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Clinical and Pathological Spectrum of Wilson Disease in Children at a Tertiary Care Hospital of Faisalabad, Pakistan

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ABSTRACT

Wilson disease is a genetic disorder related to copper metabolism that follows an autosomal recessive pattern. **Objectives:** To document the clinical and pathological spectrum of Wilson disease at a tertiary setting in Punjab, Pakistan. **Methods:** This cross-sectional study was conducted at the Department of Pediatric Gastroenterology, Children's Hospital, Faisalabad, Pakistan, from December 2019 to October 2024. A total of 60 children of both genders aged below 18 years, and presenting with Wilson disease were analyzed. Physical and clinical examinations were performed and medical history was taken in all Wilson disease cases. Demographic and clinical characteristics were noted, and relevant laboratory investigations were done. **Results:** In a total of 60 children with Wilson disease, 42 (70.0%) were boys. The mean age was 10.25 ± 3.10 years. The most frequent signs and symptoms were Jaundice, hepatomegaly, ascites, and coagulopathy, noted in 53 (88.3%), 41 (68.3%), 36 (60.0%), and 24 (45.0%) children respectively. Kaiser Fischer ring was noted in 16 (26.7%) children. The mean Wilsons index score was 9.77 ± 2.98 while 31 (51.7%) children had scores ≥10. The mean ceruloplasmin and 24-hour urinary copper levels were 7.03 ± 7.51 mg/dl and 746.03 ± 451.06 µg. **Conclusions:** It was concluded that hepatic manifestations are the most common among children with Wilson disease. The most frequent signs and symptoms among children were Jaundice, hepatomegaly, and ascites. There is a need to identify factors that contribute to early diagnosis and prompt treatment, thereby preventing severe brain damage and liver failures in affected patients.

INTRODUCTION

Wilsons disease (WD) is a genetic disorder related to copper metabolism that follows an autosomal recessive pattern. Its prevalence globally ranges from 1 in 10,000 to 1 in 30,000 individuals [1]. The condition arises due to mutations in a gene responsible for copper transport, leading to reduced or absent copper transportation into bile. This leads to the accumulation of toxic copper in the liver, causing damage to hepatocytes [2]. As the disease advances, copper deposition occurs in other organs such as the brain, cornea, kidneys, and heart. The clinical manifestation of the disease directly corresponds to the location of copper accumulation and the extent of tissue harm [3]. WD presents with various clinical forms, with hepatic involvement being the most common in individuals under 11 years old [4]. Hepatic presentations range from asymptomatic cases with elevated liver enzyme levels to severe conditions like fulminant hepatic failure, chronic liver disease, spleen enlargement, and liver cirrhosis. While neuropsychiatric symptoms are more frequently observed in individuals in their second or third decade of life, they can

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also manifest in pediatric patients [5]. Isolated neurological symptoms are present in about 8-22% of pediatric patients [6]. Neurological signs can be diverse and include behavioural irregularities, decline in school performance, handwriting deterioration, dysarthria, and excessive saliva production [7, 8]. Psychiatric issues such as depression, anxiety, and even psychosis can coexist [9]. Neurological symptoms in Wilson's disease may or may not be accompanied by symptomatic liver disease. Atypical presentations of Wilson's disease may encompass conditions such as renal stones, early-onset osteoporosis, cardiomyopathy, pancreatitis, and hypoparathyroidism [10, 11]. The primary goal of pharmacological treatment for WD is to prevent further copper accumulation by decreasing absorption or enhancing its elimination through urine bile, or both. Liver transplantation is indicated in cases of progressive liver failure, worsening neurological symptoms, portal hypertension complications (even with medical and dietary intervention), and acute liver failure [12]. The available literature has limited detailed studies on pediatric WD cases. In Pakistan, there is scarce data on the disease burden and its various presentations.

Wilson's disease is a rare autosomal recessive disorder of copper metabolism that can lead to severe hepatic and neurological complications in children if not diagnosed and treated early. However, in Pakistan, especially in Punjab, there is limited locally generated data describing the full clinical and pathological spectrum of Wilson's disease in pediatric populations. Most existing studies are small, fragmented, or focused on isolated clinical features, leaving a gap in comprehensive characterization of disease presentation and biochemical profiles. We aimed this research to shed light on the diverse manifestations of WD in children. This study might help add to what little is already known about the various sociodemographic and clinical aspects of WD among children in Pakistan. This study was conducted to document the clinical and pathological spectrum of WD at a tertiary setting in Punjab, Pakistan.

