Review article

Wilson's Disease in Children : An Update

Sadika Kadir,[1] Tamanna Begum ,[2] Mohammed Ashraful Haque,[3] Nirupama Najim,[4] Shayma Chakravarty,[5] Anamika Roy,[6] Tanvir Ahmeed[7]

Abstract

Wilson's Disease is an autosomal recessive disorder of copper metabolism due to ATP7B gene defect. This defect result in progressive toxic accumulation of copper in liver, CNS, cornea, skeletal system and other organs. Clinical presentations of Wilson's disease (WD) in childhood ranges from asymptomatic liver disease to cirrhosis or acute liver failure, whereas neurological and psychiatric symptoms are rare. The basic diagnostic approach includes serum ceruloplasmin and 24-hour urinary copper excretion. Final diagnosis of WD can be established using a diagnostic scoring system based on symptoms, biochemical tests assessing copper metabolism, and molecular analysis of mutations in the ATP7B gene. Pharmacological treatment is life-long and aims at removal of copper excess by chelating agents as D-penicillamine, trientine or inhibition of intestinal copper absorption with zinc salts. Acute liver failure often requires liver transplantation. Genetic therapy and haplocyte transplantation represent future curative treatment for Wilson's disease.

Key Words: children, diagnosis, hepatitis, liver, treatment, Wilson's disease

Introduction:

Wilson's disease (WD) is a rare autosomal recessive disorder of copper metabolism. It was first described in 1912 by Kinnear Wilson as "progressive lenticular degeneration", a familial, lethal neurological disease accompanied by chronic liver disease leading to cirrhosis.[1] It is generally accepted that the disorder is related to excessive accumulation of copper in the liver, CNS, cornea, skeletal system and other organs. The worldwide prevalence of Wilson's disease is estimated to be 1 in 30,000, with a gene frequency of 0.56% and a carrier frequency of 1 in 90. [2]

Molecular genetics

A mutation in the ATP7B gene, located on chromosome 13, is responsible for Wilson's disease. Absent or reduced function of ATP7B protein leads to decreased hepatocellular excretion of copper into bile.[3,4] This results in hepatic copper accumulation and injury. Eventually, copper is released into the bloodstream and deposited in other organs, notably the brain, kidneys, and cornea.[5] Failure to incorporate copper into ceruloplasmin is an additional consequence of the loss of functional ATP7B protein. The hepatic production and secretion of the ceruloplasmin protein without copper, apoceruloplasmin, result in the decreased blood level of ceruloplasmin found in most patients with WD due to the reduced half-life of apoceruloplasmin.[5,6]

Liver pathology

Liver is the major organ for storage of copper.[7] Characteristic histologic findings are present but not pathognomic. Fat deposition is one of the earliest changes seen in the liver biopsy specimen. Histologic features that are indistinguishable form of autoimmune chronic hepatitis develop, as well as hepatic necrosis. The electron microscopic, findings are then relatively normal, except for excessive morphus or globuler copper containing lipofusicin granules and lipid containing lysosoms .[8]

CLINICAL FEATURES IN PATIENTS WITH WILSON DISEASE [9,10]

Hepatic

Asymptomatic hepatomegaly, Isolated splenomegaly, Persistently elevated serum aminotransferase activity (AST, ALT), Fatty liver, Acute hepatitis, Resembling autoimmune hepatitis, Cirrhosis: compensated or

1. Assistant Professor,Department of Paediatrics, Z.H.Shikder Womens Medical College, Dhaka
2. Professor& Head of the department, Department of Paediatrics, Z.H.Shikder Womens Medical College, Dhaka
3. Assistant Professor, Neurosurgery, National Institute of Neuroscience ,Dhaka
4. Medical officer,Department of Paediatrics, Z.H.Shikder Womens Medical College,Dhaka
5. Medical officer, Department of Paediatrics, Z.H.Shikder Womens Medical College,Dhaka
6. Medical officer,Department of Paediatrics, Z.H.Shikder Womens Medical College,Dhaka
7. Medical officer,Department of Paediatrics, Z.H.Shikder Womens Medical College,Dhaka

Address of correspondence:

Dr.Sadika Kadir,Assistant Professor,Department of Paediatrics, Z.H.Shikder Women's Medical College, Dhaka, Cell: 01715550952, E mail: dr.sadika_maruf@yahoo.com

decompensated, Acute liver failure,

Neurological

Movement disorders (tremor, involuntary movements), Drooling, dysarthria, Rigid dystonia, Pseudobulbar palsy, Seizures,

Psychiatric

Depression, Neurotic behaviors, Personality changes, Psychosis

Other systems

Ocular: Kayser-Fleischer rings, sunflower cataracts; Cutaneous: lunulae ceruleae; Renal abnormalities: aminoaciduria and nephrolithiasis; Skeletal abnormalities: premature osteoporosis and arthritis; Cardiomyopathy, dysrhythmias, Pancreatitis, Hypoparathyroidism, Menstrual irregularities; infertility, repeated miscarriages.

