



WILSON DISEASE IN CHILDREN; FREQUENCY AND COMPARISON WITH NON-WILSON ETIOLOGY OF LIVER DISEASES.

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ABSTRACT: Objectives: The primary objective was to determine the frequency of Wilson disease; its clinical, biochemical features and outcome. The secondary objective was to compare children diagnosed with Wilson disease to those with non – Wilson etiology. **Study Design:** A comparative cross-sectional hospital-based study. **Setting:** Department of Pediatric Medicine Nishtar Hospital Multan. **Period:** From January 2017 to December 2017. **Material & Methods:** Children age 1 – 15 years presenting with hepatic manifestations (jaundice, bleeding, ascites and encephalopathy) were included in the study. Final diagnosis, clinical and biochemical features along with outcome were noted. We calculated mean and standard deviation for continuous variables and frequency and percentages for categorical variable. **Results:** Total 84 children with hepatic manifestations were admitted during study period. Mean age was 7.21 years (\pm 3.21). Males comprised 63.1% (53/84) of the study population. Wilson disease was diagnosed in 27 (32.14%) patients. Infective etiologies included Hepatitis A, B, C and E. Most common clinical presentation was that of chronic liver disease in 58.3% (49/84). Most common sign and symptom was Jaundice (97.6%). Mean age was higher in children with Wilson disease compared to non – Wilson group (9.3 vs. 6.2). Mean serum ceruloplasmin in children with Wilson disease was 15.93 mg/dl (\pm 4.66) whereas mean urinary copper (μ g/24 hr.) before and after Vistamine challenge were 131.1 (\pm 47.66) and 1250.4 (\pm 194.43). Kayser – Fleischer rings were present in 11 (40.74%) children with Wilson disease. Mortality rate was 7.1 % (6/84) in study population and 11.1% (3/27) in children with Wilson disease. **Conclusion:** Wilson disease is not an infrequent diagnosis in our setup but has multiple masquerading presentations. A high index of suspicion is required to consider and investigate for Wilson disease as a possible and the treatable cause of hepatic manifestations.

Key words: Ceruloplasmin, Kayser – Fleischer Rings, Wilson Disease.

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INTRODUCTION

Wilson disease (also called Hepatolenticular degeneration) is an uncommon metabolic – genetic disorder of copper metabolism having autosomal recessive inheritance pattern. It has an incidence of 1/5,000 to 1/100,000. The excess deposition of copper in brain, liver, kidneys and other body organs is the underlying defect. The physiological process involved is increased copper absorption from small intestine but decreased excretion by liver.¹ The long arm of chromosome 13 carries the ATP7B gene which is responsible for copper transporting adenosine triphosphatase (ATPase) protein synthesis in the liver.² In the first decade of life patients present

with liver disease. However, neuropsychiatric manifestations dominate during the second of decade.³

The hepatic form of Wilson disease may present with acute hepatitis, cirrhosis (chronic liver disease) or acute liver failure. The acute hepatitis presentation can't be differentiated from acute viral hepatitis, except the negative viral serology. Recurrent episodes of acute hepatitis due to Wilson disease leads to misdiagnosis of chronic active hepatitis. Copper released from dead hepatocytes causes red blood cell hemolysis, giving a picture of Coomb's negative hemolytic anemia.⁴

Copper deposition in brain predominantly occurs in basal ganglia that help coordinate body movements. Thus, it is classified as a movement disorder. It manifests as slurred speech, tremors and dystonia. Dystonia may lead to facial abnormalities, including difficulty with muscles of the mouth area, which often leads to drooling. Later dystonia in the neck, back, or extremities may lead to pain and abnormal positions. Disturbed co-ordination is a frequent problem, and handwriting suffers, often leading to micrographia. Gait may be abnormal, and patients may be clumsy in walking. Dysphagia is not uncommon.^{5,6}

The study was carried out with the aim to establish various hepatic manifestations of Wilson disease, its biochemical features and outcome and its comparison with non- Wilson etiology. This will help pediatrician in early appreciation of the disease, quick diagnosis and timely treatment of the disorder.

MATERIAL AND METHODS

This hospital based comparative cross-sectional study was carried out at Department of Pediatric Medicine Nishtar Hospital Multan over a period of one year (January - December 2015) after approval from Institutional Ethical Review Committee. Children age 1-15 years, admitted through outpatient department (OPD) or emergency, presenting with hepatic manifestations i.e. jaundice, bleeding, ascites, encephalopathy were enrolled in the study after written informed consent was given by parents / guardian. Previously diagnosed children of liver disease with acute decompensation, tuberculosis, malignancy and glycogen storage disorders were excluded.

