Review Article

Hepatic presentation of Wilson's Disease in children

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Introduction

Wilson's Disease is a rare autosomal recessive genetic disorder of copper metabolism which is characterized by hepatic and neurological disease. The disease affects between one in 30000 and one in 100000 individuals and was first described as a syndrome by Kinnier Wilson in 1912. In affected individuals, there is accumulation of excess copper in the liver caused by reduced excretion of copper in bile. The great danger is that Wilson's disease is progressive, can remain undiagnosed and is to be fatal if untreated [1]. Wilson's disease presents mainly as hepatic disease in younger patients in their 1st and second decades of life [2].

Pathogenesis and Pathology

Wilson's Disease is best appreciated with an understanding of copper metabolism. The body's basic daily copper requirement is about 1-2 mg, and this is met by dietary copper intake. Copper is absorbed by the intestinal cells and stored with metallothionein in a non-toxic form. The copper is later delivered into the circulation by a copper transporter protein, copper-transporting ATPase 1 (ATP7A), which is located on the membrane of enterocytes [3]. It is then transported to the liver tagged with albumin, from where it is accepted by hepatocytes. Within these cells, the ATOX1 chaperone protein [4] directs copper to its binding targets (Figure 1). Some of the copper becomes bound to metallothionein for storage, and the remainder is excreted into ATP7B-regulated biliary canaliculi. ATP7B also mediates the transfer of copper to apoceruloplasmin to form a six-copper binding protein known as ceruloplasmin, which is an α_2-globulin [5]. Ceruloplasmin is released into the blood, carries 90% of the copper present in the plasma, and acts as a source of copper for peripheral organs such as the brain and kidney.

Schematic representation of copper metabolism within a liver cell. Abbreviation: ATP7B = Wilson's disease gene.

ATP7A and ATP7B are homologous copper-transporting proteins [6]. Mutation of the *ATP7A* gene results in the storage of copper in enterocytes, preventing entry of copper into the circulation and thereby causing a complete copper deficiency. This condition, known as Menkes disease, is an X-linked disorder characterized by severe impairment of neurological and connective tissue function. Discovery of the mutated gene in Menkes disease helped to uncover the activity of the Wilson's disease-associated gene within the liver [7]. Mutations in *ATP7B* lead to a reduction in the conversion of apoceruloplasmin into ceruloplasmin, which, as a result, is usually present at low levels in Wilson's Disease patients. In addition, a failure to excrete copper into the biliary canaliculi leads to its toxic build-up within the hepatocytes [8,9]. Excess copper damages mitochondria, which produces oxidative damage to cells and allows spillage of copper into the blood, thereby overloading other organs such as the brain, kidney and red blood cells, initiating toxic damage [8]. In Wilson's Disease, apoptotic cell death is also accelerated by the inhibition of IAPs (inhibitor of apoptosis proteins) that is caused by toxic deposits of intracellular copper [10].

Clinical Features [11,12]

The common age of hepatic menifestation is between 8 & 18 but cirrhosis may already present in children below age of 5. The spectrum of the liver disease can be highly viable ranging from asymptomatic with only biochemical abnormalities to acute liver failure. Children may be entirely asymptomatic. With hepatic enlargement or abnormal serum amino transferases found only incidentally. Some patients have a brief clinical illness resembling an

acute viral hepatitis and other may present with features indistinguishable from autoimmune hepatitis. Some present with only biochemical abnormalities or histologic finding of steatosis on liver biopsy. Many patients present with signs of chronic liver disease and evidence of cirrhosis either compensated or decompensated. Patients may present with isolated splenomegaly due to clinically inapparent cirrhosis with portal hypertension.

Diagnosis

Diagnosis is far more complex in patients with liver disease. None of the commonly used parameters alone allows a certain diagnosis of Wilson's Disease. Usually a combination of various laboratory parameters is necessary to firmly establish the diagnosis [11].

Biochemical Liver Test

Serum amino transferases activities are generally abnormal in Wilson's disease except at a very early age. In many individuals, the degree of elevation of amino transferases activity may be mild and does not reflect the severity of liver disease [12].

Ceruloplasmin

Ceruloplasmin concentration of less than 0.2g/L (normal laboratory range 0.2 to 0.5 g/L) has been regarded to be consistent with Wilson's disease and diagnostic in association with KF ring. Upto 95% of homozygotes and 20% of asymptomatic heterozygotes have serum ceruloplasmin values less than 0.2g/L.5% of homozygotes and in some studies up to 50% of affected individuals with severe decompensated liver disease have normal ceruloplasmin concentration[13]. It may be low in severely malnourished subject, in coeliac disease and in heterozygotes carriers of Wilson's disease gene[14]. Low concentrations also occur in Menke's disease and aceruloplasminaemia - both of which are very rare disorder[15,16].

