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A Study on Frequency of Renal Impairments in Wilson's disease among Children Attending at a Tertiary Care Hospital

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Abstract **Original Research Article**

***Background*:** Wilson disease (WD) is a rare autosomal recessive disorder of copper metabolism that leads to hepatic, neurological, psychiatric, and renal complications. Early diagnosis is crucial, as timely treatment can prevent severe organ damage. Although renal involvement in WD is less common, its increasing prevalence necessitates further investigation. The prevalence and spectrum of renal manifestations in Bangladeshi children with WD remain unknown. This study aims to evaluate the pretreatment renal impairments in children diagnosed with WD. ***Objective*:** To assess renal impairments before treatment initiation in children with Wilson's disease. ***Methods*:** This cross-sectional observational study was conducted in the Department of Pediatric Gastroenterology and Nutrition at Bangabandhu Sheikh Mujib Medical University from January to December 2021. A total of 36 children (both sexes, aged ≤18 years) diagnosed with WD were included. Informed written consent was obtained from parents or caregivers. Clinical, biochemical, and radiological parameters were analyzed using SPSS 20.0. ***Results*:** Among the 36 cases, 64% were male, with a predominant age range of 5–10 years. Renal impairment was observed in 19.4% of cases. The most common presenting feature was jaundice (58.3%), followed by a family history of liver disease (47%) and parental consanguinity (36%). Renal manifestations included proteinuria (55.6%), hematuria (44.5%), and bilateral pedal edema (30.6%). Hepatomegaly (69.4%), splenomegaly (63.9%), and ascites (66.7%) were frequently noted. Biochemical analysis revealed elevated serum ALT, prolonged INR, and hypoalbuminemia, indicating hepatic dysfunction. The mean hemoglobin level was low (10.09±1.38 g/dL), with Coombs-negative hemolytic anemia. Renal function tests showed elevated serum creatinine in 22.2% of cases. Urinalysis detected RBCs in 44.4% and urinary albumin in 55.6% of cases, with significant RBC (>10/HPF) in two cases and significant proteinuria in one case. Glycosuria was detected in 19.4% of cases. Ultrasonography in 24 cases revealed increased renal cortical echogenicity in two cases, an early indicator of renal involvement. ***Conclusion*:** Renal impairments, including proteinuria, hematuria, elevated serum creatinine, and edema, were observed in 19.4% of children with WD. These findings suggest that renal involvement in WD is not uncommon in the pediatric population and should be considered during disease evaluation.

Keywords: Wilson's Disease, Renal Impairment, Pediatric Nephrology, Hepatolenticular Degeneration, Kidney Dysfunction, Copper Toxicity.

INTRODUCTION

Wilson disease (WD) is an inherited, autosomal recessive, copper accumulation disorder that can affects one in 30,000 people [1]. Recently The World Health Organization has announced the global prevalence of WD is one in 10,000 to one in 30,000 people. In WD, mutations within ATP7B gene (chromosome 13q) which encodes an ATP-driven Cu transporter protein named ATP7B, is responsible for the pathogenesis [2]. It has been found that due to an excessive accumulation of copper in various organs, like liver, brain, cornea, kidneys and other tissues, patients present with different clinical manifestations. During the disease process, renal impairment can occur at any stage, the mechanism of which is unknown. It has been found that deposition of copper occurred in the epithelium of proximal and distal

