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Wilson's disease

Review Article

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Abstract: Wilson's disease is an autosomal-recessive disorder caused by mutation in the ATP7B gene. Absent or reduced function of ATP7B protein leads to decreased hepatocellular excretion of copper into bile. Subsequent copper accumulation, first in the liver but ultimately in the brain and other tissues, produces different clinical manifestations such as hepatic, neurological, hematological, ophthalmological, and psychiatric problems. Diagnosis is based on clinical suspicion, parameters of copper metabolism, ophthalmic examination (Kayser-Fleischer rings) and a liver biopsy. Genetic studies are of limited use. Early diagnosis and initiation of therapy with chelators and therapeutic plasma exchange therapy are essential for prognosis. Liver transplantation corrects the underlying pathophysiology and can be lifesaving in fulminant hepatic failure. Screening of siblings and 1st degree relatives of the patients is also important.

Keywords: *Copper metabolism • Kayser-Fleischer rings • Wilson's disease • Chelating agents • Liver transplantation*

1. Introduction

Wilson's disease(WD) was first described in 1912 by Kinnear Wilson [1,2]. This is an automosal recessive disorder of hepatic copper sequence with a prevalance of 1/30000, arising from a mutation in the ATP7B gene located on chromosome 13 [2-5]. This gene was identified in 1993. It occurs primarily in hepatocytes and functions in the transmembrane transport of copper [4,6,7]. Deficient or low function of ATP7B protein leads to decrease in hepatocellular release of copper in the bile. This results in hepatic copper deposition and hepatic damage. When the hepatocellular storage capacity is exceeded, free copper (failure to incorporate copper into ceruloplasmin as a result of ATP7B mutation) is released slowly into the blood and is deposited in various organs such as the brain, eyes (corneal copper deposits- Kayser-Fleisher rings (KFR)) and kidneys [4,8,9]. Sometimes fulminant hepatic failure, extensive intravascular hemolysis (Coombs' negative) and renal dysfunction could be seen due to massive release of copper into circulation [4,10].

2. Clinical Features

The usual age range for clinical presentation is 5-45 years. Young people tend to have hepatic disease. However, it could be found even in the eighth decade of life [4]. It may be presented as a hepatic, neurological or psychiatric disorder (Table 1) [2,4].

Various hepatic disorders arise from WD. Persistant asymptomatic hepatomegaly or high serum aminotransferases [1,4]. Some patients have acute hepatitis with autoimmune features (high serum IgG, positive non-specific autoantibodies like anti smooth muscle antibody). It may sometimes mimic non-alcoholic steatohepatitis (NASH) [1,4]. It may occur as fulminant hepatic disorder or cirrhosis [1,4,5]. Extensive hepatocelullar apoptosis liberates free copper into the circulation. These free toxins may destroy erythrocyte membranes and cause renal tubulopathy. This produces characteristic features; severe Coombs'-negative hemolytic anemia, early and rapidly progressive renal dysfunction, quite low (200-1500U/L) serum aminotransfeases and low-normal or strikingly subnormal serum alkaline phosphatase. Serum copper is normal

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Table 1. Clinical features of Wilson's disease.

Hepatic	Hepatomegaly
	Splenomegaly
	Elevated serum aminotranferases(AST and ALT)
	Hepatitis
	Fatty liver
	Fulminant hepatic failure
	Cirrhosis
Neurological	Tremor
	Dystony
	Seizure
psychiatric	Depression
	Anxiety
	Psychosis
Others	Renal abnormalities
	Skeletal abnormalities
	Coombs'-negative hemolytic anemia
	Cardiomyopathy, dysrhythmias, Hypoparathyroidism
	Infertility

or high, but urinary copper is extremely elevated. It may be confused with acute viral hepatitis or drug-induced hepatitis [4]. Correct diagnosis and urgent treatment is important and life saving [1,4,5].

Neurological signs of Wilson's disease typically appears later than hepatic disease (mostly in the third decade of life, but it may also appear during childhood). It usually presents with movement disorders (e.g. tremor) or with rigid dystonia resembling a parkinsonian disorder. Epileptic seizures are uncommon [1,4].

Psychiatric symptoms include depression, anxiety and even frank psychosis [4]. Other infrequent presentation types are renal abnormalities including aminoaciduira and nephrolithiasis, skeletal abnormalities like premature osteoporosis and arthritis, cardiomyopathy, pancreatitis, hypoparathyroidism, infertility and abortion [1,4].

3. Investigations

3.1. Biochemical liver tests

Serum aminotransferases are generally abnormal in WD except for the early stages. The degree of elevation of aminotransferase activity may be mild and does not reflect the severity of liver disease [1,4].

3.2. Ceruloplasmin

This copper-carrying protein is mainly synthetized in the liver and is an acute phase reactant. Its level may be measured by oxidase activity related to this substance enzymatically or antibody-mediated tests like radioimmunoanalysis [1,4]. A level of ceruloplasmin less than 200 mg/L (even though different laboratory ranges are present) related with Keyser-Fleisher ring is considered as compatible with Wilson disease [1,4,11,12].

Serum uric acid may be decreased at presentation with symptomatic hepatic or neurological disease because of associated renal tubular dysfunction (fanconi syndrome) [4,13].

