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Review Article

Wilson's disease: A Review on Clinical Presentation, Diagnostic Methods and Treatment

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ABSTRACT

Wilson's disease is an inherited disorder characterized by the excessive accumulation of copper or abnormal copper metabolism. It occurs predominantly in the liver and brain. The genetic factor leading to Wilson's disease is the mutation of copper transporting gene ATP7B.The main clinical symptoms in Wilson's disease include neurological, psychiatric and hepatic. The primary treatment in Wilson's disease is use of copper chelating agent such as D-penicillamine and trientine. This review discusses the pathophysiology, etiology, clinical presentation, diagnosis and management of Wilson's disease.

Key words: Wilson's disease, Copper, liver, Kayser-Fleischer ring.

INTRODUCTION

Wilson's disease is an autosomal recessive disorder occurs due to abnormal copper metabolism, copper accumulation or copper toxicity. [1] In 1912, Dr. Samuel Alexander Kinner Wilson first defined the condition of Wilson's disease. [2] Worldwide the prevalence of Wilson's disease is approximately 1 in 30000 and the carrier frequency is approximately 1 in 90. [3,4] The majority population with WD presents between 5-35 years of age .The youngest patient reported with cirrhosis due to WD was 3 year old. [5]

PHYSIOLOGICAL ROLE OF COPPER

Copper is an essential nutrient and a major trace element required for the growth, development and maintenance of bone, brain, heart, connective tissue. The recommended daily dose of copper intake is 1-2mg/day. [6] Copper is mainly absorbed in stomach and duodenum which binds with albumin and histidine thereby transported to liver. [7] The liver has a significant role in copper absorption, distribution and excretion. [8] Copper reaches the digestive tract and enters the absorption system through copper transported protein. The copper then binds to metallothionein in the cell. ATP7A gene releases copper into liver. ATP7B gene in the liver encodes a metal transporting P type adenosine triphosphatase which is responsible for binding of copper to ceruloplasmin and the elimination of copper into the bile. ATP7B is responsible for hepatic copper metabolism.

In 1993, mutation of ATP7B in WD was identified. [9] Abnormal function of ATP7B results in decreased hepatocellular excretion of copper into the bile and leads to hepatic accumulation of copper. Secondly, copper gets incorporated into blood stream and is accumulated in brain, kidney and cornea. Mutation of ATP7B protein also causes failure in binding of copper-ceruloplasmin. [6]

ETIOLOGY

Genetic factor associated with WD is the mutation of ATP7B gene, which causes accumulation of copper in different organs. [10]

PATHOPHYSIOLOGY

Excretion of copper is damaged in WD.ATP7B mutation reduces the conversion of apoceruloplasmin in to ceruloplasmin and also results in the decreased excretion of copper in to the biliary canaliculi. [11,12] Increased accumulation of copper destroys the mitochondria and produces oxidative damage to cells. It also leads to copper overload in other organs such as brain, kidney and blood cells. [11] Inhibition of IAPs (inhibitor of apoptosis proteins) leads to apoptotic cell death in WD. [13] Excess of copper include generation of free radical, lipid peroxidation of membranes and DNA, inhibition of protein synthesis and altered level of cellular antioxidants. Low ceruloplasmin level is seen in majority of the patients with WD.

Brain is the main organ which is affected in WD. The lenticular nuclei of brain appear brown in colour due to accumulation of copper. [14] Progression of disease leads to degeneration, necrosis, gliosis and cystic changes can be seen in the brain stem, thalamus, cerebellum and cerebral cortex. The other organs affected by WD are kidney and cornea. [15]

CLINICAL PRESENTATION

Ocular Presentations

The most common clinical symptom present in WD is Kayser-Fleischer ring. Copper gets deposited on Descemet's membrane of the cornea. Golden-brownish pigment band were visible by direct inspection using a slit lamp. [16] The presence of Kayser-Fleischer ring is an indicative of copper accumulation in the brain. [15] Kayser-Fleischer rings are not specific for WD, as it may be present in patients with cholestatic diseases and in neonatal cholestasis. [17-19] It seems to be positive in 95% of patients with neurologic symptoms and also in half of patients without neurological symptoms. [20,21] Kayser-Fleischer ring are absent in children with liver disease. [22] Other ophthalmological changes such as sunflower cataracts and abnormalities in ocular movements such as slow horizontal saccades, upward gaze restriction and impaired convergence also occur in WD. [23]

