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Wilson's Disease: a review

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Introduction and Genetics

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.

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.

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 than 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 psy-

chiatric evaluation before the diagnosis.⁹

Hepatic manifestation is more common in childhood, although it has been documented in patients beyond age 40.¹¹ Thus in patients between age 40 and even 50 who present with hepatic dysfunction, WD should be considered in the differential diagnosis. The clinical spectrum of liver disease associated with WD ranges widely. The type of the liver disease can be highly variable, ranging from asymptomatic with only biochemical abnormalities to fulminant hepatic failure. Hepatocellular carcinoma is very rare and copper may be protective.¹²

Kayser-Fleischer (KF) rings: These represent copper deposition on Descemet's membrane at the limbus of cornea are almost always bilateral, but unilateral KF rings have been described.¹³ KF rings are not pathognomonic of WD, since they can be seen in other non-Wilson's hepatic conditions including primary biliary cirrhosis, chronic active hepatitis, possible partial biliary atresia, cirrhosis and chronic cholestatic jaundice.¹⁴ Sun-flower cataracts, another ophthalmologic change, much less common than KF rings, represent deposits of copper in the lens.

Both Kayser-Fleischer rings and sun-flower cataracts will gradually disappear with effective medical treatment or following liver transplantation, although the rate of disappearance does not correlate with resolution of clinical symptoms. The reappearance of either of these ophthalmologic findings in a medically treated patient in whom these had previously disappeared, suggests noncompliance with therapy.

Diagnostic Testing

The most important single factor in early diagnosis of WD is suspicion of the disease, when the diagnosis is not considered, it will not be made. WD should be considered and excluded in any individual between the age of 3 and 40 years with unexplained neurological (especially with extrapyramidal or cerebellar motor disorder), hepatic, or psychiatric dysfunction with or without family disorder of neurological or hepatic disease.

Slit lamp Examination

All suspected WD patients should undergo a slit-lamp examination by an experienced ophthalmologist for the detection of KF rings. KF rings are almost invariably present in patients with a neurological presentation, but even in these patients they may not be found in 5%.¹⁵ Large series of patients with WD show that KF rings are present in only 50% to 62% of patients with mainly hepatic disease at the time of diagnosis.¹⁶

24 Hour Urinary Copper

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24 Hour Urinary Copper

Very useful and relatively simple screening test for WD. Urinary copper is derived from the circulating plasma free copper. The conventional level taken as diagnostic of WD is greater than 100 $\mu\text{g}/24$ hours in symptomatic patients.¹⁷ Recent studies indicate that basal 24-hour urinary copper excretion may be less than 100 μg at presentation in 16% to 23% of patients diagnosed with WD.¹⁸ In asymptomatic subjects, where copper is still accumulating in the liver, urinary copper may still be in the normal range.

Serum Ceruloplasmin Concentration

This should be considered as a screening test in all suspected WD patients. 5-15% of individuals with WD may have normal or only slightly reduced ceruloplasmin, whereas 10-20% of heterozygotes may have reduced serum ceruloplasmin. A serum ceruloplasmin level less than 20 mg/dL has been considered consistent with WD and diagnostic if associated with KF rings.¹⁹ Most reports indicate that 90% to 100% of patients had serum ceruloplasmin in the subnormal range.²⁰

Serum Free-Copper Concentration

Routinely, total serum copper (ceruloplasmin copper plus free copper) are frequently obtained as a screening test for WD but is actually of little real value. Determination of free serum copper directly measures the unbound copper in the blood, which is typically elevated in symptomatic WD patients and has been proposed as a useful diagnostic test of WD.¹⁰ It is elevated above 25 $\mu\text{g}/\text{dL}$ in most untreated patients.²¹ The serum non-ceruloplasmin copper concentration may be elevated in acute liver failure of any etiology, not only WD.