Serum Copper

The serum non ceruloplasmin bound copper concentration has been proposed as a diagnostic test for Wilson's disease. It is elevated above 25 ug/dl in most untreated patients[11]. The serum non ceruloplasmin bound copper concentration may be elevated in acute liver failure of any etiology. Not only in Wilson's disease [17,18], it may be elevated in chronic cholestasis[19], and in case of copper intoxication from ingestion or poising[20].

Urinary Copper Excretion

The amount of copper excreted in the urine in a 24 hr period may be useful for diagnosing Wilson's disease and for monitoring of treatment. The conventional level taking as diagnosing of Wilson's disease is > 100 ug/24 hrs in symptomatic patients[20]. But finding > 40 ug/day indicates Wilson's disease and requires further investigation[21,22].

Urinary copper excretion with D penicillamine administration may be useful diagnostic adjunctive test. This test has only been standardized in a pediatric population. In which 500mg of D penicillamine was administered orally at the beginning and 12 hrs later during the 24 hr urine collection, irrespective of body weight values. For the penicillamine challenge test of > 1600ug copper/24 hrs are found in patients with Wilson's disease.

Recent reevaluation of penicillamine challenge test in children found it valuable for the diagnosis of Wilson's disease in patients with active liver disease (sensitively 92%) but poor for excluding the diagnosis in asymptomatic siblings (sensitivity only 46%)[23].

Hepatic Copper

Hepatic copper content ≥ 250 ug/gm dry weight remains the best biochemical evidence for Wilson's disease. Normal concentration rarely exceed 50ug/g dry weight of liver. Patients with chronic cholestatic disease, neonate and young children and subjects with exogenous copper overload have increased hepatic copper concentration > 250 ug/gm. Therefore the results of hepatic copper concentration estimation should be taken in the contest of the histological, clinical and biochemical data[24].

Family Screening[12]

First degree relatives of any patient newly diagnosed with Wilson's disease must be screened for Wilson's disease. Assessment should include: brief history relating to Jaundice, liver disease & subtle features of neurological involvement: physical examination; S/copper, ceruloplasmin, liver function test, slit lamp examination of eyes for K.F rings and basal 24 hrs. urinary copper. Individuals without kayser Fleischer rings who have subnormal ceruloplasmin and abnormal liver test undergo liver biopsy to confirm the diagnosis.

If available molecular testing for ATP 7B mutates or haplocyte studies should be obtained and may be used as

primary screening. Treatment should be initiated for all individuals greater than 3 yrs old identified as patients by family screening.

New Born Screening[12]

Measurement of ceruloplasmin in Guthrie dried blood spots or urine samples from new born may promote detection of individuals affected with Wilson's disease.

Treatment

Today the mainstay of treatment for Wilson's disease remains lifelong pharmacologic therapy. Liver transplantation, which corrects the underlying hepatic defect in Wilson's disease is reserved for severe or resistant cases. In general the approach to treatment is dependant on wheither there is clinically evident disease or laboratory or histological evidence of aggressive inflammatory injury whether neurologic or hepatic or whether the patents is identified period to the onset of clinical symptoms. The recommended initial treatment of symptomatic patients or those with acute disease is with chelating agents[12].

Once disease symptoms or biochemical abnormalities have stabilized typically is 2-6 months after initiation of therapy maintenance dosages of chelators or zinc therapy can be used for treatment[25].

Available Treatments

Penicillamine: - Penicillamine was introduced as the first oral agent for treating Wilson's disease in 1956. Like dimercaptopropanol (or BAL) it has a free sulfhydryl group, which functions as the copper chelating moiety. The major affect of D penicillamine in Wilson's disease is to promote the urinary excretion of copper. D penicillamine may also act by inducing metallothionein in individuals in Wilson's disease. It has some immunosuppressant actions.

D- Penicillamine is best administered 1 hr prior or 2 hrs after meals, because food interfere its absorption.

In children the dose generally used 20mg/kg/day in 2 or 3 divided doses. D-penicillamine use is associated with numerous side effects. Severe side effects requiring the drug to be discontinued occurs in approximately 30% of patients[26].