Hepatic Presentations

The liver enzymes such as serum amino transaminases (SGPT & SGOT) elevate permanently and low levels of alkaline phosphatase were observed. The patient may also present with acute fulminant or chronic hepatitis. [24] In the advanced stages of disease, cirrhosis of macronodular type may develop. [15] Other hepatic signs include mild hepatosplenomegaly, ascites, jaundice and hematemesis with melena caused by portal hypertension. [25,16]

Marked hemolysis is commonly associated with severe liver disease. Liver damage may result in increased release of stored copper which exaggerates hemolysis. Rarely, hepatocellular carcinoma associated with chronic cirrhosis and inflammation can be seen in WD. [24]

Neurological Presentations

Neurological symptoms are present in the 40-50% of the cases with WD. [26] The symptoms may appear between 2-5 years after the detection of liver disease. Dysarthria, tremor, dystonia and Parkinsonism are the most frequently observed neurological signs. Dystonia is evident in the facial muscles, jaw, neck, trunk and limb. The involvement of facial muscles produces vacuous smile (due to gapping mouth) and causes a smirking look. The tongue and pharyngeal muscles involvement result in speech abnormality and swallowing problems. [24] The dystonia affecting limb may affect the writing and walking of the patients. Speech changes and drooling are the initial presentation of WD.

In patients with Parkinsonism symptoms such as rigidity, bradykinesia, tremor and micrographia are common. Irregular proximal upper limb movement

(wing-beating tremor) can be observed. [27] Cerebellar finding such as limb incoordination, abnormal gait and ataxia occurs. Autonomic dysfunction includes postural hypotension; abnormal sweating, sphincter and sexual dysfunction were present. [28] Rarely, seizures, cognitive and behavioural impairment may develop in WD. [29]

Psychiatric Presentations

Psychiatric symptoms may be present in 30-50% of the patients. [24] In children, changes in school performance, mood disorders, anxiety, impulsiveness, attention deficit hyperactivity disorder and inappropriate behavior are present. Paranoid, psychosis, obsessive behavior, depression and suicidal tendencies are other commonly observed psychotic symptoms. [30]

Others

Skeletal muscle abnormalities like osteomalacia, osteoporosis and osteoarthritis, renal dysfunctions such as aminoaciduria, nephrolithiasis, hypercalciuria and nephrocalcinosis, cardiomyopathy, hypoparathyroidism, pancreatitis, infertility or repeated pregnancy loss, gigantism and lunulae are the less common symptoms seen in WD. [16]

Table 1: Clinical Presentations of Wilson's Disease

Ocular
Kayser- Fleischer Ring Sunflower catarcts Impaired convergence Upward gaze restriction
Hepatic
Hepatic elevated liver enzyme (SGOT & SGPT) Low alkaline phosphatase Fulminant or chronic hepatitis Mild hepatosplenomegaly Hemolytic Cirrhosis
Neurological
Dysarthria & Dystonia Drooling Parkinsonism (tremor, rigidity, bradykinesia) Seizure episodes (Rare) Cognitive Dysfunction Ataxia Abnormal gait
Psychiatric
Depression Psychosis Behavioural changes
Other Systems
Orthopaedics- Osteomalacia, Osteoporosis, osteoarthritis, juvenile polyarthritis, chondrocalcinosis Renal- Hypercalciuria, aminoaciduria, nephrolithiasis, nephrocalcinosis, kidney stone Cardiovascular-Cardiomyopathy, arrhythmia Gynecological- infertility, repeated miscarriage, amenorrhea

DIAGNOSTIC CRITERIA

Ceruloplasmin

Ceruloplasmin is the major copper carrier in the blood. It is mainly synthesized in the liver. The normal level ranges between 200-400mg/L or 0.2-0.5g/L. Ceruloplasmin is a ferroxidase and is a nitric oxide oxidase which influences nitric oxide homeostasis. [31,32] Serum ceruloplasmin levels may be measured by their copper-dependant oxidase activity towards the substrates or using antibody dependent assay such as radioimmunoassay, nephelometry and radial immunodiffusion. In conditions such as inflammation, pregnancy, estrogen supplementation and use of oral contraceptives pills there is an increase in the serum ceruloplasmin concentration. [16] Serum ceruloplasmin level is typically reduced in majority of case of WD. Any value below 200mg/L or less than 0.1g/L seems to be abnormal. The other conditions in which low levels of ceruloplasmin can be found is Menkes

disease, hereditary aceruloplasminemia, renal or enteric protein loss, severe end stage liver disease and in heterozygous carrier of WD. [34] Thus, low levels of serum ceruloplasmin alone are not an indicative of WD.