convoluted tubules in WD patients [3]. Renal presentations in WD are found in only 1% case [4], usual presentation can be renal insufficiency with fulminant hepatic failure and hemolysis [5]. Though the percentage of the renal manifestations of Wilson disease are less in number, but the outcome can be fatal if not diagnosed and treated properly. Recently in one study done at Bangabandhu Sheikh Mujib Medical University (BSMMU) where 63% of the children were diagnosed as WD out of 62 cases of acute liver failure [6] and another study shows hepatic manifestation of WD were 76% among the hundred WD diagnosed cases [7]. From the above mentioned studies it has been shown that there are a good number of children are now suffering from WD. But in Bangladesh there is no documentation about the prevalence of renal involvement of WD so far. Daily,1.5 -5 mg Cu is taken with our normal diet, 50-60% of which remained unabsorbed and excreted by feces, rest 25-40% is absorbed from duodenum and bound to metallothionines (non-toxic form) within enterocytes. From this pool, 75% goes to portal system with albumin or transcuprein and taken up by the liver. Then remaining 25% is bound to albumin in circulation [8]. In hepatocytes, ATP7B protein allows Cu to enter the trans-Golgi network for incorporation into poceruloplasmin (apo-Cp) to form ceruloplasmin (holo-Cp) and regulates copper exocytosis into the bile duct which is 20% of Cu enter into liver [9]. In absence of controlled regulation of Cu exocytosis, Cu accumulates in cells and induces widespread free radical mediated damages, causes hepatocyte apoptosis and liberation of toxic free Cu in the blood. Toxic free Cu affects the brain, eyes, skeleton and rarely heart [10]. Renal tubular injury (8%) occurs due to the deposition of copper in epithelium of proximal and distal convoluted tubules and glomerular injury (10%) is found in [11]. Tubular injuries can be manifested as nephrocalcinosis (microscopic hematuria) and nephrolithiasis (renal colic). Glomerular injury can be seen due to the mesangial deposition of copper [12]. This is the reason, children present with the features of Wilsons disease should be screened for renal tubular dysfunctions. A routine urine examination and microscopy should be done at the time of diagnosis, while on follow up after starting treatment, proteinuria should be assessed to detect drug mediated glomerular injury. A combination of serum ceruloplasmin, KF rings, and 24-hour urine copper is most commonly used to diagnose WD. A diagnostic score based on available tests was proposed at 8th International meeting on Wilson`s disease in Leipzig on 2001 [13]. And researchers found the scoring system as a good diagnostic tool for WD [14].

OBJECTIVES

General objectives: To observe the pretreatment renal impairments in children with Wilson's disease.

Specific objectives:

- To see the clinical spectrum of renal manifestations of Wilson's disease in children.
- To document the blood urea nitrogen (BUN), serum creatinine level, hyperkalemia and to observe the proteinuria, hematuria and glycosuria in children having renal manifestations of WD.

METHOD MARTIALS

Study Design: Cross-sectional observational study.

Place of Study: Department of Pediatric Gastroenterology and Nutrition, Department of Pediatric Neurology and Neurodevelopment BSMMU, Dhaka, Bangladesh.

Period of Study: After receiving clearance from Institutional Review Board, the study was conducted From January 2021 through December 2021.

Study Population: Children diagnosed as Wilson's disease were studied population.

Inclusion Criteria: Children of either gender, age 2- 18 years diagnosed as Wilson's disease. Children fulfilled the diagnosis criteria of modified Leipzig score. Family member of Wilson's disease fulfilled the criteria.

Exclusion Criteria: Any other co-morbid conditions (like coma, shock) at the time of diagnosis.
Patients on penicillamine treatment.

Study Procedure: Patients aged 2 to 18 years who attended the Department of Pediatric Gastroenterology and Nutrition, BSMMU, and met the modified Leipzig score criteria at or after admission were enrolled. Informed written consent was obtained from parents or legal guardians after explaining the study objectives and ensuring patient safety. Data were collected using a structured sheet, covering case history, physical examination, and laboratory findings. History included jaundice, hematemesis, melena, hematuria, proteinuria, ascites, neurological signs, encephalopathy, coagulopathy, drug history, consanguinity, family history of liver diseases, Wilson's disease, and hepatitis B vaccination. Physical examination focused on renal impairment (edema, hemolysis, puffy face), stigmata of chronic liver disease (spider angioma, palmar erythema, muscle wasting), and other relevant signs. A slit-lamp examination for Kayser-Fleischer (K-F) ring was performed by a single ophthalmologist to aid in the diagnosis of Wilson's disease.

Statistical Analysis: After collection, data was checked manually and statistical analysis was done using computer-base program Statistical Package of Social Science (SPSS) version 20 for Windows.

Data Analysis: The data of different biochemical and serological tests and presenting clinical features were examined and statistical significance were determined by Chisquared test and paired Student's t-test. P values <0.05 was considered statistically Significant.

