ORIGINAL ARTICLE

Clinical Characteristics of Wilson Disease in Children: Our Experience from a Tertiary Care Hospital

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Pak Pediatr J 2025; **49(3&4):** 250-56

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Received for publication: July 7, 2025
Revision received: Sept. 3, 2025
Revision accepted: Oct. 2, 2025

How to cite this: Hamdani SSB, Saeed A, Anjum MN, Alvi MA, Fayyaz Z**,** Fazlani S
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Pak Pediatr J. 2025; 49(3&4): 242-48

ABSTRACT

Objective: This study aims to describe the clinical characteristics of Wilson disease (WD) in our genetically homogenous (inbred) population.

Study Design: Cross sectional observational study.

Place and Duration of Study: This study was conducted at the Liver unit of Children's Hospital & University of Child Health Sciences, Lahore, from January 2021 to December 2024.

Material and Methods: Children under the age of 18 and diagnosed with Wilson disease were enrolled based on Leipzig criteria. Data analyzed includes demographic, clinical presentation, and diagnostic modalities especially Kayser-Fleischer rings, serum ceruloplasmin and 24-hours urinary copper estimation. Data were analyzed using SPSS v26 (Chicago, IL, USA).

Results: A total of 50 children met the diagnostic criteria for Wilson's disease; 27 (54%) were male, with a mean age of 9.67 ± 2.31 years. Most children (88%) were symptomatic, while 12% were diagnosed via sibling screening. Consanguinity was observed in 64% of cases, while 16% had a positive family history. Acute liver failure was the most common presentation. Jaundice, edema, encephalopathy, hemolysis, and portal hypertension were frequent findings. Liver disease was the predominant presentation, while neurological and other rare manifestations were less frequent. Serum ceruloplasmin was low in 78%, and urinary copper elevated in almost all children. Medical treatment was effective in 23 patients; 8 required transplantation, and 19 (38%) died.

Conclusion: Pediatric Wilson disease, though not uncommon, most often presents as chronic liver disease but should also be suspected in acute liver failure or unexplained hemolysis. Diagnosis relies on serum ceruloplasmin, liver function tests, urinary copper, Kayser–Fleischer rings, and relevant family history.

KeyWords: *Wilson disease, Clinical features, Hemolysis, Chronic liver disease.*

INTRODUCTION

Wilson disease is an inherited metabolic disorder first described in 1912 by Kinnear Wilson.[1] Since his description of WD, lot of work has been done on this important and treatable disorder in reference to diagnosis and management. The

worldwide incidence is about 1 in 37,000.[2,3]WD is an autosomal recessive disorder and the gene is located on chromosome 13 and encoded by adenosine triphosphatase 7B (ATPase 7B) which is responsible for transporting the copper out of the biliary system.[3]WD results in abnormal copper deposition in various organs of the body primarily in liver, brain, cornea and kidneys but it also affects other organs of the body like bones, joints, and heart. The clinical manifestations depend on the system involved. Generally, liver disease comes in the first decade and neurological manifestations are more common in the adolescent and adults.[3,4] Clinical manifestations range from hepatomegaly without noticeable symptoms to fulminant hepatic failure.With effective treatment options available and increasing awareness among the paediatricians, more cases are being diagnosed in the pre-symptomatic phase. Hepatic involvement may be limited to biochemical abnormalities, such as elevated transaminases, without other clinical features. The most frequent clinical presentation is chronic liver disease, followed by acute hepatitis, Wilsonian crises, and fulminant hepatic failure.[3-5]

Neuro-psychiatric manifestations are predominantly seen in adolescents and adults. Major neurological manifestations include dysarthria, dystonia, poor school performance and choreathetosis.[6,7] Depression, neurotic behaviour, personality changes are the main psychotic presentation. Rare but well reported presentations include Coomb's negative hemolytic anemia, acute renal failure, aminoaciduria, nephrolithiasis, arthritis and cardiomyopathy.[7]

Diagnosis of WD was based on Leipzig criteria[8] including clinical manifestation, family history, slit-lamp examination for Kayser Fleischer (KF) rings, low serum ceruloplasmin assay (<20mg/dl) and increased 24-hours urinary excretion of copper (>100µg/day).Wilson disease has an excellent prognosis if picked and managed at an appropriate time with chelating agents like penicillamine and trientene. Advanced liver disease including acute decompensation and hemolytic crises usually requires transplantation.[9,10]

This study was designed to present our experience from tertiary care center regarding variability of clinical presentation, diagnostic modalities and outcome of WD in children. This study was approved by the institutional review board.