3.3. Serum copper

Although a disease of copper overload, the total serum copper (including copper bound to ceruloplasmin) in WD is usually in proportion to the decreased ceruloplasmin in the circulation. In the setting of acute fulminant hepatic failure due to WD, levels of serum copper may be markedly elevated due to the sudden release of the metal from tissue stores [4,11]. Its follow-up is indicated during de-coppering treatment [11].

Urinary copper excretion: Basal 24-hour copper excretion reflects the amount of non-ceruloplasmin bound (free) copper in the blood and is related to total body copper load indirectly. A level higher than 0.6 µmol/24 hour (100µg/24 hour) is diagnostic in symptomatic patients [1,4]. The measurement of urinary copper excretion by giving D-penicillamine is a provocative test; a level higher than 25 µmol/24 hour is considered diagnostic for WD [12,14,15].

3.4. Kayser-Fleischer ring

It should be investigated by slit lamp examination [4]. It is present in 60% of adults with WD and is seen less frequently in children. It is almost always seen in neurological cases of Wilson's disease [1,4,5,11,12]. In a study from Turkey, KFR was positive in 81,8% of the symptomatic patients, while only in 33.3% of the asymptomatic patients [15].

Liver biopsy: It is generally diagnostic in WD [4]. Histological findings may include steatosis (both microvascular and macrovascular), glycogen deposition and focal hepatocellular necrosis [1,16,17]. Cirrhosis is seen in the second decade of life and is generally macronodular [4]. Hepatocyte apoptosis is a marked feature during acute fulminan injury [18]. Liver Parenchymal copper concentration in theses conditions is more than 250µg/g dry weight [1,12].

Since most patients are compound heterozygotes, genetic diagnosis of this disease is limited. Prevalance of well defined mutations are low [1,3,4]. A genetic strategy is best for identifying affected siblings and atypically young or old patients. Neuropsycologic investigation and magnetic resonance imaging (MRI) is recommended for neurologic disorders [1,4].

Table 2. Screening for Wilson's disease.

-Detailed history (hepatic,neurological,psychiatric symptoms)
-Physical examination (jaundice,organomegaly,etc.)
-Ophtalmological examination (Kayser-Fleischer rings)
-Laboratory studies (serum aminotransferases,serum ceruloplasmin, 24-h urinary copper excretion, and genetic mutation analysis)

Screening for all siblings and first-degree relatives of affected patients is needed. Molecular genetic screening in selected populations with frequent common mutation is also used. (Table 2)[1,4].

3.5. Diagnosis

Presence of the above clinical presentations should alert the physician about WD. Presence of two of the following symptoms:neurological symptoms, KFR, and low serum ceruloplasmin levels will establish the diagnosis [19,20]. The diagnosis in patients with hepatic presentation is more difficult [20].

Ferenci et al. [21], proposed a scoring system , depending on clinical, biochemical, and histological features to help the diagnosis. The dis-advantage of this proposed scoring system is that it was not been assessed prospectively [19,20].

4. Management

Patients with WD should avoid major sources of dietary cooper and abstain from alcohol. Treatment is life-long [1,4]. De-coppering treatment should not be interrupted even during pregnancy [4]. In long standing WD, screening for abdominal malignancies by ultrasonographic examination is indicated [22].

D-penicillamine has been proven to be effective in WD [5,23-25]. Worsening of neurological symptoms is reported in 10-50% of the patients treated with penicillamine during the early phase of treatment. For patients with symptomatic hepatic disease, the time for evidence of recovery of synthetic function and improvement of symptoms is typically during the first 2 to 6 months of treatment [4]. Approximately one-third of patients treated with pencillamine have to change to a different chelation because of major adverse effects including skin disorders, protein losing nephropathy, lupus-like systemic inflammatory conditions and bone marrow suppression It is generally given orally 1-2 g/day PO t.i.d. Careful monitoring for the above mentioned adverse effects is needed weekly for the 1st 6 wk then monthly for the 1st year [1]. Adequacy of treatment is determined by measuring 24-hour urinary copper excretion [1,4,12].

Trientine, which is chemically different is a good alternative for penicillamine. It causes less side effects. Typical doses are 750-1500 mg /day divided in 2-3 (maintenance dose is 750-1,000 mg) [1,4,12].

Zinc administered in pharmacological doses (50mg of elemental zinc three times daily) reduces total body copper stores by inducing enterocyte metallothionein, a cysteine-rich protein that is an endogenous chelator of metals. Metallotionein has a greater affinity for copper compared to zinc. The bounded copper is lost into the fecal contents as enterocytes are shed in normal turnover [1,12,26].

Vitamin E may be a useful adjunctive therapy [4].

Liver transplantation(orthotopic or living-related donor transplantation) is used for patients with fulminan hepatic injury or liver disease not respond to supportive treatments. Liver transplantation could improve neurological symptoms also [9], but its use in this group of patients still needs further data [1,4,12].

In WD with fulminant hepatic injury and/or hemolytic crisis, some urgent therapeutic models as therapeutic plasma exchange and hemodiafiltration are needed prior to liver transplantation [24,25]. Delay in treatment or in-effective treatment could end with death [10]. Dabrowska et al. reported that WD patients who survived exhibited higher levels of alkaline phosphatase activity, slightly higher levels of clotting factors and prothrombin time activity, and a positive KFR when compared with patients who died or underwent liver transplantation [26]. Sometimes even one session of therapeutic plasma exchange could stabilize the general condition of WD patients [5].

So early diagnosis by high suspicion and appropriate mangement (including screening of siblings and first degree relatives of the patients) could be life-saving in this group of patients.

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