Ethical Consideration: Prior to the study, the thesis protocol was reviewed and approved by the Institutional Review Board of BSMMU, Dhaka. Ethical considerations were thoroughly discussed with parents, who were informed in their local language about the study's purpose, procedures, risks, and benefits. Participation was voluntary, with the right to withdraw at any time. Written consent was obtained from parents or legal guardians. Measures were taken to prevent harm or treatment delays. Data confidentiality was strictly maintained, accessible only to the researcher and regulatory authorities. No compensation was provided for loss of work time.

RESULTS

This study was carried on 36 patients. Table I shows that most of the patients (50%), were within the age range of five to ten years in this study. The next common age group was ten years and above and total 17 (47.2 %) patients were enrolled in this age group. Below five years of age patients were found less in number (2.8 %).

Table I: Age distribution of the studied cases (n=36)

Age in years	Frequency	Percent
<5	1	2.8
5-10	18	50.0
>10	17	47.2

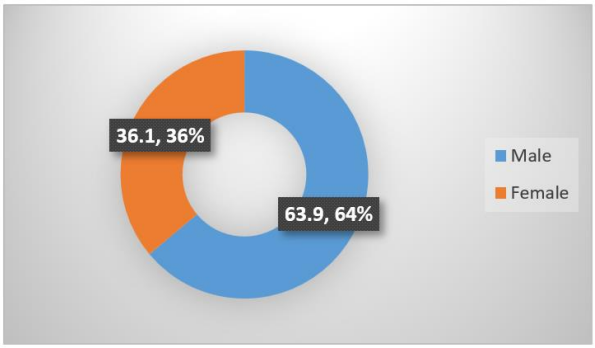

Figure 1: Sex distribution of the studied patients (n=36)

Figure 1 showed that, the sex distribution of the studied patients out of thirty six WD cases, majority were male 23 (64%). Female were less in number. The male and female ratio was 1.76: 1.

Table II: Consanguinity status of the studied patients (n=36)

Consanguinity	No. of patients	Percent
Present	13	36.1
Absent	23	63.9

Table II presented that most of the patients 23 (63.9%) did not give any history of consanguineous marriage. Consanguinity was present in 13 (36.1 %) cases in this studied population.

Table III: Presenting history of the studied cases (n=36)

Variable	n	%
Blood and blood products transfusion	8	77.8
Past H/O jaundice	15	41.7
Hepatitis B vaccination	36	100
Presenting complaint of jaundice	21	58.3
Hematemesis, melena	6	16.7
Presence of any sign (other than neurological encephalopathy)	9	25

Table III showed most of the cases (21, 58.3%) presented with the complaint of jaundice which is the early presenting feature of WD. Among the other features previous history of jaundice (15, 41.7%) were significantly common.

Table IV: Presenting clinical features of renal impairments of WD (n=36)

Variables	n	%
Hematuria	1	2.8
Proteinuria	3	8.3
Oedema	11	30.6

Table IV presented the studied patients were presented with hematuria, proteinuria and bilateral paedal oedema. Majority of the cases presented with oedema (11, 30.6%).

Table V: Presenting signs of the studied cases (n=36)

Variable	Total (N=36)	
	n	%
Jaundice	24	66.7
Skin and mucous membrane bleeding	6	16.7
Ascites	24	66.7
Hepatomegaly	25	69.4
Splenomegaly	23	63.9
Encephalopathy	8	22.2
K-F ring	27	75

Table V presented on examination hepatomegaly (25, 69.4%), splenomegaly (23, 63.9%) and ascites (24, 66.7%) were common findings among studied cases. On slit lamp examination of eyes K-F ring was found in 27(75%) cases.

Table VI: Biochemical parameters of the studied patients (n=36)

Variable	Total (n=36)
	Mean ± SD
Serum bilirubin (mg/dl)	1.39 ± 0.498
Serum ALT (U/L)	125 ± 101.999
Serum Albumin (g/ dl)	27.72 ± 9.489
BUN (mg/dl)	10.97 ± 5.091

Table VI presented Serum ALT was found two fold raised of the upper limits among the studied population. Serum albumin was found low as an indicator of impaired liver function. Serum bilirubin was not significantly increased in studied patients.