MATERIAL AND METHODS

This was across sectional observational study conducted at the Liver unit of Children's Hospital & University of Child Health Sciences, Lahore from January 2021 to December 2024. The children diagnosed as WD during the study period were enrolled and their data was retrieved using patient files and electronic record whatever was available. The sample size was calculated using world health organization (WHO) formula with 95% confidence interval and 13% margin of error estimating a population proportion with absolute precision (1 in 37000).

Diagnosis of WD was based on Leipzig criteria[8] including clinical manifestation, family history, slit-lamp examination for KF rings, low serum ceruloplasmin assay (<20mg/dl) and increased 24-hours urinary excretion of copper (>100µg/day).Copper estimation in liver biopsy tissues was not available at the time of writing of this manuscript and mutational analysis would be discussed in the upcoming publication in future. We excluded all other conditions of chronic liver disease in children like infectious hepatitis, autoimmune and drug induced hepatitis.

Leipzig scoring system for the diagnosis of Wilson disease

KF Rings (Slit lamp examination)	
Present	**2**
Absent	**0**
Neuropsychiatric symptoms suggestive of WD	
Present	**2**
Absent	**0**
Coomb's negative hemolytic anemia (+high serum copper)	
Present	**1**
Absent	**0**

Urinary Copper	
Normal 1-2× ULN1	**0**
≥2× ULN	**2**
Normal but ≥5×ULN one day after challenge with 2×0.5 g D penicillamine	**2**
Liver copper quantitative	
Normal	**-1**
Upto 5× ULN	**1**
>5× ULN	**2**
Rhodanine positive hepatocyte (if quantitative Cu measurement is not present)	
Absent	**0**
Present	**1**
Serum Ceruloplasmin (normal >20mg/dl)	
Normal	**0**
10-20	**2**
<20	**1**
Mutational Analysis	
Disease causing mutation in both chromosomes	**4**
Disease causing mutation in one chromosome	**1**
No disease causing mutation detected	**0**
Assessment of Wilson disease score	
4 or more: diagnosis of WD highly likely	
2-3: diagnosis of WD likely, needs more investigation	
0-1: diagnosis of WD unlikely	

The clinical presentation was defined as:

1. Chronic liver disease: manifestation of liver disease over a period of time with or without chronic stigmata of liver disease.
2. Asymptomatic: when there are no signs and symptoms of liver disease present and WD is diagnosed on the basis of laboratory criteria.
3. Acute hepatitis: similar presentation to acute viral hepatitis with jaundice, dark urine, tender heptomegaly and elevated liver enzymes.
4. Fulminant hepatitis: An acute hepatitis with hepatic encephalopathy within 8 weeks of liver disease symptoms.
5. Hemolytic crises: It is the worst form with jaundice, hemolysis, liver failure with high reticulocyte count and negative coombs test.

Data analyzed include age, gender, consanguinity, variety of clinical presentation, family history, outcome of WD, KF rings, complete blood count with reticulocytes, coomb's test, liver chemistry, coagulation, serum ceruloplasmin, 24-hour urinary copper and liver biopsy if performed. Statistical analysis was carried out by using the Statistical Package for Social Sciences version 20 (SPSS Chicago, IL, USA). Simple descriptive statistics were used. Mean and SD was calculated for quantitative variables like age, duration of illness and treatment time. Frequencies and percentages were calculated for qualitative variables like gender and clinical characteristics. This study was approved by institutional ethical committee and conducted according to the principles of the Helsinki Declaration.

RESULTS

Over a 4-year period, 798 children were evaluated for suspected chronic liver disease, acute hepatitis/ fulminant hepatitis, or hemolytic crises; 50 met the diagnostic criteria for Wilson disease, each with a score ≥4 at diagnosis. Twenty-seven (54%) were male and the mean age of presentation was 9.67$\pm$2.31 years. Majority of children were symptomatic 44 (88%) and 6 (12%) were picked up on sibling screening without any symptoms. Consanguinity was present in 32 (64%) and 8(16%) patients had positive family history.

