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ASSESSMENT OF WILSON'S DISEASE

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Abstract:

Wilson's disease (WD, or Wilson disease) is a clinical condition caused by mutations in the region of chromosome 13q14 that codes for the protein ATP7B. In Wilson's disease, there is a faulty copper excretion mechanism, which causes copper to accumulate in the liver and spill into the bloodstream, where it begins to accumulate in other organs and tissues such as subcutaneous tissue, thalamus, mucous nuclei, cerebral cortex, kidney and cornea. Treatment is based on removing excess copper by chelating agents such as penicillamine, trientine (25), or tetrathiomolybdate (26,27) or by blocking intestinal absorption of copper with zinc salts (28), with the ultimate goal of normalizing free plasma copper.

Key words : *Copper, Zinc, Penicillamine, Accumulation.*

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INTRODUCTION:

Wilson's disease (WD, or Wilson disease) is a clinical condition caused by mutations in the region of chromosome 13q14 that codes for the protein ATP7B. It was first identified by Kinnear Wilson (1) in 1912 and is inherited as an autosomal recessive condition. Homozygous or, more frequently, compound heterozygous mutations impair the normal excretion of copper into bile by causing a deficient incorporation of copper into apo-ceruloplasmin and the subsequent production of holoceruloplasmin. Impaired copper metabolism and subsequent copper intoxication are side effects of this condition. Despite the abnormally low levels of circulating apoceruloplasmin (ceruloplasmin), which has a shorter half-life than holoceruloplasmin and is produced by the intact gene on chromosome 3 (2), one of the most crucial clinical diagnostic markers, devices for WD. Two main mechanisms—direct oxidative stress, which results in lipid peroxidation of membranes, DNA, and mitochondria, as well as uncontrolled apoptosis—lead to cell death when copper induces changes in the anti-apoptotic protein, X-linked inhibitor of apoptosis, and its loss of inhibitory control over caspase-3 (3). Copper overload, and actually free copper as the main acting element, exerts its toxicity through these two main mechanisms. It is now understood that copper intoxication, as opposed to ceruloplasmin-bound copper, is caused by free copper in the blood, not copper buildup, which is harmful to the organism. Thus, the notion of normalizing free copper concentrations in the bloodstream has replaced the outdated paradigm of removing copper storage as the treatment objective (4). It should be noted that rather than well-designed randomized comparative studies, the majority of the knowledge that has accumulated in the decades since the first description of the disease and the foundations of treatment derive from expert opinions and some anecdotal experiences.

PATHOGENESIS

In Wilson's disease, there is a faulty copper excretion mechanism, which causes copper to accumulate in the liver and spill into the bloodstream, where it begins to accumulate in other organs and tissues such as subcutaneous tissue, thalamus, mucous nuclei, cerebral cortex, kidney and cornea. Copper is a transition metal and excess copper leads to the formation of a toxic hydroxyl group and increased oxidative stress in the cell. This oxidative stress damages cells and leads to clinical manifestations, namely liver failure, behavioral problems, movement disorders and Kayser-Fleischer rings in the cornea (5).

The body needs copper, mainly as a cofactor for several enzymes such as ceruloplasmin, cytochrome c oxidase, dopamine beta-hydroxylase, superoxide dismutase, and tyrosinase. Copper enters the body through the gastrointestinal tract with the help of a transport protein in the cells of the small intestine, transmembrane copper transporter 1 (Ctr1; SLC31A1). This transporter helps transport copper inside cells where copper is partly bound to metallothionein and partly transported by ATOX1 to an organelle known as the trans-Golgi network. In response to increased copper levels, an enzyme called ATP7A releases copper into the portal vein of the liver. Hepatocytes transport the proteins CMT1 and metallothionein, and then ATOX1 binds it inside the cell. Once here, ATP7B binds copper to ceruloplasmin and releases it into the bloodstream, removing excess copper by secretion into bile. Both functions of ATP7B are in Wilson disease. Copper accumulates in the liver and ceruloplasmin is secreted in a copper-free form and rapidly broken down into the bloodstream (6).

When copper levels in the liver exceed levels of proteins normally bound to the liver, oxidation occurs. That will cause damage to the liver through oxidation. The process is known as Fenton's chemistry. This damage leads to chronic active hepatitis, fibrosis, and cirrhosis. The liver releases copper into the bloodstream without being bound to ceruloplasmin. This free copper, precipitates throughout the body, especially in the kidneys, eyes, and brain. In the brain, copper is deposited in the basal ganglia, the nucleus accumbens, and the glomerulus (ie, the lenticular nucleus); these areas are involved in the coordination of movements and neurocognitive processes such as arousal and mood regulation. Damage to these areas produces the neuropsychiatric symptoms seen in Wilson disease (7).

