

## Wilson Disease in children -A review



### Medical Science

KEYWORDS :

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### ABSTRACT

• *Wilson's disease is a rare inherited disorder that can cause liver damage and other life-threatening conditions.*

- *In Wilson's disease, your child's body is unable to excrete excess copper (found in many foods), which builds up in the liver.*
- *This causes progressive damage to your child's liver.*
- *Eventually, the copper is released into your child's bloodstream and deposits in other organs including the brain, kidneys and eyes (corneas).*
- *It affects about one in 30,000 people worldwide.*
- *Without treatment, Wilson's disease may cause severe complications, including some that are life threatening.*

### Introduction

Wilson's disease or hepatolenticular degeneration is an autosomal recessive genetic disorder in which copper accumulates in tissues; this manifests as neurological or psychiatric symptoms and liver disease. It is treated with medication that reduces copper absorption or removes the excess copper from the body, but occasionally a liver transplant is required.

The condition is due to mutations in the Wilson disease protein (ATP7B) gene. A single abnormal copy of the gene is present in 1 in 100 people, who do not develop any symptoms (they are carriers). If a child inherits the gene from both parents, the child may develop Wilson's disease. Symptoms usually appear between the ages of 6 and 20 years, but cases in much older people have been described. Wilson's disease occurs in 1 to 4 per 100,000 people.[1] Wilson's disease is named after Samuel Alexander Kinnier Wilson (1878–1937), the British neurologist who first described the condition in 1912

The major physiologic aberration is excessive absorption of copper from the small intestine and decreased excretion of copper by the liver.

The genetic defect, localized to chromosome arm 13q, has been shown to affect the copper-transporting adenosine triphosphatase (ATPase) gene (ATP7B) in the liver.

### Pathophysiology:

The estimated total body copper content is 50-100 mg, with an average daily intake of 1-2 mg.

Copper is an important component of several metabolic enzymes, including lysyl oxidase, cytochrome c oxidase, superoxide dismutase, and dopamine beta-hydroxylase. Intestinal copper absorption and transport into hepatocytes is intact in Wilson disease. In Wilson disease, the processes of incorporation of copper into ceruloplasmin and excretion of excess copper into bile are impaired. The transport of copper by the copper-transporting P-type ATPase is defective in Wilson disease secondary to one of several mutations in the *ATP7B* gene.

The excess copper acts as a promoter of free radical formation and causes oxidation of lipids and proteins. In the earliest stages of hepatocellular injury, ultrastructural abnormalities involving the endoplasmic reticulum, mitochondria, peroxisomes, and nuclei have been identified. Initially, the excess copper is stored in the liver and causes damage to the hepatocytes. Eventually, as liver copper levels increase, it is released into the circulation and deposited in other organs.

### Epidemiology;

**Prevalance;1:30000,carrier 1:100**

Incidence; The worldwide incidence rate is 10-30 million cases, with increased rates in areas of consanguinity.

**Mortality/Morbidity:** Fulminant Wilson disease leads to rapidly progressive liver failure, encephalopathy, coagulopathy, and, eventually, death if emergent liver transplantation is not performed.

**Sex:** The fulminant presentation of Wilson disease is more common in females than males (4:1).

**Age:** Wilson disease manifests as liver disease in children and adolescents, peaking at ages 10-13 years, and as neuropsychiatric illness in young adults aged 19-20 years. **CLINICAL**

The condition may also manifest as acute hepatitis. Hepatic dysfunction is the presenting feature in more than half of patients. The 3 major patterns of hepatic involvement are

- (1) Chronic active hepatitis,
- (2) Cirrhosis, and
- (3) fulminant hepatic failure.

The most common initial presentation is cirrhosis.

