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Wilson's Disease, a Brief Review.

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Abstract:

Wilson's disease is an autosomal recessive illness which is caused by abnormal copper metabolism. It would lead to involvement of a few organs including liver and nervous system. Patients are treated using copper chelating agents.

Key Words: Wilson's disease, Review of Literature.

Introduction:

Wilson's disease is an autosomal recessive inherited disorder of hepatic copper metabolism resulting in the accumulation of copper in many organs and tissues. The hallmarks of the disease are the presence of liver disease, neurological symptoms and Kayser-Fleischer corneal rings. The condition is characterized by excessive deposition of copper in the liver, brain, and other tissues.

Pathophysiology:

The estimated total body copper content is 50-100 mg, with an average daily intake of 1-2 mg. Copper is an important component of several metabolic enzymes. Intestinal copper absorption and transport into hepatocytes is intact in Wilson disease. After copper reaches the hepatocyte, it is incorporated into copper-containing enzymes, including ceruloplasmin. Excess copper may be rendered nontoxic by forming complexes with apo-metallothionein to produce copper-metallothionein, or it may be excreted into bile.

In Wilson disease, the processes of incorporation of copper into ceruloplasmin and excretion of excess copper into bile are impaired. The genetic defect, localized to chromosome arm 13q, has been shown to affect the copper-transporting adenosine triphosphatase (ATPase) gene (ATP7B) in the liver. The excess copper acts as a promoter of free radical formation and causes oxidation of lipids and proteins. Initially, the excess copper is stored in the liver and causes damage to the hepatocytes. Eventually, as liver copper levels increase, it is released into the circulation and deposited in other organs such as liver, brain, kidney, and cornea.

Clinical Manifestations:

Wilson's disease may present with a variety of clinical conditions, the most common being liver disease and neuropsychiatric disturbances.

Hepatic Involvement:

Without treatment, patients progressively deteriorate and may die of liver failure. Most patients with Wilson's disease, whatever their clinical presentation or pre-symptomatic status, have some degree of liver disease. The most common age of hepatic manifestation is between 8 and 18 years; however, cirrhosis may be present in children below the age of 5 years, or may be diagnosed in patients presenting with advanced chronic liver disease in their fifties or sixties, without neurological symptoms and without Kayser-Fleischer rings. Liver disease may mimic all forms of common liver conditions, including asymptomatic transaminasaemia, acute or chronic hepatitis, fulminant hepatic failure and cirrhosis. Consider hepatic Wilson disease in the differential diagnosis of any unexplained chronic liver disease, especially in individuals younger than 40 years. Hepatic dysfunction is the presenting feature in more than half of patients.

Chronic Hepatitis and Cirrhosis Due to Wilson's Disease: Wilson's disease may present with a clinical syndrome indistinguishable from chronic hepatitis or cirrhosis of other etiology. Liver biopsy shows chronic hepatitis or advanced cirrhosis, but the diagnosis may be missed if the hepatic copper content is not measured.

Acute Wilsonian Hepatitis and Fulminant Wilson's Disease: Acute Wilsonian hepatitis is indistinguishable from other forms of acute (viral or toxic) liver diseases. Kayser-Fleischer rings and neurological abnormalities may be absent in most patients. The disease may rapidly deteriorate and resemble fulminant hepatic failure. Rapid diagnosis may be very difficult. Serum aminotransferase activity is usually less than 10 times normal and thus is much lower than the values commonly recorded in fulminant hepatitis of other aetiologies. The combination of anaemia, marked jaundice and relatively low aminotransferase activities in young patients should always raise the suspicion of acute Wilson's disease.

Neuropsychiatric Involvement:

The initial neurological symptoms may be very subtle, such as mild tremor and speech and writing problems, and are frequently misdiagnosed as behavioural problems associated with puberty. The hallmark of neurological Wilson's disease is a progressive movement disorder characterized by dysarthria, dysphagia, apraxia and a tremor-rigidity syndrome ('juvenile Parkinsonism'). About one-third of patients present with psychiatric abnormalities, such as emotional lability, impulsiveness, disinhibition, self-injurious behavior, reduced performance in school or at work, depression, labile mood, sexual exhibitionism and frank psychosis. The reported percentage of patients with psychiatric symptoms as the presenting clinical feature is 10-20%. The range of psychiatric abnormalities associated with Wilson disease has been divided into 4 basic categories,as follows: behavioral, affective, schizophreniclike, cognitive.

