Original article

Clinical profile analysis of Wilson Disease in a tertiary care hospital of Bangladesh

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Abstract

Aim: This study aimed to present clinical and laboratory features of 30 children with Wilson's disease.

Material and Methods: This cross-sectional study was carried out at the Department of Z.H. Sikder Women's Medical College Hospital, Dhaka on 30 children more than three years old fulfilling the diagnostic criteria of Wilson's disease.

Result: Mean age of WD patients was 8.9±2.78 years, with a male female ratio of 1.3:1 Regarding presentation of WD 79.3% patients presented only with hepatic manifestation, 3% only with neurological features and 15% manifested with others. Among hepatic presentation 16(53.3%) patients presented with chronic liver disease, 3(10%) with Acute hepatitis and 3(10%) with Acute liver failure.Two patients(6%) were diagnosed on family screening & one patient(3%) was HBsAg positive. Other (15%) patients presented with WD with Acute glomerulonephritis (1), WD with betta Thalassemia (1), WD with Acute pancreatitis (1). There was significant low level of serum ceruloplasmin (35 of 40 patients) / 93.33% of cases (p<.001). After penicillamine challenge, 24-hour urinary copper excretion was found significantly higher in patients with WD (median 3626.5±1698 µg/24h, range 1262- 195000) (p<.001). K-F ring was found in 15 (50%) patients, that was statistically significant .

Conclusion: Wilson's disease in children is frequently missed due to its diversity of clinical presentation. So, for early detection and treatment any children with liver injury of unknown etiology should be screened for Wilson's Disease.

Keywords: Wilson's disease; children; chronic liver diseases; copper metabolism; neurological involvement;

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Introduction

Wilson's disease (WD) is a disorder of copper metabolism, resulting from the autosomal recessive occurrence of the ATP7B mutation in the short arm of chromosome 13. It is a rare congenital disorder of metabolism, with a frequency of 1/30,000 in live births.[1,2] Decreased biliary copper excretion and reduced combining of copper into ceruloplasmin, leading to excessive copper accumulation in many organs, predominantly to the liver, brain, and cornea. The clinical manifestations of WD are widely variable due to more than 500 disease-causing mutations.[3] It often presents with hepatic manifestations in early childhood, neurological manifestations after the age of 20 years.[4] Due to lack of such descriptive tests, the diagnosis should be established on the combination of clinical features, laboratory findings, and the results of mutation analysis. In adults, the presence of typical clinical and laboratory findings, such as Kayser Fleischer (K-F) rings and low serum ceruloplasmin levels can establish the diagnosis easily. However, in children typical clinical features are rarely seen before the age of 5 years and making the diagnosis of the disease more difficult than in adults.[5,6] In this study, clinical and laboratory features of 30 children with Wilson's disease were presented.

Materials and methods

This Cross-sectional study was conducted in the Department of Paediatrics Z.H.Sikder Womens Medical college hospita, Dhaka from January 2017 to January 2021 on the paediatric patients with liver disease admitted during the study period. Thirty WD positive children were studied. Children more than three years of age with any form of liver disease attended were screened for Wilson's disease. After case selection informed written consent was taken from legal guardians of individual patients. Then the patient's particulars were recorded in the case record file. Initial evaluation of the patients by history and clinical examination were collected by researcher herself and recorded in the preformed data collection sheet. Slit-lamp eye examination was done in each patient at ophthalmology department of ZHSWMCH by a single expert ophthalmologist and results were recorded in case record file. All the cases were numbered chronologically.

Children who presented with any form of liver disease

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after three years of age having the diagnosis of WD which was made upon the basis of presence of elevated 24-hour urinary copper excretion (≥1200µgm/24-hour after D-penicillamine challenge) plus at least one of the following three criteria in a child who presented with liver disease,Positive family history of liver disease, History of parental consanguinity, Low ceruloplasmin level and Presence of Kayser Fleiscer (KF) ring by slit lamp eye examination. Age<3 yrs and >18yrs, unwilling to give consent were excluded.

Prior to the commencement of this study, the research protocol was approved by the Institutional Review Board of BSMMU,Dhaka. Data were collected by investigator herself with a structured data sheet which included all the variables of interest. Penicillamine challenge test (PCT) was carried out in all children of Wilson's disease. For performing PCT five hundred milligrams of D-Penicillamine was given to each patient independent of body weight at the beginning of urine collection (zero hour) and five hundred milligram after twelve hours (total 1 gram of penicillamine) and then urine was collected for 24-hour from zero hour,the last voided sample urine was collected in a metal-free dispensable plastic tube, supplied by atomic energy centre, for copper estimation. Result was calculated with 24-hour total urinary volume.