- o The most common presenting neurologic feature is asymmetric tremor, occurring in approximately half of individuals with Wilson disease. The character of the tremor is variable and may be predominantly resting, postural, or kinetic.
- o Frequent early symptoms include difficulty speaking, excessive salivation, ataxia, masklike facies, clumsiness with the hands, and personality changes.
- o Late manifestations -include dystonia, spasticity, grand mal seizures, rigidity, and flexion contractures.
- o Psychiatric features include emotional lability, impulsiveness, disinhibition, and self-injurious behavior. The reported percentage of patients with psychiatric symptoms as the presenting clinical feature is 10-20%. The range of psychiatric abnormalities associated with Wilson disease has been divided into 4 basic categories, as follows:
  - Behavioral
  - Affective
  - Schizophreniclike
  - Cognitive

### Ophthalmologic

Kayser-Fleischer rings are formed by the deposition of copper in Descemet membrane in the limbus of the cornea. Kayser-Fleischer rings are observed in up to 90% of individuals with symptomatic Wilson disease and are almost invariably present in those with neurologic manifestations.

**Musculoskeletal****osteopenia on conventional radiologic examination.**

arthropathy generally involves the spine and large appendicular joints such as knees, wrists, and hips. Osteochondritis dissecans, chondromalacia patellae, and chondrocalcinosis have also been described.

**Hematologic**

Hemolytic anemia is rare (10-15%) complication of the disease.

Coombs-negative acute intravascular hemolysis most often occurs as a consequence of oxidative damage to the erythrocytes by the higher copper concentration.

**Renal**

defective renal acidification and excess renal losses of amino acids, glucose, fructose, galactose, pentose, uric acid, phosphate, and calcium. The frequency of renal manifestations is variable.

Urolithiasis, found in up to 16% of patients with Wilson disease, may be the result of hypercalciuria or poor acidification.

Hematuria and nephrocalcinosis are reported, and proteinuria and peptiduria can occur both before treatment as part of the disease process and after therapy as adverse effects of D-penicillamine.

**Physical:** Physical findings are consistent with liver disease, to include jaundice, varices, spider angiomas, and palmar erythema.

**Causes:** An autosomal recessive mode of inheritance confirmed by extended genetic analysis of 30 families. Frydman et al localized the Wilson disease (*WD*) gene to chromosome 13.

The *WD* gene product is a 1411 amino acid protein with highest levels of expression in the liver, kidneys, and placenta. The *WD* gene codes for P-type copper-transporting ATPase, now characterized as *ATP7B*. Many of the gene defects for *ATP7B* are small deletions, insertions, or missense mutations. Most patients carry different mutations on each of their 2 chromosomes. More than 40 different mutations have been identified, the most common of which is a change from a histidine to a glutamine (H1069Q).

**DIFFERENTIALS**

Anemia  
Arthritis  
Hemochromatosis  
Hepatic failure  
Hepatocellular Adenoma  
schizophrenia

**Lab Studies:**

- The presence of Kayser-Fleischer rings and ceruloplasmin levels of less than 20 mg/dL in a patient with neurologic signs or symptoms suggest the diagnosis of Wilson disease.
- If a patient is asymptomatic, exhibits isolated liver disease, and lacks corneal rings, the coexistence of a hepatic copper concentration of more than 250 mg/g of dry weight and a low serum ceruloplasmin level is sufficient to establish a diagnosis.
- Serum ceruloplasmin
  - o levels of less than 20 mg/dL (reference range, 20-40 mg/dL).
- Urinary copper excretion
  - o The urinary copper excretion rate is greater than 100 mg/d (reference range, <40 mg/d) in most patients with symptomatic Wilson disease.
- Hepatic copper concentration
  - o A liver biopsy with sufficient tissue reveals levels of more than 250 mcg/g of dry weight even in asymptomatic patients. Special collection vials are available to help avoid contamination.
- Radiolabeled copper
  - o Radiolabeled copper testing directly assays hepatic copper metabolism. Blood is collected at 1, 2, 4, 24, and

48 hours after oral ingestion of radiolabeled copper (<sup>64</sup>Cu or <sup>67</sup>Cu).

