Mini Review Article

A review on copper, ceruloplasmin and wilson's disease

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Abstract

Objective: Copper as an essential trace element plays a vital function in biochemical systems. Its reduction or raise under/above a certain limit results consistently in disturbed physiologically functions. Wilson's disease is an auto-somal recessive copper transport disorder and clinical manifestations in adults are presentation of hepatic or neuropsychiatric symptoms. However, in children clinical symptoms may be absent that makes the diagnosis more difficult than in adults.

Methods: Many different literatures on the subject matter from different database sources were reviewed and used .

Results: Clinical diagnosis for Wilson's disease includes screening tests such as determination of serum ceruloplasmin level in addition to the slit lamp examination for kayser Fieischer rings to decide on or decline further testing such as 24 hours urinary copper excretion and liver biopsy tests. Because starting an early treatment is the most effective plan to control the condition, screening is also recommended for people who have relatives with this disorder . Furthermore, lifelong treatment by copper chelators or zinc is mandatory for patients regardless of symptoms.

Conclusion: Wilson's disease results from defective function of a copper transporting protein called P-type ATPase (ATP7B). Factors influencing its function may be genetic, nutritional or environmental. Early diagnosis of Wilson's disease is important not only to reduce or even prevent organ damage but also to ensure that patients may start on proper treatment plan.

Keywords: *Trace elements, Copper, Ceruloplasmin , Wilson's disease, Diagnosis , Prognosis.*

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Introduction

The major biochemical function of copper, an essential trace element, in the body is directly from its role in a number of copper containing metalloenzymes such as cytochrome c oxidase, ceruloplasmin, superoxide dismutase, ascorbate oxidase, monophenol monooxygenase, dopamine-β hydroxylase, ascorbate oxidase, lysyl oxidase and tyrosinase. Copper is the internal component of these metalloenzymes and since in biological systems copper may be present in both +1 and +2 valance states, the metalloenzymes bind with molecular oxygen and involve in oxidation-reduction reactions. The other possible role of copper is the indirect effect that a change in copper status may have on other enzyme systems that do not contain copper. Furthermore, Copper has an important role in iron metabolism. Copper deficiency interferes with iron absorption and anemia results from severe copper deficiency (1,2).

The copper content of foods is variable and depends on copper content of the soil in the area from which foods are obtained as well as on the other factors such as copper loss or contamination throughout processing. Liver, crustaceans, and shellfish contain large amounts of copper. The recommended and adequate dietary copper intake range for adults is 1.5 to 3.0 mg/day (1,2). In addition, the absorption amount of orally ingested copper from the intestine is variable and the intestinal absorption mechanisms as well as the regulation of biliary excretion have major role in the regulation of copper homeostasis. Absorbed copper is rapidly transported as copper-albumin or

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copper–histidine complexes to the liver that is the main storage site for it. An evidence indicates that between 50 and 80% of ingested copper is absorbed (3). Factors that affect copper absorption include gender (women absorbing a greater percentage than men), the amount ingested, chemical forms, other dietary trace elements, sulfate, various amino acids, fibers, and phytates. Furthermore, relatively high amounts of copper are found in heart, brain, and kidneys but muscle and bone copper concentrations are low and constitute about 50% of the total body copper because of their large mass (1,2).

To maintain blood levels, copper is incorporated and released from the liver mainly as ceruloplasmin,. Ceruloplasmin is a blue-colored glycoprotein that belongs to the alpha2 globulin electrophoretic fraction and contains 8 copper atoms per molecule. In addition, it is a multifunctional cuproprotein and accounts for over 95% of the total copper in plasma (1-,3). Furthermore, ceruloplasmin is an acute phase and a transport protein. Incorporation of copper into the ceruloplasmin structure occurs during its synthesis in the hepatocytes. After secretion from the liver, ceruloplasmin migrates to copper requiring tissue where the copper is liberated during catabolism of the ceruloplasmin molecule. In addition to transporting copper, ceruloplasmin has a catalytic function in the oxidation of iron (Fe2+) to Iron (Fe3+), polyamines, catecholamines, and polyphenols (4).

