Review Article

Wilson Disease in Children: Diagnosis and Management Update

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Abstract

Wilson disease is an autosomal recessive, copper storage disease, caused by a mutation in the ATP7B gene. Due to mutation in ATP7B is decreased secretion of ceruloplasmin into blood and decrease in excretion of copper into bile. Excess copper accumulate to toxic levels,mainly in the liver and secondarily in other organs. Children clinically become symptomatic after the age of 5 years. Clinical features ranges from asymptomatic raised transaminases to variable degree of liver disease, neurological symptoms and according involvement of other oragns. Diagnosis of Wilson disease is challenging. Modified Leip-zig score is useful for diagnosis. Treatment can be done with zinc and other chelators.

Key words: *ATP7B gene, Children, Copper, Wilson disease.*

Date of received: *10.07.2020.*

Date of acceptance: *25.11.2020.*

KYAMC Journal.2021;11(4):212-217.

DOI: https://doi.org/10.3329/kyamcj.v11i4.52000

Introduction

Wilson disease is an autosomal recessive, copper storage disease.[1] Wilson disease results due to accumulation of toxic levels of copper, mainly in the liver and secondarily in other organs such as the kidneys, brain, and cornea.[2]

The disease is caused by a mutation in the ATP7B gene, which codes for a protein that facilitates the incorporation of copper into proteins (such as ceruloplasmin) and also the transportation of copper into vesicles that allow it to be secreted in bile. The critical effect of a mutation in ATP7B is decreased secretion of ceruloplasmin into blood and decrease in excretion of copper into bile.[3] The ultimate results are a) reduction of ceruloplasmin in blood, b) accumulation of free Cu in hepatocytes with toxic injury to hepatocytes, c) spilling over of free Cu from liver into the circulation, d) Cu induced toxic injury of RBC (haemolysis), brain, cornea, kidney, bone, joints and parathyroids and e) concomitant increase in urinary copper excreation.[4]

Epidemiology

Incidence of the disease frequency is estimated to be between 1 in 5,000 and 1 in 30,000, and the carrier frequency is approximately 1 in 90.[5], WD may present at any age from infancy (with raised transaminases, measured for some unrelated reason) to the eighth decade (often with surprisingly

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mild neurological features). Symptoms usually appear between the ages of 5 and 35 years. Clinical presentation is rare below three years.[7,8] Based on the combined large patient series, 83% of patients presented with hepatic symptoms and 17% with neuropsychiatric manifestations prior to age 10 years; 52% presented with hepatic and 48% with neuropsychiatric symptoms at 10-18 years; and 24% presented with hepatic and 74% with neuropsychiatric symptoms after age 18 years. Considering patients of all ages using data derived from nine combined series, approximately 49% of patients present with hepatic and 46% with neuropsychiatric symptoms.[9-11]

Clinical Features

Clinical features include a) asymptomatic, with or without raised transaminases which may discovered serendipitously or detected during screening of family members. b) Hepatic presentation include Incidental finding of hepatomegaly, insidious onset of vague symptoms followed by jaundice (Figure 1), acute hepatitis, acute liver failure with haemolysis, chronic hepatitis, steatohepatitis, gallstones, portal hypertension, decompensated cirrhosis and hepatocellular carcinoma. c) Neurological and psychiatric features developed in second decade and later. Feautres include tremor (resting, intention), drooling, pseudo-laughter (Figure 2), hypersalivation, dysarthria, coordination defects, clumsiness, dystonia, writing difficulties, choreiform movements, ataxic gait, fixed grin, headache, seizures, organic dementia, neuroses, anxiety, depression, obsessive/compulsive disorder, schizophrenia, bipolar disorder and antisocial behavior etc. d) Due copper deposition in eye Kayser-Fleischer (KF) rings (Figure 3) and sunflower cataract may found. e) others: Coombs negative acute hemolytic anemia, renal tubular dysfunction (Fanconi, RTA, aminoaciduria), renal calculi, rickets/osteomalesia, amenorrhea and hyperpigmentation also found.[7,12-15]