Liver Copper Concentration

This is the single most sensitive and accurate test for WD. Hepatic copper content will be elevated in virtually all individuals with WD, even those who are clinically asymptomatic. Hepatic copper content 250 $\mu\text{g}/\text{g}$ dry weight remains the best biochemical evidence for WD. Elevated hepatic copper itself is not pathognomonic for WD and can occur in other liver diseases, particularly primary biliary cirrhosis, biliary atresia, primary sclerosing cholangitis, Indian childhood cirrhosis, and chronic active hepatitis. This test is most important in younger patients in whom hepatocellular copper is mainly cytoplasmic and thus undetectable by routine histochemical methods.¹⁹

Neuroimaging Studies

Magnetic resonance imaging (MRI) is a more sensitive indicator of brain involvement in WD. Basal ganglia are the most consistently involved brain area, with the brain stem and thalamus also frequently affected. Increased signal intensity on T2-weighted images is the characteristic abnormality.²² Significant abnormalities on brain imaging may

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Treatment

Treatment of WD can be stratified into four primary approaches: dietary therapy (by reducing copper content in diet), therapy to reduce intestinal copper absorption (by zinc, and tetrathiomolybdate), therapy to increase copper chelation and elimination (by penicillamine, trientine, and BAL), and liver transplantation. Table 3 gives the therapeutic options for WD.

Diet

Foods with very high concentrations of copper (shellfish, nuts, chocolate, mushrooms, and organ meats) generally should be avoided, at least in the first year of treatment. Diets deficient in copper may delay the onset of the disease and control disease progression, but dietary management is not recommended as sole therapy.²⁵

Zinc

Zinc is currently reserved for maintenance therapy; it has also been used as initial therapy, in asymptomatic or presymptomatic patients, and appears to be equally effective as penicillamine.²⁶ Although zinc is almost always well-tolerated, adverse effect may occur. Neurological deterioration is uncommon with zinc.²⁶ Urinary excretion of zinc may be measured from time to time to check compliance. Adequacy of treatment with zinc is judged by clinical

clinical and biochemical improvement, by measuring 24-h urinary copper (should be less than 75 μg / 24 hours), and by normalization of serum free-copper concentration on stable treatment.¹⁹

D-Penicillamine

The sulfhydryl moiety of the penicillamine molecule binds copper and forms penicillamine-copper complexes that are excreted in the urine. Penicillamine is indicated as the primary therapy of symptomatic patients with hepatic or neurologic/psychiatric disease. In the asymptomatic homozygote, penicillamine can be used. Before starting therapy baseline copper metabolic parameters should be collected (24-h urinary excretion, serum free copper, examination for KF rings) for future follow-up. Complete blood count and platelet count should also be obtained before treatment is begun. Pretreatment urine analysis and 24-h urine protein excretion are also recommended because of the possibility of penicillamine-induced proteinuria or nephritic syndrome.²⁷

The drug is administered 1 hour before or 2 or more hour after meals because food diminishes the amount of D-penicillamine absorbed by gastrointestinal tract.

One troublesome aspect of penicillamine is its propensity to produce initial deterioration in neurological function in 10% to 50% of penicillamine-treated WD patients, after treatment is begun. Half of those in whom neurological deterioration occurs on initiation of penicillamine therapy do not fully recover to their base line level of functioning.²⁸ The reason for this neurological deterioration is uncertain. Mobilization of copper from the liver with subsequent redistribution to the brain has been suggested.²⁹

Regular supplementation with pyridoxine (25 to 50 mg daily) is required because of an antipyridoxine effect of penicillamine, especially during pregnancy, during a growth spurt, or with dietary deficiency.²⁸

Trientine

Trientine and penicillamine may mobilize different pools of body copper. Whether trientine is a weaker chelator of copper than penicillamine is controversial. Trientine is indicated especially in patients who are intolerant of penicillamine or have clinical features indicating potential intolerance (history of renal disease of any sort, congestive splenomegaly causing severe thrombocytopenia, or autoimmune tendency).³⁰ Trientine has also been shown to be an effective initial therapy for patients with WD.³¹

Trientine appears to be a less toxic compound. Neurologic worsening after beginning treatment with trientine has been reported but appears much less common than with penicillamine. Adequacy of treatment with trientine is

monitored by measuring 24-hour urinary copper. This should run in the vicinity of 200 to 500 μg per day on treatment.