Ophthalmic Involvement:

Sunflower cataract and Kayser-Fleischer rings are the ophthalmologic signs. Kayser-Fleischer rings are formed by the deposition of copper in the Descemet membrane in the limbus of the cornea. The color may range from greenish gold to brown. Kayser-Fleischer rings are observed in up to 90% of individuals with symptomatic Wilson disease and are almost invariably present in those with neurologic manifestations. Although Kayser-Fleischer rings are a useful diagnostic sign, they are no longer considered pathognomonic of Wilson disease unless accompanied by neurologic manifestations. They may also be observed in patients with carotenemia arcus senilis, chronic active hepatitis, chronic cholestasis, chronic jaundice, cryptogenic cirrhosis, intraocular foreign body with <85% copper, multiple myeloma, primary biliary cirrhosis, topical copper solution treatment of the eye,and trypanosomiasis. The finding of a Kayser-Fleischer ring is a useful indicator of severe copper overload. If the ring is not detected by clinical inspection, the cornea should be examined under a slit lamp by an experi-

enced ophthalmologist. Kayser-Fleischer rings are present in 95% of patients with neurological symptoms, in 50-60% of patients without neurological symptoms and in only 10% of asymptomatic siblings.

Other Manifestations:

Skeletal involvements such as osteoporosis, osteomalacia, chondrocalcinosis, osteoarthritis,and joint hypermobility are common features of Wilson disease, with more than half of patients exhibiting osteopenia on conventional radiologic examination.

Hemolytic anemia is a recognized but rare (10-15%) complication of the disease. Coombs-negative acute intravascular hemolysis most often occurs as a consequence of oxidative damage to the erythrocytes by the higher copper concentration.

The frequency of renal manifestations is variable. Urolithiasis, found in up to 16% of patients with Wilson disease, may be the result of hypercalciuria or poor acidification. Hematuria and nephrocalcinosis are reported, and proteinuria and peptiduria can occur both before treatment as part of the disease process and after therapy as adverse effects of D-penicillamine.

Some female patients have repeated spontaneous abortions, and most become amenorrhic prior to diagnosis.

Diagnosis:

The presence of Kayser-Fleischer rings and ceruloplasmin levels of less than 20 mg/dL in a patient with neurologic signs or symptoms suggest the diagnosis of Wilson disease. If a patient is asymptomatic, exhibits isolated liver disease, and lacks corneal rings, the coexistence of a hepatic copper concentration of more than 250 mg/g of dry weight and a low serum ceruloplasmin level is sufficient to establish a diagnosis.

Laboratory Studies:

- *Serum ceruloplasmin:* Approximately 90% of all patients with Wilson disease have ceruloplasmin levels of less than 20 mg/dL (reference range, 20-40 mg/dL). Ceruloplasmin is an acute phase reactant and may be increased in response to hepatic inflammation, pregnancy, estrogen use, or infection. Falsely low ceruloplasmin levels may be observed in any protein deficiency state, including nephrotic syndrome, malabsorption, protein-losing enteropathy, and malnutrition.

- *Urinary copper excretion:* The urinary copper excretion rate is greater than 100 mg/d (reference range, <40 mg/d) in most patients with symptomatic Wilson disease. The rate may also be elevated in other cholestatic liver diseases. Both the sensitivity and the specificity of this test are suboptimal for use as a screening test; however, it may be useful to confirm the diagnosis and to evaluate the response to chelation therapy.

- *Hepatic copper concentration:* This test is regarded as the gold standard for diagnosis of Wilson disease. A liver biopsy with sufficient tissue reveals levels of more than 250 mcg/g of dry weight even in asymptomatic patients.