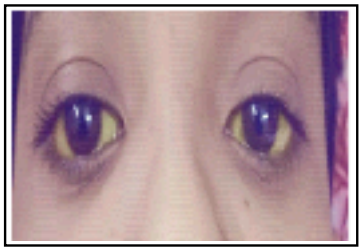

Figure 1: Jaundice

Figure 2: pseudo-laughter and dystonia

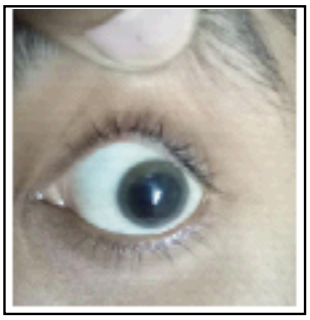

Figure 3: K-F ring

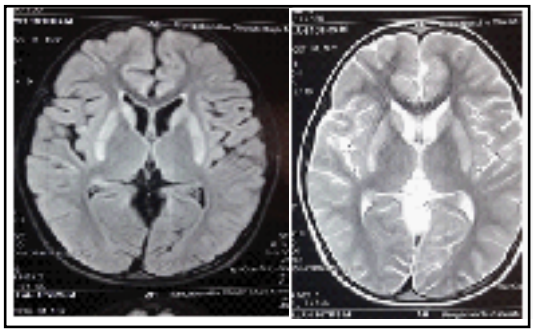

Figure 4: Hyperintense signal from caudate nucleus and putamen.

Diagnosis

Wilson disease remains a diagnostic challengeas the symptoms are often nonspecific with multi-organ involvement.[16] Currently, the diagnosis of Wilson disease is based on clinical features and a range of laboratory tests. Diagnostic tests for Wilson disease in children include liver function tests, ceruloplasmin, total serum copper, urinary copper excretion, mutation analysis, liver biopsy and liver copper content, Kayser-Fleischer ring on slit-lamp examination of eye, neuroimaging studies, scoring system.[8,17] All patients diagnosed with Wilson's disease should undergo neurological evaluation.[8]

The presence of neurological symptoms, Kayser-Fleischer rings and a low caeruloplasmin level is usually sufficient to confirm a diagnosis. The absence of Kayser-Fleischer rings does not exclude Wilson's disease.[18] Another characteristic, but less common ophthalmologic feature of Wilson disease is the grayish brown sunflower cataract that may develop because of deposits of copper in the anterior and posterior lens capsule.[19]

A diagnostic score for diagnosing Wilson disease was proposed by the working party at the 8th International Meeting on Wilson's disease, Leipzig 2001.[7,20] The scoring system includes thefollowing diagnostic elements: (1) serum caeruloplasmin, (2) 24-h urinary copper excretion, (3)the presence of nonimmune (Coombs-negative) haemolytic anaemia, (4) hepatic copper, (5) the presence of Kayser-Fleischer rings on slit-lamp examination, (6) neurologic or neuroimaging features, and (7) mutation analysis. A score of 4 or more provides good accuracy to diagnose Wilson disease.[7,20]

Magnetic resonance imaging (MRI) common findings included atrophy of cerebrum, brainstem and cerebellum; hyperintensity on T2 magnetic resonance imaging in the region of the basal ganglia, tectal-plate and central pons (Figure 4). The characteristic "Face of giant panda sign" was seen in 12%.[8,15]

The Leipzig score of was modified by consensus group members of Indian national association for study of the liver, the Indian society of pediatric gastroenterology, hepatology and nutrition, and the Movement disorders society of India and the new "modified Leip-zig score" (Table I). In this new score, additional points were given for family history suggestive of WD.[21]

Table I: Modified Leipzig Scoring System for Diagnosis of Wilson Disease

KF rings	Score
Present	2
Absent	0
Serum ceruloplasmin	
Normal (>20 mg/dl)	0
0– 5 mg/dl	3
6–11 mg/dl	2
11–20 mg/dl	1
24 - h urinary copper (in the absence of acute hepatitis)	
>100 mcg	2
40 –100 mcg	1
<40 mcg	0
Coomb's-negative hemolytic anemia with liver disease	
Present	1
Absent	0
Mutational analysis	
On both chromosomes detected	4
On one chromosome detected	1
No mutation detected/test not done	0
Liver biopsy for histology S/O WD with	
Orcein- or rhodanine-positive granules	1
Neurobehavioral symptoms	
Present	2
Absent	0
Typical features on MRI brain	
Present	1
Absent	0
History of Wilson disease in a family member	
Sibling death from liver disease/Present	1
Absent	0

Evaluation	
e"4 or more	Diagnosis established
3	Diagnosis possible, more tests needed
2	Diagnosis very unlikely

Family screening

All first-degree relatives of a patient with newly diagnosed Wilson's disease must be screened for Wilson disease because the probability of finding a homozygote in siblings is 25%.[22] The chance amongst the offspring is 0.5%. In such cases, liver function tests, serum copper and caeruloplasmin concentration, and 24-h urinary copper excretion analysis are performed.[23]

Treatment

Drug therapy for Wilson disease focuses on decoppering from the use of chelators (to promote copper excretion) or zinc which reduces intestinal copper absorption, or both.[20,24] Treatment phases divided into initial phase and maintenance Therapy. The aims of initial phase is to reduce the body copper levels to sub-toxic threshold. The choice is between chelators (D-Penicillamine or trientine) alone, zinc alone, or a combination of both.[11] After initial chelation therapy of typically 3-6 months, usually until symptoms or biochemical abnormalities have stabilized, then maintenance dosages of chelators or zinc mono-therapy can be used for treatment.[20,24]

