SPECTRUM OF WILSON'S DISEASE IN CHILDREN ADMITTED WITH LIVER DISEASE IN A TERTIARY CARE HOSPITAL OF BANGLADESH

Rifat Jahan[1*] Salina Hoque[1] Bazlur Rahman[2] Asma Ferdousi[1] Mitra Datta[1] A.S.M. Bazlul Karim[3]

Abstract

Background: Wilson Disease (WD) is a rare genetic disorder found in children and high index of suspicion is needed to screen for such diseases in any child presents with liver diseases after the age of 5 years. This study was aimed to find out the frequency and profile of WD in children admitted with liver diseases at a tertiary care hospital of Bangladesh.

Materials and methods: This cross sectional descriptive study was carried out at the Department of Paediatric Gastroenterology and Nutrition, BSMMU in 166 consecutively admitted children with predominant liver diseases aged 3-14 years. Diagnosis of WD was considered as presence of two of the following 3 criteria: i) Presence of Keyser-Fleischer ring by slit lamp examination. ii) Low serum ceruloplasmin level (<20mg/dl). iii) Urinary copper excretion of >1200 µgm /24 hours after D-penicillamine challenge.

Results: Most frequent liver disease was infective hepatitis (50%) followed by WD detected in 30 (18%) patients. Mean age of the cases of WD was 10.2 (±2.7) years with 66.7% male patients. The most common presenting features of WD cases were jaundice (53.3%).Twenty two (66.7%) patients present with purely hepatic and 10 (33.3%) with both hepatic and neurological manifestation. Low serum ceruloplasmin level was found in 66.7% and 24 hours urinary copper excretion of >1200 µgm/day was found in 86.7% cases.

Conclusion: WD was found to be common causes of liver disease next to infective hepatitis.

Key words : Wilson's Disease, Prevalence, Liver disease, Children.

Introduction

Wilson's Disease (WD)-a rare autosomal recessive disorder of copper metabolism is first described in 1912 by Kinnear Wilson.[1] The condition is characterized by excessive deposition of copper in liver, brain and other tissues. The accumulation of copper in liver is toxic and may lead to hepatitis, fulminant hepatic failure, cirrhosis and death.[2]

The worldwide prevalence of WD is estimated to be 1 in 30,000 live births, a gene frequency of 0.58% and a carrier frequency of 1 in 86.[3] It is caused by mutation in the ATP7B gene encoding a copper transporter P-type ATPase, which results in decreased biliary copper excretion and diffuse accumulation of copper in liver. With increasing copper overload overtime, deposition of copper occurs in other organs such as nervous system, cornea, kidneys and heart.[4] The clinical presentation of WD varies widely, a typically hepatic form which presents in the first decade of life is followed by neurologic symptoms and psychiatric symptoms which usually presents after the age of 20 years.[5,6] Laboratory parameters such as low ceruloplasmin and elevated 24 hours urine copper and observation of KF rings in an ophthalmological examination carried out in combination direct toward the diagnosis.[4] Due to the lack of a single diagnostic test with adequate sensitivity, diagnosis should be based on the combination of clinical features, laboratory findings and the results of mutation analysis in a patient with liver and/or neuropsychiatric manifestations.[3]

Considering the rarity of disease, diagnosis has a great impact because a specific treatment of proven efficacy exists and without timely management, the disease is invariably fatal.[7-10] In Bangladesh, to the best of our knowledge, study on WD had been scarcely done so far. Moreover, limited studies are available that have described exclusively pediatric samples. Therefore this study was undertaken to find out the various presentations of WD in a group of Bangladeshi children suffering from liver diseases. Study findings are expected to increase the awareness of the clinician about the distribution of WD in pediatric age group in our setting.

1. Assistant Professor of Pediatric
Chittagong Medical College, Chattogram.
2. Associate Professor of Pediatric
Army Medical College, Chattogram.
3. Professor of Gastroenterology & Nutrition
Bangabandhu Sheikh Mujib Medical University (BSMMU) Dhaka.

***Correspondence:** **Dr. Rifat Jahan**
E-mail: rifat112381@gmail.com
Cell : 01825 86 69 69

Submitted on : 15.10.2020
Accepted on : 10.12.2020

Materials and methods

This descriptive study included a total of 166 consecutive patients of 3-14 years of age with liver diseases who got admitted at Department of Pediatric Gastroenterology and Nutrition, Bangabandhu Sheikh Mujib Medical University (BSMMU) Dhaka between October 2010 and March 2011. Very sick children were excluded from the study. Clinically a child presented with jaundice with or without hepatomegaly/ splenomegaly along with biochemical evidence of liver disease (Increased serum ALT) serum bilirubin and viral markers was selected for the study. A preseted data sheet was filled up by the researcher herself. Detailed medical and family history was taken. Thorough physical examination was conducted to assess the presence of jaundice, hepatosplenomegaly, ascites and signs of liver failure. Neurologic and psychiatric assessments were done.