Tetrathiomolybdate (TM)

Tetrathiomolybdate is another chelating agent currently undergoing evaluation as an initial treatment of patients with neurologic symptoms. The first reports on the use of tetrathiomolybdate in this setting suggest no worsening of neurologic symptoms and a rapid reduction in circulating free copper during the first 8 weeks of therapy.³²

Experience with TM in the treatment of WD is currently limited and experimental. In United States of America, commercially it is not available.

Orthotopic Liver Transplantation (OLT)

This may be a lifesaving and curative treatment for WD and is indicated for all WD patients with decompensated liver disease unresponsive to medical therapy. It is the only effective option for those who present with fulminant hepatic failure. One-year survival following OLT ranges from 79% to 87%, and those who survive this early period continue to survive long term.³³ Liver transplantation is not recommended as primary treatment for neurologic WD since the liver disease is stabilized by medical therapy in most of these individuals, and outcomes with liver transplantation are not always beneficial.³³ **Family Screening**

First degree relatives of any patient with WD must be screened for WD. Assessment should include history of liver disease and subtle features of neurological involvement slip lamp examination for KF rings, serum free copper, ceruloplasmin, liver function tests and 24-h urinary copper. Liver biopsy with liver copper concentration should be checked in individuals with subnormal ceruloplasmin and abnormal liver function in the absence of KF rings. If available, haplotype studies should be obtained as a primary screening. Treatment should be initiated for all individuals over 3 to 4 years old identified as patients by family screening.¹⁹

Prognosis

Untreated WD is progressive and fatal. The greater danger is that the patient remains undiagnosed and dies untreated. The prognosis for patients who comply with pharmacotherapy is excellent, even if cirrhosis or chronic hepatitis is present at the time of diagnosis.³⁴ In the acute neurological form the prognosis is poor. Dystonia also carries a poor prognosis, being little affected by chelation therapy. The fulminant cases are frequently fatal despite chelation therapy. The final prognosis also depends on the response to 6 months of continuous penicillamine therapy. At present, there is no better way to judge the extent of reversibility of a patient's disease than awaiting a response

At present, there is no better way to judge the extent of reversibility of a patient's disease than awaiting a response to treatment.

Practice Guidelines and Recommendations

Recently the American Association for the Study of Liver Diseases (AASLD) has published practice guidelines.¹⁹ Some important recommendations are: (1) WD should be considered in any individual between the ages of 3 and 45 years with liver abnormalities of uncertain cause. (2) KF rings should be sought by slit-lamp examination by an experienced ophthalmologist. The absence of KF rings does not exclude the diagnosis of WD. (3) An extremely low serum ceruloplasmin level (<5 mg/dL) should be taken as strong evidence for the diagnosis of WD. (4) 24-hour urinary copper should be measured in WD, and it is typically greater than 100 µg in symptomatic patients. (5) Neurologic evaluation and radiologic imaging of the brain, preferably by MRI, should be considered prior to treatment in all patients with neurologic WD. (6) First-degree relatives of any patient newly diagnosed with WD must be screened thoroughly for WD. (7) Initial treatment for symptomatic patients should include a chelating agent (penicillamine or trientine). (8) Treatment of presymptomatic patients or maintenance therapy of successfully treated symptomatic patients can be accomplished with the chelating agent penicillamine or trientine, or zinc. (9) Patients with fulminant hepatic failure or patients with severe liver disease unresponsive to chelation treatment should be treated with liver transplantation. (10) Treatment is lifelong and should not be discontinued, unless a liver transplantation has been performed.

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