Maintenance therapy consists of a lifelong therapy and prevents copper reaccumulation after the patient has been effectively decoppered. Prevention of reaccumulation can be achieved with chelators or by use of zinc salts. Zinc, in view of its good efficacy, low cost, and toxicity, is the drug of choice. DP in low dose is an alternative but patients should be monitored for side effects.[21] Typically doses of chelation can be reduced by approximately 33 percent from that used for initial treatment and copper removal. Lifelong treatment is necessary unless the patient has had a liver transplant, because Patients who discontinue treatment are at high risk of fulminant hepatic failure.[25]

Treatment of presymptomatic patients and neonate discovered on genetic testing: An asymptomatic sibling diagnosed to have WD by biochemical or genetic testing should be treated to prevent symptomatic disease. Zinc is the drug of choice, because it is more physiologic and less toxic. Treatment of neonate discovered on genetic testing, should not be start in the first year. Because clinical presentation is rare below three years, commencement at the age of 2 years is a defensible.[17,26]

Diet

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. Diets deficient in copper may delay the onset of the disease and control disease progression, but dietary management is not recommended as sole therapy.[27] A high protein diet should be consumed because the increased excretion of amino acids can increase urinary excretion, thereby reducing the deposition of copper.[18]

Drug used in Wilson disease

D-Penicillamine

D-Penicillamine act by inducing hepatic metallothionein, a cytosolic metal-binding protein which sequesters copper, and renders it nontoxic. Dose ranges 20-35 mg/kg/day. Should be given before or 2 hours after meals apart from zinc. Its absorption is decreased by as much as 50 percent when taken with food. Several adverse events may encounter during D-Penicillamine therapy. Early (1-3 weeks) adverse events include hypersensitivity, fever, cutaneous eruptions, lymphadenopathy, neutropenia, thrombocytopenia, and proteinuria. Late (3 weeks-3 months) adverse events include hypersensitivity, lupus-like syndrome (proteinuria, hematuria, positive ANA), goodpasture syndrome, severe thrombocytopenia, total aplasia of bone marrow, optic neuritis and skin lesion like pemphigus, pemphigoid lesions involving skin, mouth, vagina, buccal ulcerations, apthous stomatitis, hair loss. Very late (after 1 year) adverse events include nephrotoxicity, severe allergy on restarting drug, myasthenia gravis, polymyositis (<1%), loss of taste, immunoglobulin A depression, retinitis, hepatotoxicity (transaminitis), copper depletion leading to neutropenia, sideroblastic anemia, and hemosiderosis. Direct dose dependent adverse events include pyridoxine deficiency (common), mammary hypertrophy,

skin lesion likes elastosis perforansserpiginosa, lichen planus, progeria-like skin changes, D-penicillamine dermopathy. Neurological deteriorationmay occur, incidence ranges from 10% to 50%.[20-26]

Triethylenetetramine hydrochloride/trientine

Trientine act as chelating agent in WD patients who had become intolerant of penicillamine. Dose ranges 500-750 mg/day in 2 or 3 doses and given before or 2 hours after meals. Side effects usually few. No hypersensitivity observed. Neurological deterioration is less common. Side effects include fixed drug eruption, iron deficiency, bone marrow depression, sideroblastic anemia, hemorrhagic gastritis, loss of taste, and skin rash.[20-26]

Zinc acetate

Zinc act by induction of metallothionein in enterocytes. Copper absorbed in the small intestine is thereby sequestered in enterocytes which at the end of their life cycle carry copper into the lumen. Zinc also induces hepatocyte metallothionein, so, like Dpenicillamine, may "detoxify" liver copper. Dose ranges depend on age and weight. Up to 5 years 25 mg two times/day, 6-15 years 25 mg three times/day, from 16 y or if >57kg 50 mg three times/day. Drug should be given 2 hours after meal. Very few side effects encounter. Neurological deterioration is described but very uncommon. Gastric irritation, asymptomatic elevation of serum amylase and lipase may occur.[20-26]

Other agents: Ammonium tetrathiomolybdate, Dimercaprol (BAL), potassium sulfide and carbacrylamine resins [25,28]

Special situation: WD presenting as acute liver failure

Wilson disease may present as acute liver failure and characteristic features suggesting a diagnosis include Coombs-negative haemolytic anaemia, coagulopathy unresponsive to parenteral vitamin K, renal failure, relatively modest rises in serum aminotransferase (AST/ALT > 2.2), normal or markedly subnormal serum alkaline phosphatase (ALP), elevated serum copper and 24-h urinary copperexcretion, and a ratio of alkaline phosphatase to bilirubin of <2.[23] A combination of an ALP to bilirubin ratio of <4 and an AST to ALT ratio >2.2 provided a sensitivity and specificity of 100% in identifying acute liver failure due to Wilson'sdisease.[29]

A prognostic score (New Wilson's index for predicting survival) incorporating serum bilirubin, aspartate aminotransferase, international normalized ratio, leucocyte count and serum albumin, determines survival without liver transplantation (Table II). A score of >11, is associated with high probability of death without a liver transplant.[23]

Table II: New Wilson's index for predicting survival.