The laboratory investigations included liver function tests, viral serology (Hepatitis A, B, C and E), serum ceruloplasmin, 24 – hour urinary copper pre – and post D – penicillamine challenge and slit lamp examination for Kayser – Fleischer rings. Liver biopsy for copper content is invasive procedure and genetic mutation analysis is expensive and were not available for the diagnosis of Wilson Disease. The diagnosis

of Wilson Disease was made on the score of 4 or more using the scoring system developed at the 8th International Meeting on Wilson's disease, Leipzig 2001⁷ Table-I. The demographic (age, gender), clinical (duration of illness, sign and symptoms, clinical presentation) and laboratory data were recorded on performa specifically designed for the study. The outcome in our study included discharged, referred and expired. The data obtained were entered and analyzed in the Statistical Package for Social Sciences (SPSS Version 20 software). We calculated mean and standard deviation (median and interquartile range where applicable) for continuous variables and frequency and percentage for qualitative variables. P-value of ≤ 0.05 is taken as significant. The results are shown in the form of tables and figures.

RESULTS

Wilson disease was diagnosed in 27 (32.14 %) patients out of 84 children with hepatic manifestations admitted during the study period. Other etiologies included Hepatitis A 17 (20.24%), Hepatitis B 23 (27.38%), Hepatitis C 7 (8.33%) and Hepatitis E in 10 (11.9%) patients (Figure-1). Males constituted 63.1% of the study population. Mean age was 7.21 years (± 3.25). Age distribution showed 54.7% of the study population was 5 – 10 years of age. Median duration of illness was 3 weeks (IQR – 5). Clinical presentation was that of chronic liver disease in 58.3% (49/84), acute hepatitis 34.5 % (29/84) and acute fulminant hepatic failure 7.1 % (6/84) (Table-II). The presenting symptoms were jaundice (also as clinical sign) in 82 (97.6 %), bleeding in 69 (82.1%) and encephalopathy in 45 (53.6%). Common clinical signs observed were hepatomegaly in 39 (46.4 %), splenomegaly in 44 (52.4 %) and ascites in 41 (48.8 %) patients (Figure-2). When compared with non-Wilson group, children with Wilson disease were older (9.3 vs. 6.2 years), higher in age group ≥ 5 years (96 % vs. 58 %), had prolonged duration of illness (4 weeks vs. 2), higher percentage presented with chronic liver disease (85 % vs. 45 %) and more cases were discharged and expired (88.89 % and 11.11 % vs. 49.12 % and 5.26 %) and were statistically significant (Table-III).

Symptom	Score	Symptom	Score
KF – rings		Neurologic symptoms	
Present	2	Severe	2
Absent	0	Mild	1
		Absent	0
Serum ceruloplasmin		Liver copper	
Normal (>0.2 g/L)	0	>5x ULN (>4 μmol/g)	2
0.1-0.2 g/L	1	0.8-4 μmol/g	1
<0.1 g/L	2	Normal (<0.8 μmol/g)	-1
Coombs-negative hemolytic anemia		Urinary copper	
Present	1	Normal	0
Absent	0	1-2x ULN	1
		>2x ULN	2
		Normal, but >5x ULN after D-penicillamine	2
Mutation analysis			
On both chromosomes detected	4		
On 1 chromosome detected	1		
No mutations detected	0		
TOTAL SCORE Evaluation:			
4 or more Diagnosis established			
3 Diagnosis possible, more tests needed			
2 or less Diagnosis very unlikely			

Table-I. Scoring system developed at the 8th International Meeting on Wilson's disease, Leipzig 2001 (7).

Age (years, mean ± SD)	7.21 ± 3.21
Age distribution	
< 5 years	25 (29.8 %)
5 – 10 years	46 (54.7%)
> 10 years	13 (15.5 %)
Gender	
Male	53 (63.1 %)
Female	31 (36.9 %)
Duration of illness (in weeks) (median IQR)	3 (5)
Laboratory Investigations	
ALT (IU/ml)	467.56 ± 373.19
AST (IU/ml)	253.83 ± 207.88
Bilirubin (mg/dl)	7.26 ± 3.59
INR	2.8 ± 1.31
Albumin (g/L)	3.3 ± 1.28
Serum ceruloplasmin (n=27) (mg/dl)	15.93 ± 4.66
24 hr urinary copper excretion (n=27)	
Pre-vistamine challenge (μg/24 hr)	131.11 ± 47.66
Post- vistamine challenge (μg/24 hr)	1250.37 ± 194.43
Keyser – Fleisher rings	11 (40.74 %)
Clinical diagnosis	
Acute hepatitis	29 (34.5 %)
Acute fulminant hepatic failure	06 (07.1 %)
Chronic liver disease	49 (58.3 %)
Outcome	
Discharged	52 (61.9 %)
Referred	26 (31.0 %)
Expired	06 (07.1 %)

Table-II. Demographic Characteristics of children presenting with hepatic manifestations (N = 84).