Chronic liver disease and hemolytic crises (Wilsonian crises) were more frequent presentations followed by acute liver failure without hemolysis. Regarding clinical manifestations, jaundice was the most noticeable

finding followed by peripheral edema, encephalopathy, hemolysis and signs of portal hypertension. Rare presentations included neurological manifestations followed by hepatopulmonary syndrome (HPS), hepatorenal syndrome (HRS), cardiac and arthritis. A summary of demographic and clinical characteristics is given in **table 1 and 2**.

The serum ceruloplasmin was abnormally low in 39 (78%) children, urinary copper was positive in all (100%). KF Rings were positive in 14 (28%) children. Liver biopsy was performed in only 7 children, showing non-specific features of chronic liver disease; copper estimation and Rhodanine staining were not available at our center. Biochemical parameters are summarized in **table 3**. Mutational analysis could not be done because of unavailability and cost constraint. Twenty-three patients showed good response to medical management and 8 (16%) were referred for liver transplant and 19 children died either because of fulminant hepatic failure or hemolytic crises.

TABLE 1: Baseline characteristics of children with Wilson disease (n=50)

Characteristics	Number	Percen-tage
Male	27	54.0
Age	9.67±2.31	
Wilson diagnostic score >4	39	78.0
KF rings	14	28.0
Family history	08	16.0
Consanguinity	32	64.0
Asymptomatic	06	12.0
Symptomatic	44	88.0
Chronic liver disease	26	52.0
Acute fulminant hepatitis	10	20.0
Wilsonian crisis	14	28.0
Outcome		
Referred for liver	08	16.0
transplant	23	46.0
On medical management	19	38.0
Expired		

TABLE 2. Clinical manifestations of children with Wilson disease (n=50)

Characteristics	Number	Percentage
Jaundice	47	94.0
Edema	22	44.0
Upper GI bleed	15	30.0
Hemolysis	14	28.0
Encephalopathy	13	26.0
Ascites	13	26.0
Neurological	02	04.0
Hepatopulmonary syndrome	02	4.0
Hepatorenal syndrome	06	12.0
Cardiomyopathy	02	4.0
Dysarthria	02	4.0
Arthritis	02	4.0

TABLE 3: Laboratory parameters of children with Wilson disease (n=50)

Hemoglobin gm/dl	8.5±1.7
Reticulocyte count %	2.1±2.08
Serum ceruloplasmin mg/dl	10.37±6.32
Urinary copper after penicillamine challenge microgram/day	1670.02±982.1
ALT IU/L	109.8±108.2
AST IU/L	257.08±217.6
Alkaline Phosphatase	347.5+307.6
INR seconds	2.4±1.68
Albumin gm/dl	3.01±0.60

ALT- alanine amino transferase, AST- aspartate amino transferase, INR- international randomized ratio

DISCUSSION

Wilson disease also known as hepatolenticular degeneration is a disorder of copper metabolism with variable presentation in all age groups. The prevalence of WD is known to be 1 in 37000 worldwide but a major contribution comes from consanguineous family relationships and communities with inbred generations as in Pakistan.[2,6,11] WD has strong genetic background with autosomal inheritance and familial clustering of disease has been described in the literature.[2,3] In the present study, consanguinity and family history was observed in 64% and 16% respectively. Gender distribution is almost same except in acute fulminant hepatic failure where female sex is predominantly seen as reported in the literature.[12] Liver disease usually manifests at an earlier age and neuro-psychiatric presentation comes at a little older age group.[6] In our study mean±SD age 9.67±2.31 years which is consistent with the international literature. Our youngest child with liver disease was 4-year-old and all the neurological cases were in their teens.

WD has protean manifestations and may present with liver disease, neuro-psychiatric disorders and some rare presentations.[5,6,13] Chronic liver disease (CLD) is the commonly seen form in WD followed by asymptomatic/sibling screening detection and fulminant hepatic failure with or without hemolytic crises. In the present study CLD

was the predominantly seen chunk followed by acute hepatic failure and hemolytic crises. In the symptomatic patients, jaundice has been the most common observed findings followed by visceromegaly and signs of portal hypertension including bleeding esophageal varices, ascites and splenomegaly with or without hypersplenism.[5,9,13] Current study showed jaundice most commonly seen findings in the symptomatic patients followed by signs of portal hypertension. Wilson disease complicating with hepatopulmonary and hepatorenal syndrome can be the presentation though rare as seen in the present study. Asymptomatic patients are detected either on routine physical examination, sibling screening or transaminasemia.[13]