METHODS

This cross-sectional study was conducted at the Department of Pediatric Gastroenterology, Children's Hospital, Faisalabad, Pakistan from December 2019 to October 2024. Considering the proportion of isolated neurological symptoms in WD as 8% [6], with a 95% confidence level and 7% margin of error, the required sample size was calculated to be 58. For this study, 60 children who fulfilled the eligibility criteria were considered. Inclusion criteria were children of both genders, aged below 18 years, and newly diagnosed cases of WD. Children with incomplete medical records or unclear diagnoses were excluded. Approval from the "Institutional Ethical Committee" was taken (letter number: 05/2019). Informed consents were obtained from parents/guardians. Demographic characteristics like gender, age, residence, clinical information like presenting signs and complaints, children's score, Wilson index, and relevant laboratory parameters like liver function tests, ceruloplasmin and urine copper were noted. A comprehensive physical examination was performed, focusing on the identification of jaundice, hepatosplenomegaly, ascites, and indicators of liver dysfunction. Neurological and psychiatric evaluations were also conducted. All cases underwent a slit-lamp eye examination by an ophthalmologist to detect the presence of Kayser-Fleischer (KF) rings and/or sunflower cataracts. The diagnosis of WD was established based on 24-hour urinary copper excretion and serum ceruloplasmin levels. Urinary copper excretion >100 µg/24 hours was used to diagnose WD, and this test was performed using atomic absorption spectrophotometry (PerkinElmer Analyst 400 [USA]) after ensuring proper sample collection and excluding other liver diseases [13]. Serum ceruloplasmin levels <20 mg/dL were considered diagnostic for WD, measured using nephelometry. Family history was considered positive if there was a history of WD in a sibling or 1st degree relative. Consanguinity was considered "yes" if the parents of the affected children were 1st cousins. Penicillamine, zinc acetate, and liver-supportive fat-soluble vitamin supplements were advised to all patients. All the study data were entered and analyzed utilizing "Statistical Package for Social Sciences (SPSS)", version 26.0. Descriptive representations of the qualitative data were made as frequency and percentages. Quantitative data were shown as calculating mean along with standard deviation.

RESULTS

In a total of 60 children with WD, 42 (70.0%) were boys representing a boy-to-girl ratio of 2.3:1. The mean age was 10.13±3.08 years ranging between 5 to 16 years while 47 (78.3%) children were aged between 5-12 years. The residential status of 35 (58.3%) children was rural. Family history of WD was present in 15 (25.0%) children whereas consanguinity of marriage among parents was noted in 27 (45.0%) cases. Details about the demographical and clinical characteristics of children are shown in table 1.

Table 1: Demographic and Clinical Characteristics at the Time of Diagnosis of Wilson's Disease (n=60)

Demographic and Clinical Characteristics		N (%)
Gender	Boys	42 (70.0%)
	Girls	18 (30.0%)
Age	5-12	47 (78.3%)
	13-18	13 (21.7%)
Residence	Urban	25 (41.7%)
	Rural	35 (58.3%)
Child Score	A	29 (48.3%)

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	B	12 (20.0%)
	C	19 (31.7%)
Family History		15 (25.0%)
Consanguinity		27 (45.0%)

The most frequent signs and symptoms were Jaundice, hepatomegaly, ascites, and coagulopathy, noted in 53 (88.3%), 41 (68.3%), 36 (60.0%), and 24 (45.0%) children respectively. The details about the most frequent signs and symptoms among children with WD are shown in figure 1.

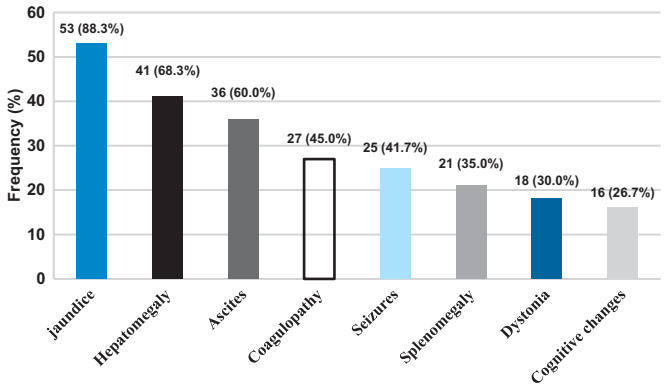

Figure 1: Frequency of Signs and Symptoms in Children at the Time of Diagnosis of Wilson's Disease (n=60)

Kaiser Fischer ring was noted in 16 (26.7%) children. The mean Wilsons index score was 9.77±2.98 while 31 (51.7%) children had scores ≥10 shown in figure 2.

