WILSON'S DISEASE (HEPATOLENTICULAR DEGENERATION)

Background

1. Definition: An inherited disorder of copper metabolism in individuals with two mutant ATP7B genes on chromosome 13.
2. General Information: Occurs in every ethnic and geographic population; autosomal recessive defect

Pathophysiology

1. Pathology of Disease:
   - Impairment of the normal excretion of hepatic copper results in toxic accumulation of copper in liver, brain, and other organs.
   - Excess copper acts as a pro-oxidant and promotes the generation of free radicals, leading to tissue necrosis and fibrosis.
   - Patients most often present with liver disease or with neuropsychiatric disease.
   - Clinical manifestations are rare before age 6, occur most frequently in mid-adolescence, and eventually develop in all untreated patients.
2. Incidence, Prevalence:
   - Approximately 1 case in 30,000 live births
   - Heterozygous carrier frequency of about 1 in 90
3. Risk Factors:
   - Presence of the autosomal recessive Wilson's disease gene, ATP7B.
4. Morbidity / Mortality:
   - Asymptomatic liver function abnormalities
   - Acute hepatitis
   - Parenchymal liver disease
   - Cirrhosis
   - Fulminant hepatitis
   - Spasticity, rigidity, chorea
   - Schizophrenia, manic-depressive psychoses
   - Primary or secondary amenorrhea
   - Repeated spontaneous abortions
   - Nephrolithiasis
   - Untreated, symptomatic disease progresses to death in all patients
   - Overall mortality from disease treated medically has not been assessed prospectively, but approximates 20%.

Diagnostics

1. History:
   - Should be considered in any patient younger than 40 years with:
     - Unexplained disorder of central nervous system
     - Signs or symptoms of hepatitis
     - Unexplained persistent elevations of serum aminotransferases
     - Unexplained cirrhosis
     - Hemolytic anemia in presence of hepatitis
     - Any patient who has a relative with Wilson's Disease
   - Age alone should not be the basis for eliminating a diagnosis of Wilson's

2. Physical Examination :
    - Kayser-Fleischer ring-brownish or gray-green fine pigmented granular deposits in Descemet's Membrane in cornea-diagnosed by slit lamp exam.- pathognomonic sign.
        - Absence does not exclude diagnosis
    - Splenomegaly
    - Neurologic abnormalities (30%)
    - Psychiatric abnormalities (10%)
    - Sunflower cataracts
3. Diagnostic Testing:
    - Reasonable to begin with lab evaluation as follows and referral to ophthalmology for slit-lamp examination; if any positive findings refer to hepatology/gastroenterology
    - Laboratory evaluation
        - Liver biochemical tests
        - CBC
        - Serum ceruloplasmin
        - 24 hour basal urinary copper excretion-no dietary restrictions; maintain at room temperature
        - Other associated lab findings: intravascular hemolysis, renal tubular acidosis (Fanconi like syndrome)
    - Imaging
        - MRI brain considered in any patient presenting with neurological symptoms consistent with Wilson's[1]
    - Liver biopsy- histology and copper content
    - Slit lamp exam for Kayser-Fleischer rings
    - Genetic testing a reasonable option, but a specific mutation will not be identified in all patients- not test of first choice; more than 300 mutations, but not all gene changes have been established as causing disease.
4. Diagnostic "Criteria": no formal diagnostic criteria established
    - Serum ceruloplasmin < 20 mg/dl and Kayser-Fleischer rings[1] or,
    - Serum ceruloplasmin < 20 mg/dl and a concentration of copper in a liver biopsy sample > 250mg/g dry weight[1]
    - Most symptomatic patients excrete > 100 µg copper per day in urine and have histologic abnormalities on liver biopsy[1]

Differential Diagnosis

1. Key Differential Diagnoses:
    - Acute viral hepatitis
    - Chronic hepatitis
    - Drug or alcohol induced liver disease
    - Heterozygous carriers
2. Extensive Differential Diagnoses
    - Malabsorption
    - Nephrotic Syndrome
    - Menke's disease

Therapeutics

1. Acute Treatment:- Chelation therapy
   - Symptomatic:
     - Penicillamine orally in an initial dose of 1 gram daily. Pyridoxine at 25 mg/day supplementation required. Monitor CBC, urine first month and daily body temperature and skin checks by patient (to look for hypersensitivity reactions)
     - Trientine in penicillamine intolerant patients.
     - Acute liver failure-immediate liver transplantation.
   - Asymptomatic:
     - Chelation therapy with penicillamine or trientine
     - Zinc
2. Long-Term Care:
   - Lifelong chelation therapy unless liver transplantation performed
   - Low copper diet- avoid shellfish, nuts, chocolate, mushrooms, organ meats, well water, copper containers and cookware
   - Continue treatment during pregnancy with penicillamine at lower dose
   - Zinc acetate or gluconate alone effective as maintenance
   - Liver transplantation for patients with decompensated chronic disease who fail to respond to medical therapy.

Follow-Up

1. Return to Office
   - At least twice annually-Serum copper, ceruloplasmin, LFT's, CBC, urinalysis, INR
   - PE at least twice annually to confirm clinical improvement, identify adverse side effects, look for evidence of liver disease and neurologic symptoms.
   - 24 hour urinary excretion of copper measured yearly

Prognosis

1. Excellent except for those with advanced disease or with rapidly progressive liver failure and hemolysis.
2. Neurologic, psychiatric, hepatic abnormalities gradually improve with treatment

Prevention

1. Screen all 1° relatives of patients with Wilson's Disease
2. Children younger than age six retested over 5 to 10 years.
3. Genetic testing of siblings reasonable when mutation found in proband.

Patient Information

1. http://ghr.nlm.nih.gov/condition/wilson-disease (Accessed 9.12.2010)
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References

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