Serum Free Copper

Serum free copper is the estimation of unbound copper in the blood or measures nonceruloplasmin toxic copper in the blood. The normal values ranges between 8-12µg/dl. In WD, the total serum copper is decreased in proportion to the reduction of ceruloplasmin in the blood. Acute liver failure due to WD may result in marked elevation of serum copper level as there is a sudden release of metal from the liver tissue stores.

Other proposed diagnostic test for WD is the serum non-ceruloplasmin bound copper concentration. In the most untreated patients, the level may be elevated above 25µg/dl. Non-ceruloplasmin bound copper is usually measured from the serum copper and ceruloplasmin. In cases such as acute liver injury, chronic cholestasis, copper intoxication may also lead to the elevated concentration of serum non ceruloplasmin copper. [34-36]

The main disadvantage of the non ceruloplasmin bound copper as a diagnostic test for WD is that it is dependent on the adequacy of measuring both serum copper and ceruloplasmin.

24 Hour Urinary Excretion of Copper

The test estimates the total amount of copper excreted in the urine in a period of 24 hours and is considered as a reliable test for the confirmation of diagnosing WD and monitoring the therapeutic outcome. In normal individual, the amount excreted is between 20-50 µg/day. The patients with WD the level of excretion is found to be increased up to 100µg/day. In untreated patients, basal measurements are taken as diagnostic of WD.

The common barriers in measuring 24 hour urinary excretion of copper includes incomplete urine collection and copper contamination of the device in which the urine is collected. To avoid this problem a disposable polyethylene containers are provided and the patient should be on copper deficient diet. [16]

Urinary copper excretion with D-penicillamine administration was another useful diagnostic test. The test is mainly used in pediatric population. It is performed by administering 500 mg of D-penicillamine orally at the beginning and again 12 hours later during the 24 hour urine collection. This test has been adults at different dosages and timing for administration of D-penicillamine. [34]

Hepatic Parenchymal Copper Concentration

Hepatic accumulation of copper is a major indicative of WD. The measurement of hepatic parenchymal copper concentration is the best method of choice in diagnosing WD. The value more than 4 µmole/g dry weight of hepatic parenchymal concentration provides the diagnostic information of the disease.

The major problems associated with this diagnostic test are that as the disease progress, distribution of copper within the liver is often inhomogeneous. In certain cases nodules which lack histochemically detectable copper were found next to the cirrhotic nodules with abundant copper. Thus the concentration is under estimated due to sampling error. A marked elevation of hepatic parenchymal copper concentration was found in idiopathic copper toxicosis syndrome and in long standing cholestatic disorders. [7]

Liver Biopsy

In WD there is a marked hepatocellular degeneration and parenchymal collapse due to the formation of cirrhosis. Apoptosis of hepatocytes is a prominent feature with acute liver failure due to the disease. The liver biopsy seems to be the most reliable laboratory test for WD. [37] Normal copper concentration level of 250 µg/dry tissue weight may be found in healthy individuals and in most cases of WD this value exceeds in the normal limit.

Radioactive Copper Study

Radio copper is a noninvasive method to detect the copper metabolism especially in patients where biopsy is contraindicated. In WD cases with normal serum ceruloplasmin radio copper incorporation into this protein is reduced compared with normal individuals and most heterozygotes. Due to the difficulty in obtaining isotopes this test is not commonly used in diagnosing WD. [7]

Neuroimaging

Magnetic resonance imaging and computerized tomography of the brain is useful in detecting structural abnormalities in the basal ganglia. CT scans may reveal hypodensities and atrophy of bilateral basal ganglia, brain stem, cerebellum and cerebral cortex. But they are considered as relatively insensitive test. MRI is more sensitive method for detecting abnormalities in WD. [38,39] Proton magnetic resonance spectroscopy is an invasive method which provides information about the biochemistry of a defined volume of brain.

TREATMENT

The main goal of treatment for WD is to reduce the excess of copper accumulated in the body. Non pharmacological approach includes a copper deficient dietary intake. Foods such as chocolates, walnuts, mushrooms and organ meats should be avoided from the diet and also stop patients from cooking or taking food from copper bowl and plates. Well water or water brought into the house through the copper pipes should be checked for the copper content and water purifying system may be used.

First line pharmacological treatment of WD is use of copper chelating agent. Penicillamine and trientene are most commonly used chelating agents in WD.