The eye was examined by slit lamp for K-F ring by a single Ophthalmologist at BSMMU. Necessary investigations such as liver function tests, complete blood count with peripheral blood film etc were done. For the diagnosis of WD serum ceruloplasmin and 24 hours urinary copper estimation after penicillamine challenge were done. It was done by "Atomic absorption spectrophotometer" in the Atomic energy centre, Dhaka.

WD was diagnosed on the basis of the presence of at least two of the following criteria: presence of K-F rings, low serum ceruloplasmin level (20 mg/dL) and 24-hour urine copper excretion of >1200 μg/day.

Clinical manifestations of WD were defined as follows:

- Asymptomatic form: characterized by an absence of signs and symptoms of liver disease or of neurological or ophthalmological involvement, but with laboratory findings compatible with Wilson's disease.
- Acute, chronic and fulminant hepatic forms:

i) Acute hepatitis: Similar to acute viral hepatitis, with jaundice, choluria, hepatomegaly and increased aminotransferase levels

ii) Chronic hepatitis: Signs of portal hypertension, hepatomegaly, splenomegaly, elevated hepatic enzyme levels with or without jaundice

iii) Fulminant hepatic failure: Clinical manifestations of acute hepatitis and encephalopathy up to 8 weeks after appearance of the clinical manifestations of liver disease

- Neurological form: characterized by neuropsychiatric symptoms such as altered behavior, psychoses, speech disorders and others.

Data were expressed as frequencies, means and standard deviations. To determine the association between age groups and presentation chi-square tests was used. Data were analyzed with SPSS-23. p value <0.05 was considered as statistical significant.

The study protocol was reviewed and approved by the Ethical Clearance Committee of BSMMU. Before data collection, informed written consent was taken from the legal relatives of the patients and assent from the patients where needed. Objectives, procedure, risks and benefits of participation in the study were included in the informed consent sheet.

Results

Out of 166 included children most frequent diagnosis was infective hepatitis (50%) followed by WD in 30 (18.1%) cases. Of 30 children with WD, 15 (50%) belonged to the age group of 5-10 years followed by 14 (46.7%) to age group of 10-14 years and only 1 (3.3%) children belonged to the age group of 3–5 years (Table I). The male-to-female ratio in the study population was 2:1 and the mean (±SD) age was 10.2 (±2.7) years (Table I).

Table I : Age and sex distribution of children with Wilson disease (n=30).

Age groups	Male	Female	Total
<5 years	1 (100)	0 (0)	1 (3.3)
5-10 years	10(66.6)	5(33.3)	15 (50.0)
>10 years	9 (64.3)	5 (35.7)	14 (46.7)
Total	20 (66.7)	10 (33.3)	30 (100)

Data were expressed as frequency (Percentage).

A total of 12 of 30 children had family history suggestive of WD. Consanguinity of parents was found in 16 (53.3%) cases, of which seven children were born to the 2nd degree consanguineous parents and nine children were born to the 3rd degree consanguineous parents. six patients (20%) had history of death of a family member from liver diseases. Jaundice and hepatomegaly was the commonest (53.3%) presentation in the patients followed by splenomegaly (40%) and ascites (40%). Twenty children (66.7%) were presented with purely hepatic and 10 (33.3%) with both hepatic and neurological manifestations. Elevated serum bilirubin was observed in 13 (43.3%) children

and prolonged prothrombin time in 4 (13.3%) children. The mean (±SD) value of 24 hours urinary copper excretion (after penicillamine challenge) and was 1998.13 (± 643.21) µg/day and serum ceruloplasmin was 14.01 (±3.97) mg/dL respectively. Low serum ceruloplasmin level was found in 66.7% and 24 hours urinary copper excretion of >1200 µgm/day was found in 86.7% cases (Table II).

Table II : Clinical characteristics of children with Wilson disease (n=30).