In human blood copper is distributed between the erythrocytes and the plasma. In erythrocytes, 60% of copper occur as copper–zinc metalloenzyme superoxide dismutase and the remaining 40% loosely bind to other proteins and amino acids. Total erythrocyte copper in normal humans is around 0.9-1.0 ug/mL of packed red cells (4,5). In plasma, about 93% of copper is firmly bound to the ceruloplasmin that is involved in iron mobilization as well (1,2). The remaining (7%) is bound to albumin, transcuprein, and copper amino acid complexes. Plasma or serum copper in normal humans is in the 0.8-1.2 ug/mL range and is not significantly influenced by cyclical rhythms or by feedings(4). Hypocupraemia occurs when serum copper level is 0.8 ug/mL or less and since about 93% of serum copper is normally bound to ceruloplasmin, hpocupraemia is usually accompanied by hypoceruloplasmin. Hypercupraemia occurs naturally during pregnancy and is also associated with "acute phase" reaction that occurs in a different number of disease statues. Moreover, it is almost always accompanied by hyperceruloplasmin (5,6).

In spite of different dietary forms of human copper deficiency, the importance of maintaining copper homeostasis is well demonstrated by two hereditary disorders in humans, Menkes disease due to copper deficiency and Wilson's disease due to copper accumulation (5). However, copper accumulation or overload occurs in acquired toxicity as well as other conditions associated with abnormal copper metabolism that cause serum copper to rise (6.) Acquired copper toxicity may result from ingesting or absorbing excess copper. Patients with acquired copper toxicity show systematic toxic complications such as hemolytic anemia, anemia, tachycardia and hepatotoxicity. This condition is treated with prompt gastric lavage or penicillamine, a copper chelator agent. Occasionally, copper toxicity is fatal despite treatment (6). Wilson's disease is a disorder that affects both men and women at equal rate with a frequency of 1 in 30000 to 1 in 100000 live births. The age of onset is vary, however, it usually presents itself between 6 and 40 years of age (7-9). Furthermore, new cases have been reported in people between age 3 to 75 (8).

Wilson's disease is a genetic disorder and results from defective function of a copper transporting protein called P-type ATPase (ATP7B). The gene is located on chromosome 13 and affected people are homozygous for the mutant gene. In heterozygous carriers only a single abnormal copy of the gene is present (9). The genetic defect impairs copper transport and prevents incorporation of copper into ceruloplasmin. Thus results in severely depressed and low serum ceroluplasmin level. Heterozygous carriers show either no decrease at all or just mild decrease in ceroluplasmin level. Furthermore, the defected transport decreases copper secretion into the bile and the blood and causes copper to overload and accumulate in the liver, brain, periphery of the iris, kidneys and reproductive organs. The copper accumulation cause developments of cirrhosis, neurological symptoms; Kayser Fleischer rings; hematuria, proteinuria, aminoaciduria respectively (7-9).

Even though Wilson's disease is present at birth but symptoms and signs in patients usually develop between ages 6 and 40 (8). Symptoms and signs in Wilson's disease may be of any kind but usually involve hepatic and neurological damages and they do not appear until copper builds up in the liver, the brain, or other organs of the body. In addition, patient's laboratory tests show low serum ceruloplasmin level, high 24 hours urinary copper excretion but serum copper level may be high, normal, or low. Moreover, they develop Kayser Fleischer rings (Fig.1) that are green-brown copper deposits ring around the edge of iris and in the rim of the cornea of the eyes. Rarely, kayser Fleischer rings occur in other liver disorders, for example, biliary atresia and primary biliary cirrhosis. Studies

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have indicated that patients with Wilson's disease, who show signs of nervous system damage, usually have Kayser-Fleischer rings. However, the rings are present in only 40% to 66 % of patients with signs of liver damage alone (10,11). In children the diagnosis of the disease is more difficult than in adults because clinical symptoms may be absent and the typical Kayser Fleischer rings are rarely seen before the age of 7 years olds (8).