24-hour urinary copper excretion ≥ 1200 µgm was regarded as compulsory diagnostic parameter for WD.The remaining 3 ml of blood was taken into the test tube from the haematology laboratory containing 0.2 ml 3.8% trisodium citrate and sent to the Haematology Department of BSMMU for estimation of CBC with PBF and the prothrombin time (PT). Then serum bilirubin, was measured by auto analyzer (Back man coulter auto analyzer, USA, model-5x) and result was expressed as µmol/l. Serum ALT & Serum albumin was also measured by same method and the result of serum ALT & Serum albumin were expressed subsequently as U/L &gm/L.2 ml of venous blood was collected for determination of serum ceruloplasmin. The test is done at BSMMU so the blood sample was sent to a biochemistry department for estimation of serum ceruloplasmin. Data were analyzed statistically by SPSS analysis.

Results:

A total of 30 cases were included in the study and their age range was 3 - 15 years. The mean age of patients was 8.9±2.78 years. Most of the patients (66.67%) were in the age ranges of 5–10 years. The age was not statistically significant (Table-I).

Among the 30 WD patients 17 (56.6%) were male and 13 (43.3%) female (ratio 1.3:1).

Regarding presentation of WD 79.3% patients presented only with hepatic manifestation, 3% only with neurological features and 15% manifested with others. Among hepatic presentation 16(53.3%) patients presented with chronic liver disease, Acute hepatitis 3(10%) and Acute liver failure 3(10%).Two patients(6%) were diagnosed on family screening & one patient(3%) was HBsAg positive. Other(15%) patients presented with WD with Acute glomerulonephritis(1),WD with betta Thalassemia(1),WD with Acute pancreatitis(1) respectively. Out of 30 WD positive cases, 26.67% had normal ALT level, 36.67% had mildly elevated ALT level, 26.67% and 10% had moderate and severely raised ALT levels respectively. Fifty Six percent of WD cases had serum bilirubin level within 2-10 mg/dL, 23% had <2 mg/dL and 20% had >10 mg/dL. Coagulopathy and hypoalbuminaemia was found in 60% and 86.64% of cases respectively. Among these 30 WD cases 10% were severely pale, while 36.67% had moderate palor and 60% cases had hemoglobin level >9 gm/dL (Table-III).

Parental consanguinity and positive family history were present in 9 (30%) and 5 (16.67%) of cases respectively. At the time of diagnosis of WD patients, K-F ring was found in 15 (50%) patients. It was statistically significant, p<.001 (Table-IV) . Twenty eight (93.33%) cases in had serum ceruloplasmin level of <20 mg/dl. This level was significantly lower (p<.001).

Discussion

In Bangladesh liver disease is a common medical problem. In case of children with Wilson̓ s disease hepatic manifestations are more common than in older patients.[5]Early diagnosis of WD is essential for better patient management. But diagnosis of this disease may be a challenge as there is no single ideal diagnostic test that can exclude or confirm the disease with certainty. Twenty four hour urinary copper excretion after penicillamine challenge is a useful test for the diagnosis of WD in children, but it is time consuming and difficult to collect. Most (93.3%) of the patients in the present study were in the age ranges from 5–15 years. The mean (±SD) age of WD patients was 9 ± 2.68 years. Similar result was also observed in another study done in Bangladesh .[6,7]

Wilson's disease is an autosomal-recessive disorder. In autosomal-recessive disorder both male and female may be affected equally. Male female ratio of this study was 1.3: 1. Seventeen (53.3%) of 30 WD patients were male and 13 (43.3%) female. A male predominance (2:1)also found in another study in Bangladesh,[7] In the present study we found 79.3% patients presented only with hepatic manifestation, 3% only with neurological features and 15% manifested with others. In the present study chronic liver disease 16(53.3%) was the commonest presentation. Similar observation was made earlier in another three studies of three different countries. [6,7,8] They found chronic liver disease as the most common presentation. Taly et al. in Bangalore, India, demonstrated parental consanguinity in 54% of cases and positive family history of liver disease in 47% of cases. In the present study parental consanguinity was found in 9 (30%) cases and positive family history of liver disease in 5 (16.67%) cases. In another study done in Bangladesh by Karim et al. parental consanguinity was found in 12.5 % cases, which is consistent with the

present study.In the present study, among the 30 WD cases, Most common symptom was jaundice (61.6%), followed by as hepatosplenomegaly (40%), ascites (35%), Splenomegaly(28.4% hepatomegaly (16.67%). In another study Jaundice & Ascitis were found to be the most common clinical presentations which is consistent with the present study.[8,9]