Characteristics	Frequency (%)/Mean (±SD)
Consanguineous parents	16 (53.3)
Presence of affected siblings	12 (40.0)
H/O death of family member from liver disease	6 (20.0)
Examination findings	
Jaundice	16 (53.3)
Hepatomegaly	16 (53.3)
Splenomegaly	12 (40.0)
Ascites	12 (40.0)
Type of presentation	
Hepatic	20 (66.7)
Hepatic and Neurological	10 (33.3)
Laboratory findings	
Elevated serum bilirubin	13 (43.3)
Prolonged prothrombin time	4 (13.3)
24 hrs urinary copper estimation (µg/day)	1998.13 (± 643.21)
24 hrs urinary copper estimation >1200 µg/day	26 (86.7)
Serum ceruloplasmin (mg/dl)	14.01(±3.97)
Serum ceruloplasmin < 20mg/dl	20 (66.7)

Out of 30 patients with WD, 20 (66.7%) presented with features of chronic liver disease, 7 (23.3%) with the features of acute hepatitis and only 3 (10%) present with the features of fulminant hepatic failure (Fig-1).

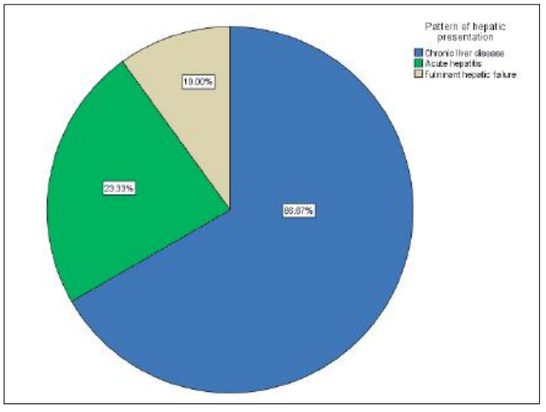

Fig 1: Pattern of hepatic presentation in the children with Wilson disease (n=30).

Among the children with Hepatic presentation,13 (65%) belonged to the age group of 5-10 years followed by 6 (30%) in 10–14 years and 1 (5%) in 3–5 years of age group. Among the 10 children who presented with neurological symptoms in addition to hepatic symptoms, 8 (80%) belonged to the age group of 10–14 years and 2 (20%) in the age group of 5-10 years (Table III). It indicates that, neurological manifestation was observed in significantly higher age.

Table III : Age distribution between children with different presentations of WD (n=30).

Age groups	Hepatic (n=20)	Hepatic + Neurological (n=10)	p value
<5 years	1 (5.0)	0 (0)	
5-10 years	13 (65.0)	2 (20.0)	0.034*
>10 years	6 (30.0)	8 (80.0)	

Data are expressed as frequency (Percentage).*p value obtained from Chi-square test.

Discussion

WD is one of the rarer causes of liver disease in children. There are few studies that have described exclusively performed on pediatric samples and data regarding WD is in short supply from Bangladesh.[7-10] So, this study was a small initiative to determine the frequency and pattern of WD among the children admitted in BSMMU, a tertiary care center of Bangladesh. In this study 166 children aged between 3-14 years with liver diseases were investigated and among them 18.1% were found to have WD. This finding is in consensus with other studies.[11,12] A Study was done in Department of Paediatric Gastroenterology and Nutrition, BSMMU, Dhaka Wilson s disease was found in 31(43.7%) of 71 children among them chronic liver diseases were 18 (58%) acute hepatitis 6 919.4%) acute liver failure 6 (19.4%) and asymptomatic WD case was 1 (3.2%) about one third of children presented with liver diseases were diagnosed as Wilson"s disease.[13] However, our findings were considerably lower from other studies conducted in Bangladesh or other country like, Borotolotti et al from Italy reported out of 196 patients with CLD, WD was identified in only 3 (1.53%) patients.[14] Alom et al reported among total of 164 pediatric patient WD was identified in

4.3% cases.[15] Difference in the frequencies between studies was might be attributable to the sampling method and inclusion criteria. All of the above mentioned studies including the current one follow non probability sampling technique and it is not suitable for determining the prevalence.

Majority of the children (50%) with WD belonged to the age group of 5-10 years followed by 14 (46.7%) to age group of 10-14 years and only 1 (3.3%) children belonged to the age group of 3–5 years. The mean age of presentation in our study group was 10.2 years. Similar results were also noted in studies by Sánchez-Albisua et al (Mean age=9.8±3.4 years) Yüce et al (10.1±2.5 years), and Kalra et al (7.2 years)[16,8,17]. It is to be noted that, mean age depend on the overall age range which significantly varies among studies.[8,16,17] The male children predominated in the current study with male to female ratio of 2:1 which was quite comparable with studies from India but European study on the other hand had shown a higher female predominance.[18-20] This could be due to society norm which pays higher attention to male children, which invariably increases the visits to hospital.