Score	Bilirubin (mg/dl)	INR	AST (IU/L)	WCC (10 y/L)	Albumin (g/dl)
0	0-5.8	0-1.29	0-100	0-6.7	e"4.5
1	5.9-8.7	1.3-1.6	101-150	6.8-8.3	3.4-4.4
2	8.8-11.6	1.7-1.9	-200	8.4-10.3	2.5-3.3
3	11.7-17.5	2.0-2.4	201-300	10.4-15.3	2.1-2.4
4	17.6	2.5	300	15.4	0-2.0

Acute liver failure with encephalopathy

Child should be managed in ICU setup and should be listed for urgent transplantation. While awaiting transplant, trientine and zinc should be started, even if the diagnosis of WD is not certain. These two drugs should be given 6 hours apart to prevent chelation of zinc by trienine. Routine management of ALF should be given. There have been many attempts to remove copper from the WD-ALF patient, include plasmapheresis, plasma exchange with continuous hemodiafiltration, and albumen hemodialysis with continuous venovenous haemodiafiltration.[30-32] There are cases in which the Molecular Adsorbents Recirculating System (MARS alone or MARS with albumin-CVVH) has provided a successful bridge to transplant.[26,33]

Liver Failure Without encephalopathy

Here the decision whether to list a patient for transplant is more difficult. Because delay may increase the risks of rapid deterioration and development of encephalopathy, while on the other hand, there is a chance of recovery of native liver with chelation therapy. The scoring system developed at Kings College Hospital, and subsequently modified should be applied daily. A score >11 indicates the need to list urgently. Trientine and zinc should be started as described above.[26]

Liver transplantation

Liver transplantation is considered in those with acute liver failure, unresponsive to medical therapyand end-stage liver disease.[20,22] Liver transplantation is curative for WD, and patients do not require treatment for WD following transplantation.[25] New Wilson's Index has been used as a predictor of LT (forboth acute or chronic presentation). Rising bilirubin, advanced hepatic encephalopathy, and acute hemolysishave been suggested as better predictors for LT. Living donor liver transplant from heterozygous sibling iseffective and safe for both donor and recipient.[21,34] Liver transplantation is not indicated for isolated severe neurological WD. When the liver is also diseased, the decision should be individualized because significant neurological disease is a predictor of poor outcome.[21,35]

Treatment monitoring

Patients should be regularly monitored for ensuring compliance, efficacy of therapy, and early recognition of side effects. In hepatic WD, clinical improvement is characterized by decreasing jaundice, ascites, and portal hypertension. Effective decoppering is assessed on 24-hour urine copper and serum free copper value. Serum free copper is calculated by the formula: serum copper - 3 ? serum ceruloplasmin. This is initially done after a month, then 3 monthly, and subsequently 6-12 monthly. For biochemical recovery and to see the side effects of drug - Complete blood counts, urine analyses, liver function tests (ALT,AST, Gama GT, PT), are performed initially after a week, then at 2 and 4 weeks followed by 3 months, 6 months, and then yearly. KF ring should be evaluated annually. Hepatic treatment failure, defined as an increase in activity of liver enzymes, which indicate to reevaluate the treatment protocol. Child- Pugh score (based on serum bilirubin, prothrombin time, serum albumin, presence of ascites, and encephalopathy). and MELD score (based on bilirubin, creatinine, and INR) should be documented in those with severe liver disease.[21]

Long-term outcomes

WD is well recognized as one of the treatable genetic disorders and early recognition and institution of therapy is the key of good outcome. The response to therapy is dependent on various factors including drug compliance and duration/severity of symptoms at the time of institution of therapy. The outcome for neuropsychiatric disease less good.[21]

Conclusion

Wilson disease in children is uncommon but not rare. High degree of suspicion and clinical correlation is the key of diagnosis. Early initiation of treatment and adherent to medication ensure the good outcome.

Acknowledgement

We are grateful to Professor Dr. A S M Bazlul karim, Chairman,Department of Pediatric Gastroenterology and Nutrition, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

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