Review Article

Wilson's Disease : A Review

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ABSTRACT

Wilson's disease is an autosomal recessive inherited disorder of copper metabolism. It can occur sporadically as well. The defect lies in the mutation on chromosome 13q14, which encodes for protein product ATP7B resulting into defective incorporation of copper into ceruloplasmin and defective copper excretion leading to accumulation of copper in various tissues. The excess copper is predominantly deposited in liver (leading to chronic liver disease, cirrhosis), cornea (leading to KF ring), basal ganglia (leading to neurological manifestations.). Untreated, the disease is slowly progressive and fatal. However therapy with available agents is quite effective and alters prognosis favorably. A high index of suspicion is needed for diagnosis of this treatable disease.

Introduction :

Kinnear Wilson first described Wilson's disease way back in 1912. He first described the neurological form of disease, which ran in family. He speculated that it was caused by liver disease[1]. The generic location of the defective protein product was discovered in 1993 by three separate groups and was an important landmark in history of Wilson's disease[2,3,4]. Till today more than 500 mutations have been identified. The genetic mutations have geographical patterns but occur randomly also. Most patients are compound heterozygotes i.e. they carry two different mutations.

Highest incidence of the disease is found in Costa Rica : 4.9 / 100000 inhabitants 5 followed by Japan : 2.5 / 100000, Austria : 3/100000 and Germany : 2.5 / 100000. The degree of consanguious marriages in the society influences the disease prevalence considering autosomal recessive nature of the disease. The exact prevalence in India is not known.

Pathogenesis of Wilson's disease

Wilson's disease is a disease of copper toxicity. The absorbed copper from enterocytes enters portal circulation after albumin binding. It is extracted avidly by hepatocytes. In the hepatocytes, copper is either used for cellular metabolic needs or incorporated into apoceruloplasmin to form ceruloplasmin or is excreted into the bile. The excretion of copper into bile is through Golgi apparatus and is dependent on ATP7B. The incorporation of copper into apoceruloplasmin is also governed by ATP7B. Since in Wilson's disease ATP7B is mutated, the protein encoded by it is deficient. This leads to poor excretion of copper into bile resulting in accumulation into hepatocytes. Secondlythe synthesis of ceruloplasmin from apoceruloplasmin is decreased leading to hypoceruloplasminemia. Thus low ceruloplasmin is the effect and not cause of the disease.

The excess copper in hepatocytes causes hepatocyte damage by oxidative stress, lipid peroxidation of membranes, DNA and mitochondria. Also there is increased apoptosis[6,7]. The damage to hepatocytes leads to release of free copper, which enters blood leading to increase in serum free copper. This excess copper gets preferentially deposited in some organs like cornea, basal ganglia and other structures causing the damage.

Clinical features : Wilson's disease can present in various forms. These are not mutually exclusive but usually individual patients have predominance for neurological or hepatic presentation.

Modes of presentation -

1. Neurological form :
   a. Motor abnormalities
   b. Behavioral & psychiatric abnormalities.

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Received on 6th February 2018 Accepted on 26th May 2018

2. Hepatic form :
   a. Asymptomatic, detected on routine liver function tests or family screening.
   b. Chronic hepatitis or Cirrhosis of liver and its complications.
   c. Fulminant hepatic failure.
3. Hemolytic Anemia.
4. Uncommon presentation like myopathy, renal abnormalities, infertility etc.

Hepatic presentation can range from asymptomatic liverabnormalities to frank cirrhosis and its complications. Wilson's disease accounts for nearly 6% patients of acute liver failure (ALF)[8,9]. It is four times more common in female than male patients[10]. Usually these patients have severe Coomb's negative hemolytic anemia, disproportionately low alkaline phosphatase, and rapid progressive course. Combination of Alkaline Phosphatase / Total bilirubin ratio < 4 and AST / ALTratio > 2.2 has sensitivity and specificity of 100 % in diagnosing Wilson's disease as cause of FHF[11]. Patients who have stopped their medications are at more risk of developing ALF[8].

Neurological presentation can be -

1. Akinetic - rigid syndrome like Parkinson's disease. Juvenile Parkinsonism should raise suspicion of Wilson's disease.
2. Pseudo sclerosis dominated by tremors, which are generally coarse proximal, wing beating type.
3. Ataxia
4. Dystonic syndrome. Dystonia can be focal, segmental or very severe.

Patients can have combination of these to varying degrees[12-14].

Psychiatric and behavioral abnormalities are also common and can precede neurological or hepatic signs and symptoms. Personality changes, impulsiveness, labile mood, sexual exhibitionism are observed[14,15]. These can be confused with puberty-associated problems. In older patients, psychotic features resembling schizophrenia, depression can be found.