Acute hepatic failure is present in only 5-8% of patients in WD and the outcome is usually poor with rapid decompensation requiring emergency transplant.[12,14] High serum and urinary copper, elevated bilirubin and slightly deranged liver enzymes and coagulopathy differentiates from the acute fulminant hepatitis of other causes. In the current studied patients, acute fulminant hepatic failure was the second most common group with high mortality. Many of patients improve by careful supportive treatment and turn the corner instead of going into Wilsonian crisis as calibrated from Wilson index score improvement.[8,15]

Hemolysis happens in WD and typically is associated with coomb's negative anemia due to copper induced break down of red blood cells. Hemolytic crises usually is recognized as ongoing hemolysis seen in acute on chronic Wilson disease characterized by typical cola colored urine, pallor, coagulopathy unresponsive to Vitamin K, progressive renal failure, low uric acid and alkaline phosphatase and reversed AST/ALT ratio.[16] Current study showed significant number of children with hemolytic crises with coomb's negative hemolytic anemia and required multiple transfusions for stabilization. The frequency of hemolytic crises in our study is in contrast to international literature but it might be the case that our center is a referral center draining a large catchment area.

Among the neurological presentation, dysarthria is the most common presentation followed by dystonia and psychiatric range of symptoms in addition to poor school performance and chorea.[15]

In the present study, we had two patients with liver and neurological involvement one had dysarthria and other had psychiatric symptoms. Joint involvement is quite rare but documented and commonly involving knee joints, in the present study two patients had arthropathy at the time of presentation. Like arthropathy, cardiac involvement is also very common but two of our children had developed cardiomyopathy over few years after the diagnosis of WD.[17-19]

The diagnosis of WD include high index of clinical suspicion, liver function tests including synthetic function, serum ceruloplasmin, 24-hours urinary copper with or without challenge, liver biopsy and copper estimation hepatic tissue and genetic testing in addition to family history and KF rings.[8,9,20] Disproportionate hyperbilirubinemia with 2-3 times upper normal limit of enzymes is a classical feature of Wilson disease, however, anicteric and significantly high level of enzymes are also seen in WD.[13] The screening yield of serum ceruloplasmin for WD has been validated in many studies as seen in the current study, around 78% children had lower values suggesting WD diagnosis.[21] 24-hour collection of urine with and without penicillamine challenge for copper estimation has been in use for decades and is the mainstay of diagnosis in the developing countries like Pakistan due to unavailability and financial constraint on liver tissue copper estimation and genetic testing respectively.[22-23] In our cohort, almost all children had elevated 24-hour urinary copper after challenge with penicillamine suggestive of Wilson disease.

Patients without advanced liver disease but with adherence to treatment have normal life expectancy. However, children with acute liver failure have mortality of 95% without liver transplantation.[10,24] In the present study, majority (38%) of children died were those of acute liver failure or Wilsonian crises. Those who adhere and receive early treatment in the form of penecillamine and zinc acetate really turn the corner and survive without transplantation. Other than penecillamine, trientene has fewer side effects when used as primary therapy. Ammonium tetrathiomolybdate has been proposed as more effective for neurological Wilson disease.[24,25] Sixty-two percent (31/50) of our studied children were managed medically and showed good response but 16% (8/50) ultimately required liver transplantation and doing good post-transplant.[25]

Limitations: The study include the fact its retrospective nature and single center data which cannot be generalized to all the settings. Moreover, the potential of missing data cannot be ruled out. More prospective studies with larger sample size are required to see the various clinical presentation of this condition just to prevent the morbidity and mortality from this treatable condition if managed earlier.

CONCLUSION

Pediatric Wilson disease is not an un-common condition in our population and mostly present with chronic liver disease but in the setting of acute liver failure and hemolysis one must not forget WD if more common conditions are ruled out. Useful and reliable biomarkers such as serum ceruloplasmin, specific liver chemistry and 24-hours urinary copper can help establish the diagnosis in addition to KF rings and family history.

Source of funding: None
Conflict of interest: None

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Author's Contribution

SSBH: Proposed topic, basic study design, material and methods and manuscript writing
AS: Data collection, statistical analysis and interpretation of result etc.
MNA: Literature review & referencing and quality insurer
MAA: Data collection, analysis report
ZY: Data collection
SF: Material and methods, literature review

All the authors have approved the final manuscript draft and accept the responsibility of research integrity.