Wilson's Disease: a review

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Introduction

Wilson's disease (WD; Hepatolenticular degeneration) is an autosomal-recessive disorder of copper metabolism due to absence or dysfunction of a copper-transporting, P-type ATPase which is essential for the transport of copper into bile. Affected patients accumulate excessive copper within the liver as well as the brain and other tissues. This is mainly a disease of children, adolescents, and young adults, and is characterized by hepatobiliary, neurologic, psychiatric and ophthalmologic (Kayser-Fleischer rings) manifestations. If diagnosed early and properly managed, WD is one of the more easily treated inborn errors of metabolism. In 1912, Samuel Alexander Kinnier Wilson (British Neurologist, 1878-1937), while serving as a Senior Resident at the National Hospital for Nervous Diseases, London, published his experience of "Progressive Lenticular Degeneration: A Familial Nervous Disease Associated with Cirrhosis of the Liver", as part of his dissertation for the MD degree.1 He speculated that the brain disease characterized by extra pyramidal features was caused by the liver disease.

The discovery of the gene for Menkes' disease and its product ATP7A, a cation-transporting P-type adenosine triphosphatase (ATPase) involved in copper transport in many tissues, 2 was a breakthrough in the understanding of the molecular basis of the defect of copper metabolism in Wilson's disease. Just after this discovery, Wilson's disease was identified as the result of a defect in a gene, designated ATP7B that encodes a copper transporting P-type ATPase.3 WD occurs worldwide with an average prevalence of ~ 30 affected individuals per million populations.4 Table I gives the description of milestone of WD.

Pathophysiology

Wilson's disease is a disease of copper toxicity. Absorbed dietary copper is bound mainly to albumin in the portal circulation from which it is avidly extracted by hepatocytes. Hepatocellular copper is subsequently used for cellular metabolic needs, incorporated into ceruloplasmin or excreted into bile. The transport of hepatocellular copper to bile is thought to involve a vesicular pathway (Golgi apparatus) that depends on ATP7B (copper transporting P-type ATPase) function.4 The absence or diminished function of ATP7B results in a decrease in biliary copper excretion, which is responsible for the hepatic accumulation of this metal in Wilson's disease.

Initially the copper is stored in the liver, when it accumulates beyond the cellular capacity for its safe storage, hepatocellular injury may result. Toxic effects of excess copper include the generation of free radicals, lipid peroxidation of membranes and DNA, inhibition of protein synthesis and altered level of cellular antioxidants. When storage capacity of the liver for copper is exceeded or when hepatocellular damage occurs, unbound copper splits out of liver and finds its way to other organs and tissues where it also begins to accumulate. The brain is the most important site for the extrahepatic accumulation of copper.

Table 1. Milestones of Wilson's disease

1912	Recongnition of Wilson's disease as an inherited disorder. and description of Kayser-Fleischer rings
1948-1952	Description of increased urinary excretion of copper copper deposition in both liver and brain and ceruloplasmin deficiency
1951-1953	Introduction of BAL* and Penicillamine therapy as chelating agents for Wilson's 10.11
1961	Consideration of Zinc therapy for Wilson's disease
1973-1986	Introduction of Trientene and tetratiomoly bdate therapy
1988-1990	Localization of WD gene on long arm of chromosome 13 (13q14.3 region)
1993	Identification of WD gene,ATP7B , and disease specific mutation
1994-Present	Continued studies on disease-specific mutations and polymorphisms of ATP7B

* British Anti-Lewisite or dimercaptopronolol

Ceruloplasmin (a serum glycoprotein) is synthesized predominantly in the liver and functions as the major carrier for copper in the blood. Majority of patients with Wilson's disease have low ceruloplasmin levels due to decreased rate of synthesis of the ceruloplasmin molecules in the liver. Hypoceruloplasminemia has no primary role in the

pathogenesis of Wilson's disease. Copper is thought to be incorporated into ceruloplasmin in the Golgi apparatus, and during the biosynthetic process of ceruloplasmin, newly transported copper must also cross Golgi apparatus membrane which is again ATP7B dependant and which is absent or diminished in most of the Wilson's disease patients.5 A reduction of the incorporation of copper into ceruloplasmin is believed to lead to a reduced circulating level of this protein. Other conditions associated with ceruloplasmin deficiency are hereditary ceruloplasmin deficiency, Menkes' disease, and conditions with transient ceruloplasmin deficiency (such as protein losing enteropathy, nephritic syndrome, hepatic failure, sprue, etc).6

Clinical Manifestations

Wilson's disease is most frequently recognized as a trait of liver disease, neurological symptoms, and K-F rings. Nevertheless, because multiple organ system can be affected with excessive copper accumulation, Wilson's disease is remarkable clinical heterogeneity and patients may present in a number of different ways. Generally, in children the liver is chiefly involved, later neuropsychiatric features become increasingly important. While patients presenting after age 20 years usually have neurological symptoms. The two types may overlap. The spectrum of WD is summarized in Table 2.

Table 2. Presenting Clinical Features of Wilson's disease,7-10

Asymptomatic	Presymptomatic (found by family sereening)
Nearological (40-50%	Dystonia and Rigidity
	Tremors (resting Postural, or kinetic unilateral or bilateral)26
	Dysarthira and dysphonia
	Cerehellar dysfunction (scanning speech, intension tremors, ataxia)
	Seizures
Hepatic (>50%)	Asymotomatic with only biochemical abnormalities
	Acute transient hepatitis
	Chronic active hepatitis
	Cirrhosis(compensated or decompensated)
	Fulminant hepatic failure 32
Psychiatric (20%)	Depression 33 Personality changes
	Neuroses
	Psychosis
Others Systems	Renal disease aminoaciduria nephrolithiasis rolithiasis, hematuria
	Skeletal disease: arthritis premature osteoporosis, osteomalacia
	Myocardial disease: ardiomyopathy and arrhythmias others: hemolytic anemia, skin pigmentation, gynecomastia, recurrent hypokelemic muscle weakness, glucose intolerance

The average age of the patients whose first presenting symptoms of their WD are either neurological or psychiatric, is frequently later than those presenting with hepatic symptoms (18 years versus 11.4 years), although neurological symptoms have been reported as early as age 6 and as late as age 50.8 WD is a disease of motor function, and basal ganglia symptoms are the most common symptoms. The prevalence of seizures is 10 times higher in patients with WD that in the general population. The psychiatric features of WD are under-appreciated and often misdiagnosed as having primary psychosis or schizophrenia. More than 20 percent patients with WD were found to have sought psychiatric evaluation before the diagnosis.9