
- In whites, incidence of mutant allele approximately 10%; approximately 0.3% are homozygous
- Linked to *HLA* (chromosome 6) in 1970's
- Gene (now called *HFE*) identified in 1996 (Feder et al. *Nat. Genet.* 1996:13:399-408)

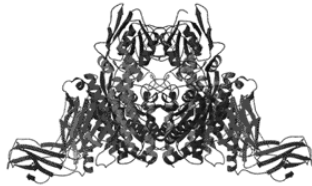
HFE Protein Structure

HFE protein is similar to HLA proteins in structure



From: www.its.caltech.edu/~bjorker/struc.html

HFE-Transferrin Receptor Complex



From: www.its.caltech.edu/~bjorker/struc.html

Hemochromatosis Treatment

- Plebotomy is effective and if instituted early can prevent complications including cirrhosis
- Iron chelating agents (e.g. desferoxamine)
- Treatment of advanced disease: liver transplantation for end-stage cirrhosis, joint replacements, treatment of diabetes, etc.

HFE Mutations

- Approximately 85% of with hereditary hemochromatosis have homozygous cysteine to tyrosine amino acid change a residue 282
- A polymorphism changing a histidine to aspartate at amino acid residue 63 has also been described but compound heterozygotes (C282Y/H63D) do not get iron overload
- Possibly other undefined mutations (promoter/enhancer) or in genes other than *HFE*

Wilson Disease

- Autosomal recessive inheritance
- Abnormal copper storage
- Affects basal ganglia and liver
- Worldwide prevalence of Wilson disease approximately 30 in 1,000,000
- In 1993, mutations in ATP7B, which encodes a copper-ATPase, shown to cause Wilson disease (some of this work done at Columbia P&S)

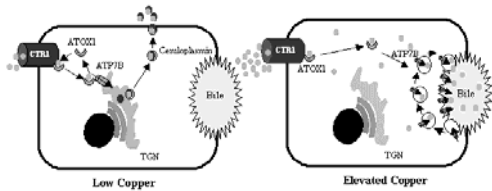
Hemochromatosis Diagnosis

- Suspect on “screening” with elevated serum transferrin saturation and ferritin
- Suspect based on symptoms (arthralgias, bronze skin, impotence)
- “Cryptogenic” cirrhosis
- Rule out secondary hemochromatosis
- Genetic test for C282Y mutation
- Liver biopsy and measure liver iron content

Wilson Disease: Clinical Presentation

- Hepatitis and cirrhosis
- Neuropsychiatric problems
- Hemolytic anemia
- Usually presents in children, teens and young adults; rare presentations in older subjects

Wilson Disease: Molecular Pathogenesis



ATP7B usually involved in copper transport into Golgi body

From: www.wilsondisease.org

Alpha-1-antitrypsin Deficiency

- Serum deficiency of alpha-1-antitrypsin, an inhibitor of neutrophil elastase
- Lung and/or liver disease
- M allele: normal
- Z allele: causes protein misfolding
- Misfolded protein in liver endoplasmic reticulum causes hepatitis and cirrhosis

Wilson Disease: Diagnosis

- Low serum ceruloplasmin*
- Kayser-Fleischer ring*
- Increased 24 hour urine copper*
- Increased liver copper on biopsy*
- Genetic testing for siblings

*These are not always present in all cases

Other “Metabolic” Liver Diseases

- Lipid storage diseases
- Some glycogen storage diseases
- Some porphyrias
- Congenital hyperbilirubinemia
- Other Inherited diseases of metabolism
- Non-alcoholic steatohepatitis (obesity/diabetes mellitus; lipodystrophy)
- Alcoholic liver disease

Wilson Disease: Treatment

- D-penicillamine
- Other copper chelating agents
- Zinc acetate
- If advanced, liver transplantation