D- Penicillamine

Penicillamine was introduced in 1956 as an oral agent for treating WD. [40] Penicillamine contains sulfhydryl moiety which binds with copper to produce penicillamine-copper complex which is excreted in urine. It also acts by inducing metallothionein in WD patient. [41] The dosing in adult is usually 750-1500mg/day in two or three divided doses and in children, 200mg/kg/day in two or three divided doses.

D-penicillamine is rapidly absorbed from the GI tract with a double peaked curve for intestinal absorption. [42,43] The drug should be taken 1 or 2 hours prior to the meal as it affects the absorption of penicillamine. If it is taken with the meal the overall absorption is decreased by about 50%. About 80% of the absorbed drug is excreted via kidney. The half-life of D penicillamine is 1.7-7 hours.

Neurological worsening is reported in 10-50% of patient treated with D-penicillamine. [44,45] Side effects include hypersensitivity reactions associated with fever, skin rash and lymphadenopathy. Neutropenia or thrombocytopenia occurs in some cases. Other late reactions includes lupus-like syndrome with hematuria, proteinuria, bone marrow suppression. Pyridoxine (Vitamin B6) 25-50 mg daily should be given due to the antipyridoxine effect of D-penicillamine.

The effect of treatment is monitored by measuring 24 hour urinary copper excretion. Immediately after starting treatment the value may exceed 1000µg/day and in maintenance treatment 200-500µg of urinary copper excretion is seen. Value of urine copper excretion below 200µg/day indicates either non-adherence to therapy or excess of copper removal.

Trientine

Trientine was introduced in 1969 as an alternative to D-penicillamine. Trientine lacks sulfhydryl groups and consist of polyamine like structure. It acts by forming stable complex with the four constituent nitrogen in a planar ring. [16] Trientine has fewer numbers of side effects as compared to penicillamine. The drug is poorly absorbed from the GI tract and the absorbed drug is metabolized and inactivated. [46] Trientine promotes copper excretion by kidney. Trientine is mainly prescribed for the patients who are intolerant to

penicillamine or have potential intolerance such as history of renal disease of any cause, congestive splenomegaly causing severe thrombocytopenia or autoimmune tendency. [47,48] The initial dose 1200-1800mg/day in two or three times in divided doses and the maintenance dose of 900-1200mg is prescribed to the patient. Trientine should be administered 1 hour before or 3 hour after meals.

Side effects include hypersensitivity reactions, sideroblastic anemia, pancytopenia and hepatic siderosis. Adequacy of treatment is reported by measuring 24 hour urinary copper and the value ranges between 200-500µg/day on treatment.

Zinc

Zinc was first used to treat WD by Schouwink in Holland in the early 1960s. [49] Zinc is used to reduce the absorption of copper in the intestine. Zinc induces enterocyte metallothionein, which has a greater affinity for copper than zinc and binds copper present in the enterocyte thereby inhibiting its entry into the portal circulation. It also acts by inducing levels of hepatocellular metallothionein. [50,51] The daily doses of zinc in children and adults are 150mg/day in three divided doses. For infants, less than 50kg in body weight the dose is 75mg/day in three divided doses. Zinc should not be administered with meals as it interferes with zinc absorption. Adequacy of the treatment with zinc is measured clinically using 24 hour urinary excretion of copper and the value ranges in less than 75µg/24 hours.

The reported side effects of zinc are very few. Gastric irritation and nausea are the common side effects experienced by the patient.

Ammonium Tetrathiomolybdate (TM)

Ammonium Tetrathiomolybdate is very strong decoppering agent which act by two mechanisms:-a) interfering with intestinal uptake of copper (taken with meals) b) binding copper from plasma (taken between meals). In low doses, TM removes copper from metallothionein and higher doses it forms an insoluble complex with copper and gets deposited in liver. [52,53] TM is still an experimental therapy and is not commercially available. Side effects include bone marrow depression, hepatotoxicity and antiangiogenic effects.

Antioxidants

Antioxidant such as vitamin E may be prescribed in WD as serum and hepatic vitamin E levels shown to be low in WD. [16]

Liver Transplantation

Liver transplantation is done in patients with acute liver failure and with decompensated liver disease. Liver transplantation corrects the hepatic metabolic defects in WD and help to initiate normalization of extrahepatic copper metabolism. [54]

CONCLUSION

The physicians should promote the well-being of patients who manifests with neurological or psychiatric symptoms and liver disease. The management of Wilson disease should be aimed to get rid of extra copper in the body.

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