- o exhibit a slow lower-level reappearance of radioactivity rather than the continued fall in radioactivity in those with Wilson disease, but there may be considerable overlap between the two. Patients with Wilson disease, even those with normal ceruloplasmin levels, do not exhibit the secondary rise in radioactivity.
- Genetic diagnosis: the use of molecular testing is currently limited to screening of family members for an identified mutation detected in the index patient.

**Imaging Studies:**

- **Cranial CT scan**
  - o The cranial lesions observed on CT scan are typically bilateral and well-defined, slitlike, low-attenuation foci involving the basal ganglia, particularly the putamen, thalamus, or dentate nucleus.
  - o Widening of the frontal horns of the lateral ventricles and diffuse cerebral and cerebellar atrophy, which correlate histologically with widespread neuronal loss, have also been described.
- **Brain MRI**
  - o MRI of the brain appears to be more sensitive than CT scanning in detecting early lesions of Wilson disease.
- **Positron emission tomography scan**
  - o Positron emission tomography (PET) scan reveals a significantly reduced regional cerebral metabolic rate of glucose consumption in the cerebellum, striatum, and, to a lesser extent, in the cortex and thalamus.
  - o PET analyses of patients with Wilson disease have also demonstrated a marked reduction in the activity of dopa-decarboxylase, indicative of impaired function of the nigrostriatal dopaminergic pathway.
- **Electron microscopy**
  - o Electron microscopic studies on ultrathin sections reveal numerous electron-dense lysosomes and residual bodies.
  - o The electron microscopic detection of copper-containing hepatocytic lysosomes is helpful for the diagnosis of early stages of Wilson disease in addition to the quantification of hepatic copper by atomic absorption spectrophotometry.

**Other Tests:**

- Resting ECG abnormalities include left ventricular or biventricular hypertrophy, early repolarization, ST segment depression, T-wave inversion, and various arrhythmias.

**Staging:** The natural history of the disease may be considered in 4 stages, as follows:

- Stage I - The initial period of accumulation of copper by hepatic binding sites
- Stage II - The acute redistribution of copper within the liver and its release into the circulation
- Stage III - The chronic accumulation of copper in the brain and other extrahepatic tissue, with progressive and eventually fatal disease
- Stage IV - The achievement of copper balance with chronic chelation therapy

**TREATMENT**

**Medical Care:** The mainstay of therapy for Wilson disease is pharmacologic treatment with chelating agents.

Penicillamine-20-35 mg/kg oral 3-4 divided dose. Lifelong, uninterrupted chelation therapy is necessary in all patients with Wilson disease.

Trientine -- Effective oral chelator used to induce cupriuresis. Useful for patients who cannot tolerate penicillamine.(750-1200 mg /day in 3-4 divided doses)

Zinc- Approved for patients initially treated with a chelating agent. Should be used for maintenance after initial therapy(

150-300 mg/day) 30 minute before food.

Pyridoxine -- Involved in synthesis of GABA within the CNS. -25mg/kg /day

Dimercaprol (BAL in Oil) -- For refractory cases of Wilson disease not responding to first- or second-line treatment. -3-5 mg/kg IM q4h

Perform a physical examination, 24-hour urinary copper excretion assay, CBC count, urinalysis, serum free copper measurement, and renal and liver function tests on a weekly basis for the first 4-6 weeks following initiation of chelation therapy.

Bimonthly evaluations are recommended through the first year, followed by yearly examinations thereafter

#### Surgical Care:

- The use of surgical decompression or transjugular intrahepatic shunting (TIPS) in the treatment of portal hypertension is reserved for individuals with recurrent or uncontrolled variceal bleeding that is unresponsive to standard conservative measures.

- Orthotopic liver transplantation is a potentially curative treatment of Wilson disease.

**Diet:** Patients should generally avoid eating foods with a high copper content such as liver, chocolate, nuts, mushrooms, legumes, and shellfish (especially lobster). Drinking water from atypical sources (eg, well water)The mainstay of therapy for Wilson disease is the use of chelating agents and medications that block copper absorption from the GI tract.

#### Prognosis:

- Prognosis after liver transplantation is relatively good.

## REFERENCE

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