Early sensitivity reactions marked by fever & cutaneous eruptions, lymphadenopathy, nutropenia or thrombocytopenia and proteinuria may occur during the 1st 1-3 wks. Late reactions include nephrotoxicity; usually heralded by proteinuria other late reactions include lupus like syndrome marked hematuria, proteinuria and positive ANA, Goodpasture Syndrome. Significant marrow toxicity includes severe thrombocytopenia or total aplasia. Dermatological toxicities reported include progeric changes in the skin and elastoses perforans serpingosa[27]. Very late side effects include nephrotoxicity, myasthenia gravis, polymyositis, depression, serious retinitis, hepatotoxicity[28] and siderosis[29] had been reported.

Trientine

Trientine is becoming recognized as an efficient initial treatment[30,31]. There are few reported side effects. Pancytopenia occurs rarely and hypersensitivity reactions & renal effects have not been reported. Sideroblastic anaemia and hepatic siderosis can occur if copper deficiency develops because of excessive treatment. The frequency of neurological deterioration is through to be less with trientine than with penicillamine but could still arise[32].

In children the dose is 20mg /kg/day in two or 3 divided doses, trientine should be administered 1 hour before or 2 hrs after meal[11].

Zinc[11]

Zinc interferes with the uptake of copper from the GI tract. Zinc induces entrocyte metallothionein, a cystine rich protein that is endogenous chelators of metals. Metallothionein has greater affinity for copper than for zinc and thus preferentially binds copper present in entrocyte and inhibits its early into the portal circulation. Once bound the copper is not absorbed but is lost into the faecal content as enterocytes are shed in normal turnover. Zinc may also act by inducing levels of hepatocellular metallothionein.

Zinc has very few side effects. Gastric irritation is the main problem. It may have immunosuppressant effects and reduce leucocytes chemotaxis. Elevation of serum lipase and amylase may occur without clinical evidence of pancreatitis.

Zinc is currently reserved for maintenance treatment; it has been used as first line therapy most commonly for asymptomatic or presymptomatic patients. It appears to be equally effective as penicillamine but much better tolerated[33].

Dosing is for lager children; 150 mg/day is administered in 3 divided doses. For smaller children < 50 kg in body weight the dose is 75mg/day in three divided doses[34].

Diet[11]

Foods with very high concentrates of copper (shellfish, nuts, chocolate mushrooms and organ meats) generally should be avoided at least in the first year of treatment.

Ammonium Tetrathiomolybdate

TM is a very strong decoppering agent which works by two mechanisms interfering with intestinal uptake of copper and binding copper from plasma. Potential adverse effects include bone marrow depression and hepatotoxicity[35].

Liver Transplantation

Liver transplantation is indicated for patients with acute fulminant hepatic failure from Wilson's disease. Liver transplant is also indicated for patients Wilson's disease in which medical therapy is ineffective as defined by a failure to stabilize and prevent progressive hepatic insufficiency[36].

Future Therapy

Genetic therapy and haplocyte transplantation represent future curative treatment for Wilson's disease along with correctly available liver transplantation[37]. However both cell and liver transplants need immunosuppresion to maintain grafted cells.

Future use of stem cells, ex. vivo modification of cells by gene therapy or better means of inducing immune tolerance might obviate the difficulty of immunosuppression and provide a cure of this disease by cell transplantation.