Characteristics	Wilson Disease (n=27)	Non-Wilson (n=57)	P-Value*
Age (years, mean ± SD)	9.3 ± 2.59	6.2 ± 3.0	<0.001
Age Distribution			
< 5 years	01 (03.70 %)	24 (42.11 %)	<0.001
5 – 10 years	17 (62.97 %)	29 (50.87 %)	
> 10 years	09 (33.33 %)	04 (07.02 %)	
Gender			
Male	15 (55.56 %)	38 (66.67 %)	0.32
Female	12 (44.44 %)	19 (33.33 %)	
Duration of Illness (in weeks) (median, IQR)	4 (3)	2 (3)	<0.001
Laboratory Investigations			
ALT (IU/ml)	337.59 ± 323.37	529.13 ± 381.93	0.02
AST (IU/ml)	200.93 ± 175.80	278.89 ± 218.43	0.11
Bilirubin (mg/dl)	6.72 ± 3.71	7.52 ± 3.54	0.34
INR	3.02 ± 1.39	2.75 ± 1.27	0.37
Albumin (g/L)	2.95 ± 0.86	3.40 ± 1.42	0.08
Clinical Diagnosis			
Acute hepatitis	01 (03.70 %)	28 (49.12%)	<0.001
Acute fulminant hepatic failure	03 (11.11 %)	03 (05.26 %)	
Chronic liver disease	23 (85.19 %)	26 (45.61%)	
Outcome			
Discharged	24 (88.89 %)	28 (49.12 %)	<0.001
Referred	00 (00 %)	26 (45.61 %)	
Expired	03 (11.11 %)	03 (05.26 %)	

Table-III. Comparison of demographic and biochemical characteristics of children diagnosed with Wilson disease and other etiologies (N = 84).

* **t-test** for comparison of means, **Mann – Whitney U** test for median comparison and **chi – square** test for comparison of qualitative variables.

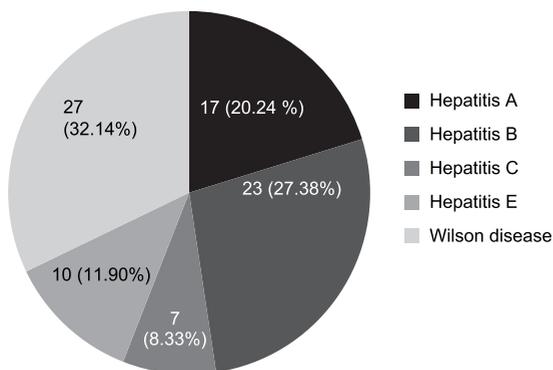


Figure-1. Etiological diagnosis of children presenting with hepatic manifestations (N = 84).

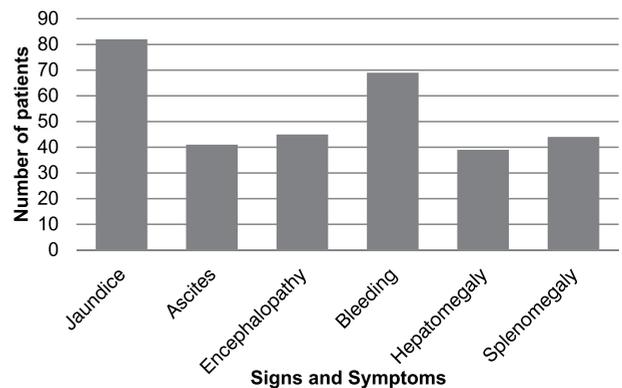


Figure-2. Clinical signs & symptoms of children (N = 84).

DISCUSSION

Pediatric liver diseases pose a significant health problem and consume ample amount of health resources. Mean age in our study population was 7.21 ± 3.21years, slightly older as compared to study from Dhaka 4.8 ± 0.3 years. However

males proportion was similar in two studies (63.1% vs. 62%).⁸ In our study 70% of the children were five years of age or older (59/84) compared to study from Nigeria showing 62% of the children in this age group.⁹ The differences in mean age, gender distribution and age distribution reflect

the regional population differences of these countries. Chronic liver disease comprised 58.3% (49/84) of the cases followed by 34.5% (29/84) of the cases with acute hepatitis in our cohort. This was discordant from Dhaka study where 53% (87/164) of the admitted cases were of acute hepatitis.