Table VII: Hematological parameter of the studied patients (n=36).

Variable	Total (N=36)		Mean ± SD
	n	%	
Hb (9-12 gm/dl)	22	61.1	10.09±1.38
Coomb's test negative	36	100	
INR >1.25	25	69.4	2.09±0.94

Table VII shown the mean ± SD value of hemoglobin (Hb) was 10.09 ± 1.38 gm/dL. Hemoglobin level was found low in the WD cases. Coombs test was negative in all the cases. Prothrombin time, INR >1.25 sec of control was considered prolong. The mean ± SD value of INR of studied patients was 2.09 ± 0.94.

Table VIII: Distribution of renal function among studied population (n=36)

Variable	n	%	Mean ± SD
Serum Creatinine (> 1mg/dl)	8	22.2	0.86 ± 0.24
Serum Electrolytes			
Na+ (135-145) mmol/l	30	83.3	
K+ (3.5-5.1) mmol/l Hco3- (20-31) mmol/l	31	86.1	
Benedict test			
a. Blue	29	80.6	
b. Green	7	19.4	

Table VIII presented the serum creatinine was significantly raised in 8 (22.2%) cases. Urinary sugar was detected by Benedict test in 7 (19.4%) cases.

Table IX: Urine routine microscopic examination findings of studied population (n=36)

Variable		n	%
Urine R/M/E			
1. Red blood cells	Absent	20	55.5
	Present	16	44.5
	(1-10) cells/ HPF	14	38.9
	> 10 / HPF	2	5.6
2. Urine Albumin	Present	20	55.6
	(+)	15	41.7
	(++)	4	11.1
	(+++)	1	2.8

Table IX shown the red blood cells in urine were found significant amount (>10/ HPF) in 2 cases (5.6%). Urine albumin was found in 20 cases (55.6 %). Significant amount was found in one case (2.8%).

Table X: Radio imaging findings of the studied population (n=36).

Variable	n	Percent
Plain X-ray abdomen done	12	33.3
1. Renal calculi	Not found	
USG of whole abdomen done	22	38.9
1. Hepatospenomegaly	8	22.2
2. Hepatospenimegaly with ascites	12	33.3
3. Increased renal cortical ecogenicity	2	5.6

Table X presented the plain X-ray abdomen was done in 12 cases (33.3 %). Findings were normal and there were no suggestive features of presence of renal calculi. Ultrasonogram of whole abdomen was done in 22 cases (61.1 %) and there were suggestive features of renal involvements in 2 cases (5.6%) in the studied population.

DISCUSSION

Wilson disease (WD) is an inherited autosomal recessive disease of copper metabolism where mutations in the copper-transporting ATPase ATP7B, responsible for biliary excretion of copper. During the course of the disease copper accumulates excessively in varies organs, mostly in the liver, brain, and eye [15]. WD may present with a variety of clinical features, including various liver disease, ophthalmologic manifestations, neurologic disorders, neuropsychiatric symptoms, osteoarthritis, renal tubular dysfunction, and cardiomyopathy [16, 17]. With the availability of diagnostic facilities more and more cases of WD are diagnosed now a days. The incidence and prevalence of WD is also increasing during the past decay [18]. Few number of studies have been done so far on Wilson's disease in children in Bangladesh, unfortunately other presentations of this disease, other than hepatic and neurological manifestations, was not done. So, this study was done to see the frequency of renal impairments at diagnosis of Wilson's disease in children. The result of this study could be helpful to identify the pretreatment renal complications of this disease, so patients will benefit from this by getting treated with less nephrotoxic drugs. In this study 36 children aged between 2-18 years, diagnosed as Wilson's disease were investigated to see the frequency of renal impairments among them. An attempt was also made to find out the different renal presentations of Wilson's disease in children. With limited facilities and resources renal impairments of WD was diagnosed in this study on the basis of presence of any of the followings: (i) Abnormal urinalysis results (proteinuria or hematuria) (ii) Tubular dysfunction (glucosuria, hypercalcinuria) (iii) Abnormal renal function (BUN > 23 mg/dL, S. Creatinine > 1 mg/L) (iv) Abnormal renal ultrasound (v) Excluding renal involvement caused by other factors. In this study out of thirty six children with Wilson's disease 7 patients (19.4 %) had renal impairments. In a study done had found different presentation of renal impairment in 25 cases (29.4%) out of 34 studied population with WD [3]. In this study, most of the cases (50%) presented between 510 years age group. The youngest patient presented with WD was a five year old girl in this study. A study had found youngest case a 3.5 years old boy during family screening in their study with WD in Bangladesh [19, 20]. Another study found an eight years old child as an early presentation in their study. Twenty one children (58.3%) cases presented with jaundice as hepatic presentation and 9 cases (25%) had mixed picture of both hepatic and neurological features of WD in studied population [20]. Both the cases, features of chronic liver disease (CLD) were more prominent and physical findings of hepatomegaly (69.4%), splenomegaly (63.9%) and ascites (66.7%) were found supportive evidence of CLD