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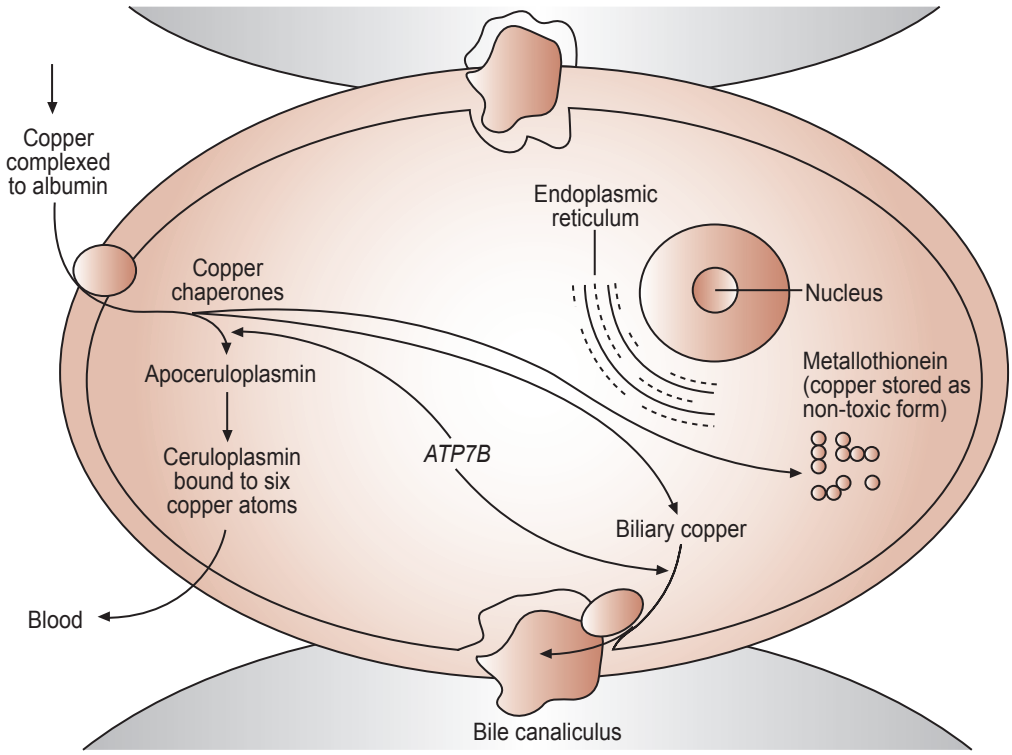

Figure 1. Schematic representation of copper metabolism within a liver cell. Abbreviation: ATP7B = Wilson's disease gene.

Serum ceruloplasmin (CPN); 24-h urinary Cu; slit lamp examination

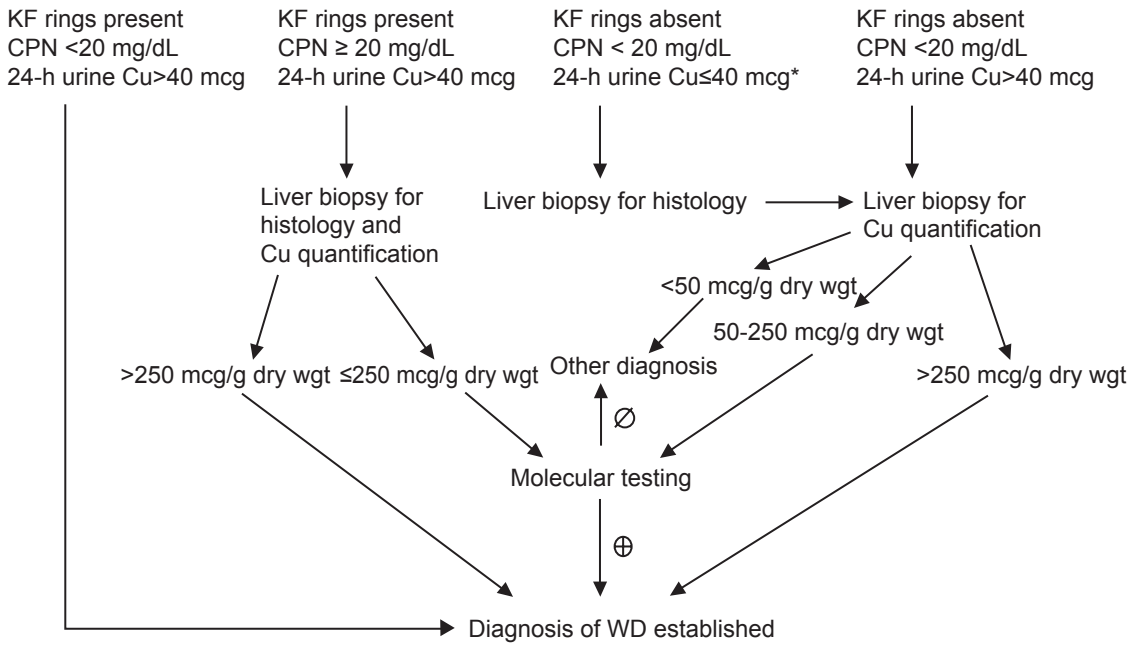

Fig. 1. Approach to diagnosis of Wilson disease (WD) in a patient with unexplained liver disease. Molecular testing means confirming homozygosity for one mutation or defining two mutations constituting compound heterozygosity. *Assure adequacy of urine collection. Conversion to SL units: CPN <20 mg/dL or 0.2 g/L; 24-hour urinary Cu >40 µg/day or 0.6 µmol/day. Note that normal ranges for CPN may vary slightly between