History of consanguinity was found in 53.3% of children. In other studies, it has been found consanguinity in 25.8% and 16.6% of studied population.[19,21] Family history suggestive of WD was noted in 12 (40%) children in the current study. Similarly, positive family history has been documented by other previous studies.[8,17,21] This correlation helps to confirm the genetic nature of disease.

Jaundice (70.5%) and hepatomegaly were the most common symptoms among the patients. Similarly, jaundice and abdominal distension were the predominant symptom noticed in studies done by Saito and Kalra et al whereas, abdominal pain (76.9%) was the predominant symptom in a study conducted by Yuce et al.[22,17,8] In terms of clinical presentations, hepatic form was most prevalent (66.7%) followed by combination of hepatic and neurologic presentation (33.3%). Other forms like hepatocerebral presentation or hemolytic anemia were not observed in this study. Similar records from the literature show, hepatic presentations as the most prevalent form in WD, except in one study by Kalra et al which showed predominance of hepatocerebal presentation.[22,23,17]

Chronic liver disease, (66.7%) was the commonest presentation of WD in the studied population. Other presentations were acute hepatitis (23.3%) and fulminant acute liver failure (10%). In a study of 55 cases of WD, 17 patients of them were presented with various form of chronic liver diseases and five with fulminant hepatitis.[24] Another study conducted at tertiary care hospital in Bangladesh in 32 WD children with hepatic presentation 65.6% presented with the features of chronic liver disease, 18.8% with fulminant hepatic failure, one with acute hepatitis and 12.5% with asymptomatic elevation of liver enzymes along with enlargement of liver and/or spleen.[25]

In the present study, prolonged prothrombin time was seen in 43.3% of children and bilirubin was elevated in 13.3% of children. Most of the children with combined hepatic and neurological presentation had a significant higher age compared to children with hepatic presentation alone. This is similar to the study of Riodan et al who have reported that, hepatic presentations were moiré common in the first decade of life and neurological presentations in second decade.[26]

Limitations

Small sample size and sample from a single tertiary care hospital and limited study period were some of the limiting factors of the current study, which might questioned its generalizability. For confirmation of WD hepatic copper estimation couldn't be done due to technological limitation.

Conclusions

WD was found to be the most common cause of liver disease in the studied children next to infective causes in this referral center. In the first decade of life hepatic presentation was the common presentation whereas neutrological manifestation was more common in second decade. The results of the present study emphasize the importance of screening the patients with liver and/or neuropsychiatric symptoms and carrying out specific tests to increase the sensitivity of diagnosis of suspected cases.

Recommendations

We further recommend conducting a study in larger population, in a multi-institution setup which will help us to draw conclusions. Further, assessment of genetic and molecular changes will definitely aid in confirmation of the disease.

Acknowledgments
It was a self funded study. The authors would like to thank all survey participants for their involvement, as well as the Physicians of Department of Paediatric Gastroenterology and Nutritionof BSMMU for their collaboration and cooperation.

Contribution of authors
RJ: Conception, design, data collection, analysis, manuscript drafting, final approval.
SH: Data collection, drafting & final approval.
BR: Data collection, drafting & final approval.
AF: Interpretation of data, critical revision & final approval.
MD: Data collection, analysis, drafting & final approval.
ASMBK: Conception interpretation of data, critical revision & final approval.

Disclosure
All the authors declared no competing interest.

References

1. Wilson SAK. Progressive lenticular degeneration: A familial nervous disease associated with cirrhosis of the liver. Brain. 1912;34(4):295-507.

2. Sokol RJ, Narkewicz MR. Copper and iron storage disorders. In: Suchy FJ, Sokol RJ, Balistreri WF, editors. Liver disease in children. Philadelphia: Lippincott Williams & Wilkins. 2001;595-640.

3. Manolaki N, Nikolopoulou G, Daikos GL, Panagiotakaki E Tzetis M, Roma E et al. Wilson disease in children: Analysis of 57 cases. J Pediatr Gastroenterol Nutr. 2009;48(1):72-77.

4. Roberts EA, Schilsky ML, Division of Gastroenterology and Nutrition, Hospital for Sick Children, Toronto, Ontario, Canada. A practice guideline on Wilson disease. Hepatology. 2003;37(6):1475-1492.