SIGNS AND SYMPTOMS

The clinical forms of the disease tend to cluster, and there are significant geographic differences (8) even though the disease was initially described as primarily neurological (1), its manifestations can be pleomorphic, and the correlation mutation-predominant manifestation has proven difficult to identify (9,10). Accordingly, WD may have predominance in the hepatic, neurological, or mental systems, and illness symptoms can range from asymptomatic to having a fulminant hepatic failure that poses a serious risk of death (11). More than 5% of Costa Rican WD patients suffer from fulminant Wilson disease (FW), which is a form of disease that mostly affects the liver (12). The liver can be affected

in a variety of ways, including asymptomatic disease with elevated transaminases, acute hepatitis, acute-on-chronic liver failure, and cirrhosis. Coomb's negative hemolytic anemia, with brief episodes of low-grade hemolysis and jaundice, is brought on by copper liberation into the bloodstream (13, 14). There are four different types of neurological symptoms, including an akinetic-rigid syndrome resembling Parkinson's disease, pseudosclerosis characterized by tremors, ataxia, and dystonic syndrome, which frequently results in severe contractures (15, 16). A more complex neurological presentation may be predicted by neuropsychiatric symptoms and indications, such as a decline in academic performance, hand-eye coordination issues, and behavioral changes (17). Drooling, spasticity, chorea, athetosis, myoclonus, micrographia, dyslalia, hypomimia, and dysarthria are additional findings (17, 18). The Kayser-Fleischer ring and sunflower cataracts in the lens are two ocular symptoms. In one case, copper deposits in Descemet's membrane; in the latter, it deposits in the anterior and posterior capsule of the lens, sparing epithelial and cortical cells. Sunflower cataracts are less frequently seen in WD, despite Kayser-Fleishcer rings being highly common, particularly in patients with neurological aspects of the disease. Seimerling and Oloff initially identified sunflower cataracts in WD patients with Kayser-Fleischer rings in 1922. They noted a striking resemblance between these lesions and those brought on by a copper-containing foreign substance lodged in the eye. With ongoing therapy, both manifestations might go better (19). Using cutting-edge methods like corneal confocal microscopy and spectral domain optical coherence tomography, small fiber peripheral neuropathy affecting the corneal nerve plexus and neuronal degeneration affecting the retina have also been described. Up to one-third of patients may experience psychiatric abnormalities before hepatic or neurological symptoms (20). These may include personality changes or decreased academic performance, as well as impulsivity, labile mood, inappropriate behavior, depression, paranoia, and schizophrenia, which can also result in suicide in some cases (21, 22).

DIAGNOSIS

A diagnostic score for WD was suggested by the working party at the 8th International Wilson Disease Meeting in Leipzig (2001) (11, 20). The basic diagnostic components are as follows:

1. Twenty-four-hour urinary copper excretion, which is typically greater than 100 mcg/24 h in adults and greater than 40 mcg/24 h in children;
2. Serum ceruloplasmin, which is typically decreased by 50% of the lower normal value, but may be elevated - and thus lead to a false negative result in inflammatory states; and
3. Serum albumin, which is typically decreased by 50% of the lower normal value; Serum free copper is typically higher than 200 mcg/L, hepatic copper is typically higher than 250 mcg/g dry weight, and Kayser-Fleischer rings are typically present on slit-lamp examination.

However, these rings may not be present in up to 50% of patients with hepatic WD, may not be present in most asymptomatic siblings, and may be present in other hepatic diseases like primary biliary cirrhosis. In contrast, neurological WD almost always exhibits the presence of Kayser-Fleischer rings. The change of at least one copper metabolism test with low ceruloplasmin in levels in the presence of clinical manifestations is sufficient to establish the diagnosis of WD, even when the majority of the Leipzig score criteria are frequently met (11). Due to the existence of more than 500 mutations and the time-consuming and expensive nature of genetic testing, the introduction of genetic testing did not produce the anticipated diagnostic yield (23). Additionally, the majority of patients are mixed (compound) heterozygotes, and 17% of confirmed cases of WD have no mutation (24). The relative exchangeable copper, denoted by the ratio of serum exchangeable copper (CuEXC)/total serum copper (CuT) > 18.5%, is another straightforward diagnostic approach. The most straightforward test is still the serum copper/ceruloplasmin ratio (g/dL), which, if it is greater than 2, indicates the presence of WD and, if it is less than 1, indicates either a healthy person or a heterozygote. Although the 24-hour urine test is frequently utilized, it is not practical and may be challenging for patients to collect. Our group has proposed a 6-hour urine copper test following a D-penicillamine challenge, which offers quick diagnostic accuracy with a cutoff level of 118 mcg Cu/6 h as diagnostic for WD. Although this test has not yet received universal validation and has not been standardized for regular diagnosis, it nonetheless offers a useful tool in some situations, particularly for patients who present with an acute on chronic condition and rapid clinical deterioration. A promising new technique that may be used as a confirmatory test to identify WD in newborns is tandem mass spectrometry, which is yet to be widely adopted. This technique allows for a quick measurement of several metabolites in various biological specimens.

