Wilson’s disease

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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-Fleisher 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-Fleisher 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 prevalence 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. Persistent asymptomatic hepatomegaly or high serum aminotransferases [1,4]. Some patients have acute hepatitits 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 hepatocellular 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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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 aminoaciduria 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 (100 µg/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 fulminant injury [18]. Liver Parenchymal copper concentration in theses conditions is more than 250 µg/g dry weight [1,12].

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