5. Socio SD, Ferreira AR, Fagundes ED, Roquete ML, Pimenta JR, Campos LF et al. Wilson's disease in children and adolescents: Diagnosis and treatment. Rev Paul Pediatr. 2010;28(2):134-140.

6. Cox DW, Robets EA, Wilson's disease. In: Feldman M, Scharschmidt BF, Sleisenger MH, editors. Gastrointestinal and Liver Disease. 6th ed. Philadelphia, PA: WB Saunders Company.1998. 1998;2(66):1104-1117.

7. Tissières P, Chevret L, Debray D, Devictor D. Fulminant Wilson's disease in children: Appraisal of a critical diagnosis. Pediatr Crit Care Med. 2003;4(3):338-343.

8. Yüce A, Koçak N, Demir H, Gürakan F, Ozen H, Saltik IN et al. Evaluation of diagnostic parameters of Wilson's disease in childhood. Indian J Gastroenterol. 2003;22(1):4-6.

9. Dhawan A, Taylor RM, Cheeseman P, De Silva P, Katsiyiannakis L, Mieli-Vergani G et al. Wilson's disease in children: 37-year experience and revised king's score for liver transplantation. Liver Transpl. 2005;11(4):441-448.

10. Arnon R, Calderon JF, Schilsky M, Emre S, Shneider BL. Wilson disease in children: Serum aminotransferases and urinary copper on triethylene tetramine dihydrochloride (Trientine) treatment. J Pediatr Gastroenterol Nutr. 2007;44(5):596-602.

11. Hanif M, Raza J, Qureshi H, Issani Z. Etiology of chronic liver disease in children. J Pak Med Assoc. 2004;54(3):119-122.

12. Malik M, Hussain M, Aslam M, Magbool S. Clinical Spectrum of Chronic Liver Disease in Pakistani Hospitalised Children. Pakistan Ped J. 2000;24:9–12.

13. Bayes F. Karim AB. Helaly L. Spectrum of Hepatic Presentation of Wilson's Disease in Children. Bangladesh J Child Health. 2014; 38(2) 79-85.

14. Bortolotti F, Calzia R, Vegnente A, Cadrobbi P, Rugge M Armigliato M et al. Chronic hepatitis in childhood: The spectrum of the disease. Gut.1988; 29(5):659–664.

15. Alam M, Ahmed F, Mobarak R, Arefin S, Tayab A, Tahera A, Mahmud S. Pattern of liver diseases in children admitted in Dhaka Shishu Hospital. IJH. 2010;1(3):18-24.

16. Sánchez-Albisua I, Garde T, Hierro L, Camarena C, Frauca E, de la Vega A et al. A high index of suspicion: The key to an early diagnosis of Wilson's disease in childhood. J Pediatr Gastroenterol Nutr. 1999;28(2):186-190.

17. Kalra V, Khurana D, Mittal R. Wilson's disease early onset and lessons from a Pediatric cohort in India. Indian Pediatr. 2000;37(6):595-601.

18. Taly AB, Prashanth LK, Sinha S. Wilson's disease: An Indian perspective. Neurol India. 2009; 57(5):528-540.

19. Sinha S, Jha DK, Sinha KK. Wilson's disease in Eastern India. J Assoc Physicians India. 2001;49:881-884.

20. Merle U, Schaefer M, Ferenci P, Stremmel W. Clinical presentation, diagnosis and long-term outcome of Wilson's disease: A cohort study. Gut. 2007; 56(1):115-120.

21. Ansari R, Malekzadeh R, Ebrahimi-Daryani N, Mirdamadi MJ, Sohrabi MR. A prospective study of the clinical and paraclinical features of Wilson's disease in Iran. Archives of Iranian Medicine. 2000;3(3):119-123.

22. Saito T. Presenting symptoms and natural history of Wilson disease. Eur J Pediatr. 1987;146(3): 261-265.

23. Gow PJ, Smallwood RA, Angus PW, Smith AL, Wall AJ, Sewell RB et al. Diagnosis of Wilson's disease: An experience over three decades. Gut. 2000;46(3):415-419.

24. Steindl P, Ferenci P, Dienes H P, Grimm G, Paringer I, Madl C et al. Wilson's disease in patients presenting with liver disease : A Diagnostic challenge. Gastroenterology. 1997; 113(1): 212-218.

25. Karim MB, Rahman MM, Islam MS. Wilson's Disease with Hepatic Presentation in Childhood. Mymensing Med J. 2007; 16: 29-32.

26. Riordan SM, Williams R. The Wilson's disease gene and phenotypic diversity. J Hepatol. 2001;34(1):165-1671.