DIAGNOSIS [11,12]

The diagnosis of Wilson disease is based on a very broad combination of laboratory tests and clinical features. The most useful laboratory tests for diagnostic purposes are those measuring 24-hour urinary copper excretion, hepatic copper concentration, serum free copper concentration and ceruloplasmin concentration. The diagnosis of WD may be made readily when the classic triad of hepatic diseases, neurologic involvement, and KF rings are present.[13]

ROUTINE TESTS FOR DIAGNOSIS OF WILSON'S DISEASE[15]

Tests	Typical findings	False "negative"	False "positive"
Serum ceruloplasmin		➢ 4-20% of WD ➢ WD with marked hepatic inflammation ➢ Pregnancy ➢ Eastrogen therapy in WD ➢ Ceruloplasmin assays using radial immunodiffusion ➢ Overestimation by immunologic assay	➢ Low levels in malsorption ➢ Severe malnutrition ➢ Acute liver failure of any etiology ➢ Hypoceruloplasminaemia or ➢ Aceruloplasminaemia ➢ 15-20% of WD carriers ➢ 25% of non WD chronic active hepatitis ➢ Normal neonates
24-hour urinary copper	>100 µg /day	➢ Asymptomatic WD. ➢ Incorrect collection. ➢ Children without liver disease.	➢ Non WD chronic active hepatitis. ➢ Indian childhood cirrhosis ➢ Chronic cholestatic liver disease. ➢ Increased hepatocellular necrosis. ➢ Contamination
Serum "free" copper	>10 µg /dl	Normal if ceruloplasmin Overestimated by immunologic assay	
Heptic copper	>250 µg /g dry weight	➢ Duo to regional variation ➢ In patients with active liver disease. ➢ In patients with regenerative nodules ➢ Active liver disease	➢ Cholestatic syndromes ➢ Indian childhood cirrhosis ➢ Liver tumors ➢ Newborn liver

(Rukonuzzaman et al,2015)

Detection of symptom free homozygotes [16,17]

Asymptomatic relatives specially sibling of patients with WD should be screened. They should have a

- Detailed history including hepatic, neurological, psychiatric symptoms.
- Ophthalmological examination (K-F rings).
- Laboratory studies including serum aminotransferases, serum ceruloplasmin, 24-hour urinary copper excretion and mutation analysis.

SCREENING OF ASYMPTOMATIC RELATIVES OF PATIENTS WITH WD

Mandatory

History and physical examination, Ophthalmological slit-lamp examination, Serum ceruloplasmin and copper estimations, Hepatic transaminase levels, 24-hour urinary copper excretion.

Additional

Blood smear for hemolysis, Reticulocyte count and haptoglobin, Urinary calcium level

Genetic analysis

(Jessica et al.,2008)

If any of the above is abnormal, liver biopsy becomes mandatory with examination of histology and measurement of quantitative liver copper content.[17,18]

Diagnostic score in Wilson's disease[10,18]

Score	0	1	2	3
K-Frings	Absent		Present	
Neuropsychiatric Symptoms suggestive of WD (or typical br MRI)	Absent		Present	
Coombs-negative haemolytic anaemia+high serum copper	Absent	Present		
Urinary copper (in the absence of acute hepatitis)	Normal	1-2xULN		
LivercopperquantitiveRhodanine-positive hepatocytes (only if quantitive) measurement is not available	Absent	Present		
Serum ceruloplasmin	>0.2g/L	0.1-0.2g/L	<0.1g/L	
Mutation detected	None	1		2

MRI, Magnetic Resonance Imaging; ULN=upper limit of normal (Eisenbach et al., 2017)

TREATMENT [19]

With the exception of liver transplantation, treatment of Wilson's disease is only palliative and intended to restore and maintain copper balance. Thus, a lifelong commitment to treatment is required.

Diet

WD cannot be prevented or controlled by low copper containing diet alone. Foods with very high concentrations of copper (shellfish, nuts, chocolate, mushrooms, and organ meats) generally should be avoided, at least in the first year of treatment along with drug treatment. [20]

Drugs

Aim of drug therapy in WD is to restore and maintain copper balance for lifelong.