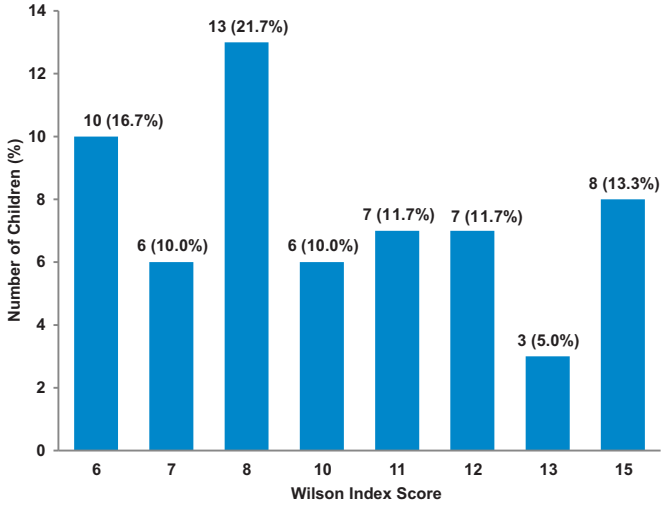

Figure 2: Distribution of Wilson Index Scores at the Time of Diagnosis of Wilson's Disease (n=60)

The mean ceruloplasmin and 24 hours' urinary copper levels were 7.03 ± 7.51 mg/dl and 746.03 ± 451.06 µg. Details about the biochemical parameters are shown in table 2.

Table 2: Biochemical Parameters at the Time of Diagnosis of Wilson's Disease (n=60)

Parameters	Mean ± SD	Normal range
Ceruloplasmin (mg/dl)	7.03 ± 7.51	20-40
Serum Alanine Aminotransferase (U/L)	102.82 ± 11.57	≤40
Serum Aspartate Aminotransferase (U/L)	134.08 ± 42.64	≤40
Serum Bilirubin (mg/dl)	3.28 ± 2.90	0.3-1.2
Serum Albumin (g/dl)	2.91 ± 0.64	3.5-5.5
24 Hours Urinary Copper (µg)	746.03 ± 451.06	<40

A comparison of demographic and clinical characteristics concerning the Wilson Index Score was done and no statistically significant associations were found (p>0.05), as in table 3.

Table 2: Comparison of Demographic and Clinical Characteristics between Wilson Index Score among newly diagnosed Wilson's Disease cases (n=60)

Demographic and Clinical Characteristics		Wilson Index Score		p-Value
		<10 (n=29)	≥10 (n=31)	
Gender	Boys	21 (72.4%)	21 (67.7%)	0.539
	Girls	8 (27.6%)	10 (32.3%)	
Age	5-12	21 (72.4%)	26 (83.9%)	0.282
	13-18	8 (27.6%)	5 (16.1%)	
Residence	Urban	14 (66.7%)	11 (35.5%)	0.315
	Rural	15 (33.3%)	20 (64.5%)	
Child Score	A	18 (62.1%)	11 (35.5%)	0.103
	B	5 (17.2%)	7 (22.6%)	
	C	6 (20.7%)	13 (41.9%)	
Family History		7 (24.1%)	8 (25.8%)	0.409
Consanguinity		11 (37.9%)	16 (51.6%)	0.287