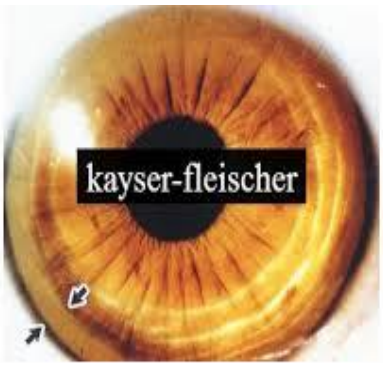

Fig.1- Kayser- Fleischer Ring in Wilson's Disease (Adapted from Google)

Wilson's disease prognosis and diagnosis are usually good unless the disease is advanced before treatment begins. It has been shown that untreated disease is fatal, usually by age 30 (11-13). Recommended screening clinical diagnosis (11,12) for Wilson's disease are determination of serum ceruloplasmin in addition to the slit lamp examination, for kayser Fieischer rings to decide on or decline further testing such as 24 hours urinary copper excretion and liver biopsy results. If any of the results are abnormal, liver biopsy is done to measure hepatic copper concentration. Infants should not be tested until after age one, because ceruloplasmin levels are low during the first few months of life. Children <6 years with normal test results should be retested 5 to 10 years later. Moreover, screening is recommended for people who have a sibling, cousin, or parent with this disorder. Therefore, it is the combination of clinical and family history, physical examination, and certain key laboratory tests that builds the diagnosis for Wilson's disease patients and no single test can confirm the diagnosis with accuracy since there is a possibility that routine tests may give false positive and false negative results.

Starting on an early treatment plan for Wilson's disease patients is the most effective plan. Medications used to control and even in some cases halt the disease are (14-16) copper chelators such as D-penicillamine, and trientine or zinc. Chelating agents remove extra copper from the body by releasing it from organs into the bloodstream. Then, kidneys filter the excess copper and pass it into the urine. The chelating agents usually recommended at the beginning of the treatment and their potential side effect are nervous system symptoms that may become worse during treatment. Zinc also is prescribed for these patients and it is taken by mouth as zinc salts (zinc acetate) that reduces or blocks the digestive tract absorption of copper from foods. Thus prevents re-accumulation of copper in patients organs who cannot tolerate copper chelators or who have neurologic symptoms that do not respond to other drugs. Most people under zinc treatment usually do not show any side effects, however, some may get upset stomach.

Long term treatment (Maintenance) for Wilson's disease patients begins when symptoms improve and laboratory tests indicate that serum and urine copper are at a normal range. Maintenance treatment usually is taking zinc or a lower dose of a chelating agent (14-16). People with this disorder need to take medications for the rest of their lives. Furthermore, follow-up and adherence to an effective treatment plan is necessary to manage symptoms and prevent organ damage. Another plan to reduce and control the amount of copper in people with Wilson's disease is changes made in lifestyle such as eating, diet, and nutrition habits. These patients should reduce their dietary copper intake and avoid taking foods that are high in copper such as shellfish, liver, mushrooms, nuts, and chocolate. In addition, in patients when the maintenance treatment plans are not effective or cirrhosis leads to liver failure or acute liver failure happens suddenly, a liver transplant may be necessary (16-20).

Conclusion

Wilson's disease, an auto-somal recessive copper transport disorder, was first defined by a British neurologist; Samuel Alexander Kinnier Wilson (1878–1937), in 1912 (7). Symptoms and signs in Wilson's disease may be of any kind but usually involve hepatic and neurological damages that do not appear until copper builds up in organs of the body. Early-onset presentations are at birth and late-onset manifestations in adults older than 70 years of age are now well recognized (8, 21). To confirm the clinical diagnosis of Wilson's disease direct genetic testing for ATP7B gene mutations are available. Moreover, early diagnosis of Wilson's disease is important not only to reduce or even prevent organ damage but also to ensure that patients may start on proper treatment plan.

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There is no financial disclosure related to this manuscript.

Conflict of Interest declaration
None.

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