In the present study abnormal liver function test was observed in 70-80% of cases. A similar observation had also been made by Zhang where abnormal liver function was found in 100% of cases.[10]

Kayser-Fleischer ring, the cardinal sign of WD is formed by deposition of copper within Descemet's membrane. In hepatic presentations it is seen in 33%-86% of patients . In the present study, K-F ring was found in 83.3% of WD cases by slit lamp eye examination. A similar observation had also been made by Muller , de Bem and Rukonuzzaman . They found K-F ring in their studies in 47%, 55.6% and 76% cases respectively.[7,11]

In paediatric population value of urinary copper after penicillamine challenge equal or above 1200 µg/day is also considered as diagnostic of WD (Carey and Balistreri, 2008). It was found that lowering the cut-off value of urinary copper excretion after penicillamine challenge from >1600 µg /day to ≥1200 µg /day, sensitivity increased by 20% (Muller et el., 2007).[11,12]

In a study at BSMMU, Bangladesh, it was found that for diagnosis of WD lowering the cut-off value of urinary copper excretion after penicillamine challenge from>1600µgm/day to 1200µg/day, positive result was increased from 70% to 86.7% (Majumder et al., 2011).[13,14]

Conclusion

Wilson disease should be considered in differential diagnosis of chronic liver diseases, prolonged hypertransaminasemia, and degenerative brain disorders of unknown origin. This report presents the clinical manifestations and laboratory findings of WD in children and underlines the importance of early diagnosis for positive clinical progress. In our study, it has been shown that WD diagnosis and follow up preserved the value of classical diagnostic methods .For early detection and treatment any children with liver injury of unknown etiology should be screened for Wilson Disease.

Table-1: Age distribution of the studied patients (N=30)

Age range (year)	(n=30) No. (%)	p value
<5	2 (6.66)	
5-10	20 (66.67)	
11-15	8 (26.67)	0.82^{NS}
>15	0	
Mean ±SD	8.9 ±2.78	

n=No of patients, NS = Not significant

Table-2: Different Presentation of Wilson's Disease(n=30)

Clinical presentation	No of patients	percent
Chronic liver disease	16	53.3
Acute Hepatitis	3	10
Acute liver failure	3	10
Family screening	2	6
NeurologicManifestation	1	3
Acute pancreatitis	1	3
HBsAg(+)ve	1	3
Arthopathy	1	3
Acute post-steptococcal Glomerulonephritis	1	3
B-Thalasamia trait	1	3

Table-3: Biochemical parameters of the patients with Wilson's disease (N=30)

Investigation	Frequency	Percent
Serum ALT		
Normal(Upto 65U/l)	8	26.67
66-100	11	36.61
101-400	8	26.67
>400	3	10
Serum Bilirubin(mg/dl)		
<2	7	23
2-10	17	56.67
>10	6	20
Prothombin Time		
Normal	12	40
Prolonged	18	60
Serum Albumin(35-55g/l)		
Normal	4	13.34
Reduced	26	86.64
Haemoglobin		
<6	1	10
6-9	2	36.67
>9	18	60

Studied patients (n=30)

Table-4: K-F Ring, Serum Ceruloplasmin & D-penicillamine Challenge Test (n=30)

Diagnostic Test	Interpretetion	percentage	P value
K-F Ring	Present	25(83)	**0.00[s]**
Serum Ceruloplasmin	≤20mg/dl	28(93.3)	**0.000[S]**
Urinary copper excretion after penicillamine challenge µg/24h	**(Median range)** 1262-195000	3626.5	**<.001[s]**

n=No of patient, S=significant

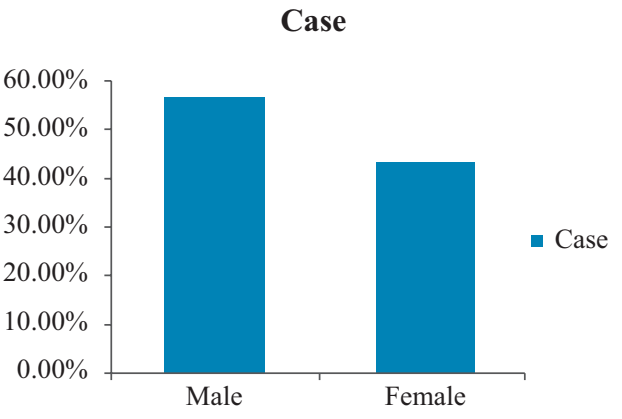

Figure 1: Sex distribution of the studied patients (n=30)

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