Jaundice was the most common (82/84, 97.6%) sign & symptom of the children presenting with hepatic manifestations. It was followed by symptoms of bleeding in 69 (82.1%) and encephalopathy in 45 (53.6 %). Common clinical signs observed were hepatomegaly in 39 (46.4%), splenomegaly in 44 (52.4%) and ascites in 41 (48.8%) patients. The frequency of these signs & symptoms matches with the study from Nigeria.⁹ Etiological classification of these hepatic manifestations showed Hepatitis A 20.24 % (17/84), Hepatitis B 27.38% (23/84), Hepatitis C 8.33% (7/84) and Hepatitis E 11.90% (10/84). This shows infective etiology and preventable (by vaccines and good hygiene) liver diseases are still common in our set-up. Increasing vaccine uptake (HBV, HAV) and community education regarding safe eating habits and hygiene practices can help lower the disease and economic burden. 61.9% of the cases were successfully treated and discharged, 31% referred (HBV & HCV related chronic liver disease cases) and 7.1% (6/84) of the children expired (3 with acute fulminant hepatic failure and 3 due to end stage liver disease due to Wilson disease). Mortality rate in our study was higher (7.1 % vs. 2.4 %) and cure / discharge rate much lower (62 % vs. 75 %) compared to the study from Dhaka.⁸ One important reason is lack of established pediatric hepatobiliary and gastrointestinal services at our hospital. For this reason, higher number of patients was referred (31%).

We found 32 % frequency of Wilson disease in children presenting with hepatic manifestations, however Ayesha H et al found 41 % of the Wilson disease patients presenting with hepatic manifestations.¹⁰ Mean age of children with Wilson disease was 9.3 years (± 2.59) significantly higher than children in non – Wilson group (6.2 ± 3.0 , p-value <0.001). It was lower compared

the study from Southern Iran 11 ± 7 years¹¹ and similar to study by Manolaki N et al 9.27 ± 3.62 years.¹² Male dominance (55.56 %) in our Wilson disease patients is similar to those found by Samiullah S et al.¹³ However, sex distribution between Wilson and non – Wilson group in our study was statistically not significant (p-value 0.32). Ninety six percent of the children in Wilson disease group were ≥ 5 years; only one child was below five years of age. Age distribution was significantly different from non – Wilson group (p – value 0.001).

The mean serum ceruloplasmin in our Wilson disease patients was 15.93 ± 4.66 mg/dl. The sensitivity of serum ceruloplasmin (< 20mg/dl) for diagnosis of Wilson disease was 77.8 % (21/27). It was reported to be 82.3 % in a study from India.¹⁴ The mean 24-hour urinary copper post – D – penicillamine challenge was $1250.4 \pm 194.4 \mu\text{g} / 24 \text{ hr}$. The sensitivity of 24-hour urinary copper post –D penicillamine challenge (> 1000 $\mu\text{g} / 24 \text{ hr}$.) was 100 % that was concordant with Indian study. The sensitivity of Keyser – Fleisher rings for Wilson disease diagnosis was 40.76 %, higher than the sensitivity (32.35 %) reported by Indian study.¹⁴

Only one Wilson disease patient (age – 4 years) presented with acute hepatitis, three with acute fulminant hepatic failure and majority (85 % - 23/27) presented with chronic liver disease. This clinical presentation was significantly different (p-value – 0.001) from non – Wilson disease group where 49 % (28/57) presented with acute hepatitis. In a study by Møller LB et al, 40 % (11/28) of Danish children with hepatic form of Wilson disease presented as chronic liver disease.¹⁵ This indicates that diagnosis of hepatic form of Wilson disease is much delayed in our population. The case fatality rate in our Wilson disease patients was 11% (3/11). It was reported to be 18% (3/17) in a study from Brazil.¹⁶

CONCLUSION

Wilson Disease in children is frequently obscure and necessitates a high intensity of suspicion and broad investigation to confirm the diagnosis. The combination of clinical, biochemical, and genetic

tests can provide the means to identify the majority of children with this disease. Early diagnosis and treatment can ensure good outcome.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Muhammad Khalid	Conception of study, Data collection tool, Data analysis & interpretation, manuscript writing and final approval.	
2	Javaria Rasheed	Data collection, Data entry and cleaning, Results interpretation, Manuscript writing and proof reading, Final approval of manuscript.	