DISCUSSION

The present study analyzed 60 children with WD and we noted that 70.0% of children were boys, representing a boy-to-girl ratio of 2.3:1. A local study from Ali *et al.*, from Islamabad described 60.8% of children with WD to be male [14]. Current findings are consistent with Mahmud *et al.*, from Bangladesh who found a boys-to-girl ratio of 2:1 among 100 WD children [15]. Similar findings exhibiting male predominance have been documented in other parts of the world [16, 17]. Merle and colleagues found female predominance among WD cases [13]. No clear elaboration about the gender's association with WD exists in the literature. In this study, the mean age of children with WD was 10.13 ± 3.08 years ranging between 5 to 16 years while 78.3% of children were aged between 5-12 years. Mahmud et al from Bangladesh found the mean age of the children with WD to be 8.42 ± 2.6 years [15]. A local study by Aaraj and colleagues found the mean age of the children with WD as 9.74 years [16]. WD is not commonly observed before the age of 5, although there have been reports of its occurrence as early as 3 years of age [17]. The youngest participant in this study was a 5-year-old boy. Consanguinity of marriage was reported by 45.0% of WD cases in this study. Literature reports consanguinity to be an important feature of WD as it is known to be an autosomal recessive disorder. Literature reports more risk of WD among children with consanguineous parents [18-20]. The spectrum of WD is wide and varies geographically.

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It is important to find out certain clinical patterns dominating different parts of the world. The most frequent signs and symptoms were Jaundice, hepatomegaly, ascites, and coagulopathy, noted in 88.3%, 68.3%, 60.0%, and 45.0% of children respectively. Local data has previously recorded that hepatic symptoms are the commonest found in around 69% of WD cases while Jaundice is observed in 85.7% of these cases [14]. Day and colleagues observed that 58.3% of cases showed hepatic involvement, which was a significant finding in their study [5]. The primary hepatic symptoms were jaundice, hepatomegaly, and ascites. These findings are aligned with those reported in both national and international studies, reinforcing the consistency of the observed symptoms [21]. Additionally, neurological manifestations of WD are the second most common clinical presentation, particularly in individuals aged 10 to 15 years. Notably, this neurological aspect serves as the initial symptom in 40-60% of WD patients, statistics described in the literature [20]. KF rings were observed in 26.7% of WD cases in this study, primarily due to patients having hepatic WD. The present study found a positive family of WD in 25.0% of cases. The literature reports a positive family history of WD ranging between 25-41% [14, 21]. Present study adds important insights to present patterns of WD among children. Low ceruloplasmin levels (7.03 ± 7.51 mg/dL) in this study, are a hallmark of WD and reflect impaired copper metabolism due to mutations in the ATP7B gene, which disrupt copper incorporation into ceruloplasmin [22]. The normal range of ceruloplasmin is 20–40 mg/dL, and levels below 20 mg/dL strongly indicate WD, particularly in symptomatic patients [23]. Elevated 24-hour urinary copper levels, with a diagnostic cutoff >100 µg, further confirm the diagnosis by reflecting excessive copper excretion due to hepatocellular damage and reduced hepatic copper-binding capacity [24]. In this study, the mean 24-hour urinary copper level was 746.03 ± 451.06 µg. The findings of this study underline the importance of early recognition and diagnosis of WD, especially in children who present with unexplained liver dysfunction, neurological symptoms, or psychiatric changes. The demographic features, including the high male-to-female ratio and the common presence of consanguinity, provide valuable insight into genetic and environmental risk factors. The biochemical markers and clinical scores provide crucial diagnostic information that can guide management and early intervention to prevent severe liver and neurological complications.

This study has limitations, including its single-center, hospital-based cross-sectional design and relatively small sample size, which may limit generalizability to the broader pediatric population. Genetic confirmation (ATP7B mutation analysis) was not performed, and long-term follow-up outcomes of patients were not assessed. Additionally, variability in disease severity at presentation may have introduced selection bias. Future research should focus on multicenter, longitudinal studies with larger cohorts and include genetic testing to better define genotype-phenotype correlations. Early screening strategies and awareness programs should also be developed to promote timely diagnosis and improve outcomes in children with Wilson's disease.

CONCLUSIONS

It was concluded that hepatic manifestations are the most common among children with WD. The most frequent signs and symptoms among children were Jaundice, hepatomegaly, and ascites. There is a need to identify factors that contribute to early diagnosis and prompt treatment, thereby preventing severe brain damage and liver failures in affected patients.

Authors' Contribution

Conceptualization: NS
Methodology: NS, HB, HSM, ZB, IA, KM
Formal analysis: NS, HB, ZB, IA, KM
Writing and Drafting: NS, HB, HSM, ZB, IA, KM
Review and Editing: NS, HB, HSM, ZB, IA, KM

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

The authors declare no conflict of interest.

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