Coombs negative hemolytic anemia is common and can be the presenting features occasionally. In one series it was seen in 12% patients as presenting feature[10]. Acute liver disease and hemolysis during peripartum period can mimic HELLP syndrome[16]. Hemolytic anemia can also be low grade and intermittent, recurrent.

Uncommon presentations include renal abnormalities including aminoaciduria, nephrolithiasis, nephrocalcinosis, Cardiomyopathy, musculoskeletal abnormalities including myopathy, chondrocalcinosis, osteoarthritis infertility or repeated miscarriages.

Diagnostic tests

Slit lamp examination for Kayser-Fleischer (KF ring) : KF ring is a golden brown ring occurring due to deposition of copper in the Descmet's membrane of the cornea. The deposition can be in the form of focal deposits, incomplete or complete ring. It is more common patients with neurological form of the disease and can be absent in as many as 50% of patients with hepatic form. It can also be found in other chronic cholestatic disorders and is not specific for Wilson's disease. The ring can disappear with treatment[17,18].

Serum Ceruloplasmin : This is most easily available and performed diagnostic test. Ceruloplasmin level is lower than 20 mg/dL and in most it is less than 10 mg/dl. However levels are unreliable as ceruloplasmin is an acute phase reactant and can give false normal levels in active hepatitis, acute inflammatory conditions, and pregnancy, in patients on oral contraceptives. Enzymatic method using copper dependent oxidase activity is more reliable for ceruloplasmin estimation. False low levels can be seen in patients with nephrotic syndrome, protein losing enteropathy, Menke's disease.

Serum Copper : Non-ceruloplasmin bound or free copper has been proposed as a diagnostic test for Wilson's disease[19]. Serum Free Cu can be calculated as.

Serum copper in µg/L - Serum ceruloplasmin bound Cu in µg/L

[Sr Cu in µg/lit = Serum Cu in µ mol/L x 63.5]

[Ceruloplasmin bound copper in µg/lit = Sr Ceruloplasmin in mg/L x 3.15].

In most untreated patients this is above 200 µg/L. It can be elevated in acute liver failure of any etiology, chronic cholestatic disorders and in copper intoxication[20]. It can be used to monitor pharmacotherapy of the disease.

Urinary copper : It reflects amount of free copper in circulation. The test is not applicable in renal failure. In untreated symptomatic patients, if more than 100 µg/24 hr, it is considered diagnostic of Wilson's disease. Post D Penicillamine urinary copper more than 1057 µg/24 hr had sensitivity of 100% & specificity of 82.3% in adult Wilson's disease[21]. However lack of standardization in the dose, timing of D Penicillamine administration makes use of this test impractical in adults.

Hepatic parenchymal copper : Quantitative estimation of hepatic Cu in liver biopsy sample is the gold standard test for diagnosis of Wilson's disease. When more than 250 µg/gm dry weight, it is considered to be diagnostic of Wilson's disease. However patchy distribution of copper within liver can lead to sampling error and erroneous results. Demonstration of Cu in the liver by Orcein or Rhodamine stain can be fallacious as most of the patients have Cu in the cytoplasm and the stains can detect only lysosomal bound copper. Thus absence of stainable copper does not exclude Wilson's disease[22].

MRI Brain : Hyper intensity on T2 MRI in basal ganglia, face of giant Panda sign[23], hyper intensitiesin tectal plate and central pons, simultaneous involvement of basal ganglia, thalamus and brainstem are pathognomonic of Wilson's disease[24].

A diagnostic score based on all the available tests was proposed by the Working Party at the 8th International Meeting on Wilson's disease, Leipzig 2001[25].

Treatment : Four approaches have been utilized in treatment of Wilson's disease

1. Dietary therapy
2. Therapy to reduce intestinal Copper absorption
3. Therapy to increase copper chelation & elimination
4. Liver transplantation.

Typical clinical symptoms and signs		**Other tests**	
KF rings		**Liver copper (In absence of cholestasis)**	
Present	2	> 4 µmol/g	2
Absent	0	0.8 to 4 µmol/g	1
Neurological symptoms		Normal < 0.8 µmol/g	-1
Severe	2	Rhodamine positive granules	1
Mild	1	**Urinary Copper in absence of acute hepatitis**	
Absent	0	Normal	0
Serum Ceruloplasmin		1-2 X ULN	1
Normal > 20 mg/dl	0	> 2 X ULN	2
10-20 mg/dl	1	Normal but > 5 X ULN after D Penicillamine	2
< 10 mg/dl	2		
Coomb's negative hemolytic anemia		**Mutation analysis**	
Present	1	On both chromosomes detected	4
Absent	0	On 1 chromosome detected	1
		No mutation detected	0
Total score		**Evaluation**	
4 or more		Diagnosis established	
3		Diagnosis possible, more tests needed	
2 or less		Diagnosis unlikely	

Diet :

Foods very high in Copper include shellfish, nuts, chocolates, mushrooms and organ meats and should be avoided. Storage of drinking water in copper utensils is also to be avoided.