The entire treatment period can be divided into two phases. [20,21]

Initial therapy

To reduce serum copper level in sub toxic level is the aim of this phase. This phase takes four to six months. Drugs of choice are D-penicillamine and Trientine . [20,21]

Maintenance therapy

To prevent copper accumulation and toxicity, a slightly negative copper balance is maintained in this phase. After adequate treatment with a chelator, stable patients may be continued on a lower dosage of the chelating agent or shifted to treatment with zinc .[21,22]

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.[22]

Future therapy

Genetic therapy and haplocyte transplantation represent future curative treatment for Wilson"s disease along with currently available liver transplantation. However both cell and liver transplantation need immunosuppresion to maintain grafted cells.[22]

References:

1. Ala, A Walker, Ashkan K ,Dooley J 2007,' Wilson's disease', Lancet, vol. 369, pp.397- 408.
2. Iacob R, Iacob S, Nastase A, Vagu C, Ene A, Constantinescu A et al. 2012,' The His1069Gln mutation in the ATP7B gene in Romanian patients with Wilson's disease referred to a tertiary gastroenterology center',Journal of Gastrointestinal and Liver Disorder, vol 21,pp.181-185.
3. Merle U, Schaefer M, Ferenci P, Stremmel W 2007,' Clinical presentation, diagnosis and long-term outcome of Wilson's disease: a cohort study',Gut, vol.56, pp.115-120
4. De Bie P, Van De SB, Burstein E, Van DB, Muller et al, 2007,' Distinct Wilson's disease mutations in ATP7B are associated with enhanced binding to COMMD1 and reduced stability of ATP7B', Gastroenterology, vol 133, pp.1316-1326
5. Roberts E, Schilsky M 2008,' Diagnosis and Treatment of Wilson Disease: An Update.,Hepatology, vol.47,pp. 2089-2111.
6. DE Bem RS, Muzzillo DA, Deguti MM, Barbosa ER, Werneck LC, Teive AG 2011,' Wilson's disease in southern Brazil: a 40-year follow-up study',Clinical Science, vol 66,pp. 411-416
7. Li X H, Lu Y, Ling Y, Fu et al.2011,'Clinical and molecular characterization of Wilson's disease in China: identification of 14 novel mutations', BMC Medical Genetics,vol12,pp.78.
8. Ferenci P, Anna C, Wolfgang S, Roderick H, William R & Michael P 2012,' EASL Clinical Practice Guidelines: Wilson's disease'. Journal of Hepatology, vol 56, pp.671-685.
9. Karim M, Rahman M & Islam M 2007,' Wilson's disease with hepatic presentation in childhood',Mymensingh Medical

Journal,vol. 16, pp.29-32

10. Dhawan A, Taylor R, Cheeseman P, De Silva P, Katsiyiannakis L & Mieli-Vergani, G 2005.ʹ Wilsonʾs disease in children: 37-year experience and revised Kingʾ score for liver transplantation ʾ,Liver Transplantation,vol 11, pp.441-448.
11. Pfeiffer R F 2007,ʾ Wilson ʾs Disease ʾ Seminars in Neurology,vol. 27, pp.123-132.
12. Svetel M, Potrebic A, Pekmezovic T, Tomic A, Kresojev et al.2009, ʹ Neuropsychiatric aspects of treated Wilson ʾs disease,ʾ Parkinsonism Related Disorder,vol.15,pp.772-775
13. Zhang, YG, Nan YM., Zhao SX, Wang TL, Jiang J 2013,ʾ Clinicopathological features of Wilson disease: report of 29 cases,ʾ Zhonghua Yi Xue Za Zhi,vol. 93,pp.18.
14. Rukunuzzaman M 2015,ʾ Wilson's Disease in Bangladeshi Children: Analysisof 100 Cases ʾ Pediatr Gastroenterol Hepatol Nutri ,vol.18 ,pp.121-122
15. Jessica DK, Irene V , Jody B, Joe W, Frank V,Schiodt, Robert H, Squires J, Robert J, Fontana, William M, Michael L, Schilsky 2008 ,ʹ Screening for Wilson Disease in Acute Liver Failure:A Comparison of Currently Available Diagnostic Tests ʾ,Hepatology, Vol. 48, pp.No.4.
16. Majumder MW 2011,ʾ Value of urinary copper estimation before and after penicillamine challenge for the diagnosis of Wilson's Disease in children in Bangladesh,ʾ MD, BSMMU.
17. Eisenbach C, Sieg O, Stremmel W, Encke J , Merle U 2007,ʾ Diagnostic criteria for acute liver failure due to Wilson disease ʾ. Journal of Gastroenterology & Hepatology,vol 13,pp. 1711-19.Wang J, Lu Y, Wang X 2010,ʾ Urinary copper/zinc ratio: a promising parameter for replacement of 24-hour urinary copper excretion for diagnosis of Wilson's disease in children ʾ, World Journal of Pediatrics, vol.6, pp.148-153
18. Hang YG, ZWu ZY 2011, ʹ Wilson ʾs disease in Asia ʾ, Neurology Asia, vol.16,pp. 103-109.
19. Zhang, YG, Nan YM., Zhao SX, Wang TL, Jiang J 2013,ʾ Clinicopathological features of Wilson disease: report of 29 cases,ʾ Zhonghua Yi Xue Za Zhi,vol. 93,pp.18.
20. Socha P, Janczyk W, Dhawan A, Baumann U, Lorenzo D, Tanner S ,ʹ Wilson's Disease in Children: A Position Paper by the Hepatology Committee of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition ʾ.J Paeditr Gastroenter Nutr 2018;66:332–344.