Imaging Studies:

- *CT of the head:* The cranial lesions observed on CT scan are typically bilateral

and are classified into 2 general categories, as follows: (1) well-defined, slitlike, low-attenuation foci involving the basal ganglia, particularly the putamen, and (2) larger regions of low attenuation in the basal ganglia, thalamus, or dentate nucleus. Widening of the frontal horns of the lateral ventricles and diffuse cerebral and cerebellar atrophy, which correlate histologically with widespread neuronal loss, have also been described.

- *MRI of the brain:* MRI of the brain appears to be more sensitive than CT scanning in detecting early lesions of Wilson disease. MRI studies have identified focal abnormalities in the white matter, pons, and deep cerebellar nuclei; high signal in the basal ganglia, thalami, dentate nuclei, and cerebellar white matter on T2-weighted images; cortical atrophy; and ventricular enlargement.

Treatment

Medications: Treatment of Wilson's disease is life-long pharmacological therapy, but the choice of drug mostly depends on the opinion of the treating physician and is not based on comparative data. According to the recent AASLD practice guidelines(American Association for the Study of Liver Diseases) on Wilson's disease, initial treatment for symptomatic patients should include a chelating agent (penicillamine or trientine). Treatment of pre-symptomatic patients and maintenance therapy of successfully treated symptomatic patients can be accomplished with the chelating agents penicillamine or trientine, or with zinc. Liver transplantation, which corrects the underlying hepatic defect in Wilson's disease, is reserved for severe or resistant cases.

Penicillamine is still the 'gold standard' for therapy. The copper is mobilized by penicillamine and excreted in the urine. Most symptomatic patients, whether hepatic, neurological or psychiatric, respond within months of starting treatment. Amongst neurological patients, a significant number may experience an initial worsening of symptoms before they get better. To avoid pyridoxine deficiency it should be used during penicillamine therapy.

Trientine is a copper chelator, acting primarily by enhancing urinary copper excretion. Trientine is licensed for the treatment of Wilson's disease and is as effective as penicillamine with far fewer side-effects.

The experience with ammonium tetrathiomolybdat (also a chelating agent) is very limited, but it appears to be useful for the initial treatment of patients with neurological symptoms.

Zinc interferes with the intestinal absorption of copper. Both zinc and copper share the same carrier in enterocytes and treatment with zinc blocks this carrier for copper transport. Also zinc induces metallothionein in enterocytes, which acts as an intracellular ligand binding metals, which are then excreted in the faeces with desquamated epithelial cells. Furthermore, zinc also induces metallothionein in the liver, protecting hepatocytes against copper toxicity.

Liver Transplantation: Liver transplantation is the treatment of choice in patients with fulminant Wilson's disease and in those with decompensated cirrhosis. In

addition to improving survival, liver transplantation also corrects the biochemical defect underlying Wilson's disease. However, the role of this procedure in the management of patients with neurological Wilson's disease, in the absence of hepatic insufficiency, is still uncertain.

Diet: Patients should generally avoid eating foods with a high copper content, such as liver, chocolate, nuts, mushrooms, broccoli, legumes, and shellfish (especially lobster). Drinking water from atypical sources (e.g., well water) should be analyzed for copper content and replaced with purified water if the copper content is greater than 0.2 parts per million. Also they must avoid most alcohol consumption and potential hepatotoxic drug therapy.

Monitoring Therapy: A physical examination, 24-hour urinary copper excretion assay, CBC count, urinalysis, serum free copper measurement, and renal and liver function tests on a weekly basis for the first 4-6 weeks following initiation of chelation therapy should be performed. The best way to monitor efficacy is to measure serum nonceruloplasmin-bound copper. An adjunctive way to monitor efficacy is to measure urinary copper excretion.

Bimonthly evaluations are recommended through the first year, followed by yearly examinations thereafter. Lifelong, uninterrupted chelation therapy is necessary in all patients with Wilson disease. Frequent follow-up with patients is necessary, secondary to patient decompensation due to noncompliance. This is one of the major causes of fulminant liver failure.

Prognosis:

Improvement usually begins 5-6 months after the start of therapy and continues for about 24 months. The deficits present at 24 months are likely to be permanent. Psychiatric symptoms usually resolve, and many neurologic symptoms improve or resolve as well. However, patients usually have cirrhosis even if liver function is normal. Patients who present with fulminant liver failure have a mortality rate as high as 70%.

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