Reducing absorption of Cu :

Zinc reduces absorption of copper by inducing in enterocytes, synthesis of metallothionines, which hav emore affinity towards copper than zinc and the copper metallothionine complex cannot enter portal circulation. The copper is eliminated in feces as enterocytes are shed[26]. Recommended dose of zinc is 150 mg/day in three divided doses, 30 min before foods. Gastric irritation is the main adverse effect. Zinc has been used for maintenance therapy, first line therapy for asymptomatic or pre-symptomatic patients. It has also been proposed as a therapy for patients who cannot tolerate D Penicillamine or who develop worsening of neurological symptoms ontherapy[27]. However in hepatic Wilson's disease zinc monotherapy can worsen liver disease and is to be used with caution.

Chelation and elimination of copper : D-Penicillamine was introduced in treatment of Wilson's disease in 1956 and today forms the cornerstone of treatment of the disease. It induces urinary copper excretion and also induces metallothionine synthesis promoting fecal excretion like by Zinc. The dose of D-Penicillamine varies from 250 to 500 mg as initial dose, maximum up to 1500 mg/day in three divided doses. In children, it is 20 mg/kg rounded off to nearest 250 mg. Food interferes with its absorption hence it has to be administered 1 hr before or 2 hr after food. Adverse effects requiring discontinuation of therapy occur in 25 to 30% patients[28]. Fever, skin rashes, nephrotoxicity, cytopenias can occur early in the course while lupus like syndrome, arthralgia, nephrotoxicity, bone marrow suppression, immunosuppression occurs late in the course. Initial worsening of neurological symptoms can occur in 10-50% patients[29]. The drug should be stopped and alternate therapy started 3 month before planned surgery as it interferes with wound healing.

Trientene : It is a chelator of many metals including copper, zinc and iron. It was introduced in 1969 as an alternative to D-Penicillamine. It favors urinary excretion of copper. Recommended dose is 750-1500 mg in two or three divided doses. Trientene absorption is hampered by food. The drug needs to be stored in a refrigerator. Adverse effects include dyspepsia, muscle cramps, dystonia, and anemia. Co-administration with iron should be avoided.

Ammonium Tetrathiomolylbdate : It is a copper-chelating agent approved in Europe since 2008. It eliminates copper through both urinary and fecal route. However clinical experience with this drug is limited and it is not available in India.

Monitoring of therapy : Therapy needs to be monitored to ensure compliance and to adjust doses of drug or to shift between drugs. Liver and kidney function test, urine examination and complete blood count are required frequently initially and later at regular interval. Urinary copper during chelation therapy should be between 500-1000 μg/24 hr initially and during maintenance 250 500 μg/24 hr. Serum free copper should be between 15-25 μg/L during maintenance therapy with chelation therapy. With zinc therapy urinary excretion should drop down to 30 80 μg/24 hr on maintenance therapy. If these values are not found compliance to therapy is questionable. Treatment during pregnancy must be maintained and drug of choice is Zinc.

Liver Transplantation : For fulminant hepatic failure, which occurs due to Wilson's disease, liver transplantation is the recommended option. The success rates are comparable to liver transplantation for other etiologies. Liver transplantation also cures the basic generic defect in liver. Neurological involvement may show little improvement with transplantation[30]. Hence, for advanced or progressive neurological disease, liver transplantation is not recommended as sole therapy.

Genetic Counseling : Sibling of index case should be screened with serum copper, slit lamp examination & 24 hr urinary copper even if asymptomatic, as they have 25% chance of harboring the disease. Children and asymptomatic siblings with negative work up should be advised genetic studies to detect heterozygous status mutation in ATR7B gene.

Our Experience : Seven patients were diagnosed as Wilson's disease at our center of which 3 were lost to follow up. Of the four patients, two were adolescents (14 & 16 yrs.) and two adults (38 & 43 yrs.). Three presented with predominant hepatic involvement and one had predominant neurological involvement. All had ceruloplasmin below normal, 3 had KF rings, and all had increased urinary copper excretion. There was history consanguity in two patients. Of the three with hepatic involvement, one developed chorea later. Two patients had variceal bleeding and required EVL, one developed SBP. All were treated with D Penicillamine, two with added zinc therapy. All tolerated the drug well. Two patients deteriorated despite treatment and were offered liver transplantation, which they could not afford.

Summary : Wilson's disease is a treatable inherited disorder of copper metabolism. It requires high index of suspicion to diagnose this disease, which can present with hepatic or neurological form. Effective treatment can favorably improve prognosis of the disease. Genetic counseling can identify asymptomatic or heterozygote individuals who can be treated or advised accordingly.

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