among the studied cases. Similar findings were also found by [21] where 69% of cases had only hepatic presentation and 14% cases had both neurological and hepatic features. During this study period five children were diagnosed as WD during family screening. Among them two sibs from a consanguineous parents had the features of asymptomatic nephritis. Their effected brother presented with neurological features of WD and developed acute renal failure shortly after starting treatment with penicillamine [22] had found approximately 10% asymptomatic children with WD during family screening. Among the studied population 17 cases (47%) had family H/O WD. In the present study eight patients (36%) were from consanguinal marriage. Another study had also found risk of occurrence of WD increased in consanguineous families [23]. This study showed male predominance in the sex distribution where the majority were male (64%). The male and female ratio was 1.76: 1. Male predominance in WD was also found in the study done [18]. Eleven out of 16 patients were found to be male in that study.

In the studied population hematuria (2.8%), proteinuria (8.3%) and bilateral paedal oedema (30.6%) were found as early features of nephritis. Bilateral paedal oedema was found more in numbers may be due to the common presentation of CLD in this study. Study found pitting oedema and abdominal distention, on examination hematuria (mainly microscopic), proteinuria as common features among 25 cases with renal impairments in WD [3]. In this study, two fold raised of Serum ALT of the upper limits, low level of Serum albumin were indicators of impaired liver function in CLD. In this study the mean value of Hb was found low, 10.09±1.38 gm/dl and Coomb`s test was negative in all the studied cases. Coomb`s negative hemolytic anemia is the feature of WD [24] found similar result in his study where anaemia was in 52 patients (94.54%). The mean value of INR of the studied patients was prolonged (2.09±0.94) which reflected the impaired liver function in CLD. A study also found prolonged PT (>4 sec of control) in 49 (89.09%) cases [24]. During evaluation of renal function, Serum creatinine was found raised in 8 cases (22.2%), urine routine microscopic examination showed presence of significant RBC in two case (5.6%) and urinary albumin was found in one case (2.8%). Urinary sugar was found in 7 cases (19.4%). In this study, it was evident that the raised serum creatine level, microscopic hematurea and proteinuria along with ultrasonogram evaluation of renal system can be helpful to diagnose early renal impairments at presentations of WD in Bangladeshi children. In near future more studies can be done to get more information regarding this topic. It will be beneficial for the health care providers for taking appropriate measurements and better outcome of the patients with this Disease.

Limitation of The Study: The sample size of the study was small regarding the population. Time and resources were limited. Study done at a single center, where there is chance of accumulation of rare diseases.

CONCLUSION

In this study renal impairments was found in 7 (19.4 %) of the cases of Wilson's diseases. So, renal impairment in Wilson's disease is not an uncommon in Bangladeshi children. Biochemical tests and ultra-sonogram findings are found to be reliable along with supportive clinical findings to diagnose the renal impairements in Wilson`s Disease in children.

Recommendation: Although this study revealed some clinical and biochemical features of renal impairments of Wilson's disease in children, further studies for a longer duration and large number of cases can be carried out to see the real picture of prevalence of renal impairments in WD in Bangladesh. Greater awareness needs to be created about renal impairments of Wilson's disease in children at diagnosis. So that the drug induced renal complications as well as organ damage by the disease itself can be prevented by early interventions.

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