TREATMENT

The objectives of treatment, therefore, are to prevent the appearance of symptoms in asymptomatic

subjects, prevent clinical deterioration in affected subjects, and can also be life-saving in cases o acute-on-chronic hepatitis. Treatment principles in WD include the establishment of a certain diagnosis since the treatment is lifelong, as well as the monitoring of compliance, early detection of complications, and integral management including early neuropsychiatric screening/evaluation and physiotherapy, as required

It is recommended that asymptomatic patients be treated with zinc salts or iron chelators at a dose lower than that used for symptomatic disease. Conversely, symptomatic patients should be treated with chelators or a combination of chelators and zinc, whereas patients with acute or chronic liver failure or those with end-stage liver disease unresponsive to Treatment should be urgently considered for liver transplantation. To determine adherence to treatment, its effectiveness, and the likelihood of developing side effects, lifelong monitoring is required (6).

Treatment is based on removing excess copper by chelating agents such as penicillamine, trientine (25), or tetrathiomolybdate (26,27) or by blocking intestinal absorption of copper with zinc salts (28), with the ultimate goal of normalizing free plasma copper. Because WD is a rare disease (20), pharmacological agents for the treatment of this disease are orphan drugs (30)and have not been developed through a process as rigorous as most drugs before there is a piece of information on pharmacokinetics and pharmacodynamics. In contrast, WD's pharmacological agents were born out of a desperate need to treat a fatal disease and even stem from knowledge in other areas, such as chemistry and zoology as in the case of tetra thiomolybdate. An exception is zinc acetate, for which formal clinical and preclinical trials were conducted before release as a therapeutic agent for WD, as required by the US Food and Drug Administration to approve an alternative zinc salt (31). However, continued use of these drugs over many years has accumulated a wealth of evidence and experience regarding the efficacy and side effects of these drugs. The orphan drug currently used to treat WD, which has no active clinical trials, research projects, or networks (32) is penicillamine D (or D-penicillamine) (Cuprimine, Cupripen, Cilamin, Trolovol, Orpha number ORPHA34567), zinc acetate (Galzin, Wilzin, Orpha number ORPHA56897), Trientine dihydrochloride (Metalite, Syprine, Orpha number ORPHA24924), and Ammonium tetrathiomolybdate (Orphan number ORPHA137334), are designated by the European Commission for the secondary agent (33) in 2008.

D- Penicillamine

It should be administered in the dose of 1-1.5 g/day in 2 – 4 divided doses an hour before or 2 hours after meals. The maintenance dose is 0.75 -1 g/day. For elderly patients and pediatrics below 12 years of age, 20 mg/kg/day is recommended (33).

The mechanism of D-Penicillamine in WD involves the inhibition of the induction of endogenous metallothionine and the advancement of the urinary excretion of copper (34).

The side effects include early allergic reactions, thrombocytopenia, lymphadenopathy, leukopenia, myasthenic syndrome, kidney function, and dermatological manifestations (35).

Vit- B6 should be given in addition to D-Penicillamine for the prevention of anemia and inflammation of peripheral nerves that occurs as the result of pyridoxine deficiency. It should be given as a dose of 25-50 mg/day (33).

Trientine

It should be titrated up to 1-2 g/day in 2-4 divided doses. The action is similar to D-Penicillamine. Side effects include pancytopenia, hemorrhagic gastritis, loss of taste, SLE, and neurological deterioration (36, 37).

Zinc

Various types of zinc salts can be used as a 1st line agent for the initial treatment of WD (38). The mechanism involved in the generation of metallothionine in enterocytes blocks copper absorption from the intestinal tract. Homophonic balance is caused by not only blocking the absorption of dietary copper but also blocking the reabsorption of significant amounts of endogenously secreted copper in saliva, gastric juices, and intestinal secretions (39,40). The advantage is a low level of toxicity, except for dyspepsia (41).

DIETARY RECOMMENDATIONS

The negative copper balance remains a relevant goal in patient management. Patients with WD should avoid copper-rich meals such as liver, chocolate, nuts, and sea foods and should drink water low in copper (42). Abstinence from alcohol and avoidance of hepatotoxic agents remain permanent lifelong recommendations. A recent report suggests that a high-calorie diet exacerbates liver and hepatocellular damage in an animal model of WD (43).

CONCLUSION:

clinical presentation of WD is due to the accumulation of copper in tissues and organs is a diagnostic challenge. Early recognition of the symptoms of disease and diagnosis may helpful to reduce the treatment delay and prognosis.

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