

# Clinical Profile, Laboratory Characteristics and Treatment of Wilson's Disease in Children from Western India

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## Abstract

To study the clinical profile and laboratory characteristics and treatment of children with Wilson's disease (WD). The current study was done at Department of pediatrics, Sir Padampat Institute of Neonatology and Pediatric Health, Sawai Man Singh Medical College, Jaipur. It was an observational study and institution ethics committee approved the study. Patients visiting the outpatient department or admitting in wards with clinical presentation suggestive of WD were enrolled in the study after obtaining a valid informed written consent. Patients subjected to detailed clinical history and physical examination. All patients subjected to routine blood count, biochemistry including liver function tests and specific laboratory investigations. They underwent ophthalmological examination. Ultrasonography abdomen and liver biopsy performed in enrolled patients. Magnetic resonance imaging brain carried out in patients with neurological WD. Ferenci score was calculated for each of the patients. Total 50 patients were included in the study. Mean age at the time of diagnosis was 9.4 years with delay of 11 months after onset of symptoms. Male to female ratio was 2/1. Hepatic manifestation were seen in 76% patients and 24% patients presented with neurological disease. Kayser-Fleischer ring was seen in 44% patients with hepatic disease and 83% patients with neurological disease. Twenty-four hour urinary copper was more than 2 time of upper limit of normal in all patients. Fifty-four percent patients showed improvement with chelation therapy and 9 patients died during the study period. WD in children has varied clinical manifestation and early diagnosis is necessary for good prognosis. It requires wide range of tests as genetic testing is not easily available. Acute liver failure has high mortality. Early chelation therapy reverses the clinical and biochemical abnormalities.

**Keywords:** Wilson's disease, KF ring, liver failure, ceruloplasmin, penicillamine

## Introduction

Wilson's disease (WD) is a genetic disorder with autosomal recessive inheritance. Kinnier Wilson first described the disease as "progressive lenticular degeneration" in 1912.<sup>1</sup> The term "hepatolenticular degeneration" was first used by

Hall in 1921. The *ATP7B* gene responsible for WD identified in 1993.<sup>2</sup> Loss of *ATP7B* gene function is responsible for various manifestation of WD. There is decrease biliary excretion of copper due to failure of incorporation of copper into ceruloplasmin. Copper get accumulated in the liver,



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brain and other tissues that results in liver toxicity and other clinical presentation of the disease.<sup>3,4</sup>

The global prevalence of WD varies from 1/30,000 to 1/50,000. Some studies have suggested prevalence of 1 in 7,000.<sup>5,6</sup> Studies had reported genetic prevalence of heterozygous carrier frequencies as high as 1/25 to 1/53.<sup>7,8</sup> Delayed diagnosis and untreated disease is responsible for high morbidity and mortality due to hepatic failure and/or severe neurological disability. Therefore, early diagnosis and proper treatment is necessary for better prognosis. Walshe proved treatment with chelators as D-penicillamine (DP) in 1956 and trientine 1969 to be successful.<sup>9,10</sup>

There are few studies from India on pediatric WD.<sup>11,12</sup> Other studies describe the neurological WD in adult population.<sup>13-15</sup> We carried out this study to highlight the clinical features and laboratory parameters of WD in children along with treatment of the patients.

## Material and Method

The current study was done at department of pediatrics, Sir Padampat Institute of Neonatology and Pediatric Health, Sawai Man Singh Medical College, Jaipur. Office of the Ethics Committee Sawai Man Singh Medical College and Attached Hospitals, Jaipur (decision no: 814, date: 26.08.2021) approved the study. It was an observational study carried out from January 2017-December 2022.

### Patient Selection

Patients visiting the outpatient department or admitting in wards with clinical presentation suggestive of WD were enrolled in the study after obtaining a valid informed written consent. All patients subjected to detailed clinical history and physical examination. All patients subjected to routine blood count, biochemistry including liver function tests and specific laboratory investigations. They underwent ophthalmological examination including slit lamp examination for evaluation for Kayser-Fleischer (KF) ring and other ophthalmological findings. Ultrasonography (USG) abdomen performed to know the liver echo texture and the type of cirrhosis. Liver biopsy performed in enrolled patients. Magnetic resonance imaging (MRI) brain carried out in patients with neurological WD. Patient meeting the diagnostic criteria were included in the study. Ferenci score was calculated for each of the patients.<sup>16</sup>

### Diagnostic Criteria

Presence of History and clinical features suggestive of WD (hepatic or neurological) plus any two of the following with or without positive family history of WD:

- 1) Presence of KF ring on ophthalmological evaluation.
- 2) Increased baseline 24-hour urinary copper excretion more than 100 µg/day in absence of acute hepatitis
- 3) Increased 24-hour urinary copper excretion with penicillamine challenge (PCT) more than five times of upper limit of normal (ULN) in equivocal cases.
- 4) Low serum ceruloplasmin, less than 20 mg/dL.
- 5) MRI brain suggestive of WD.

## Definitions

### Hepatic Disease

Presence of hepatic dysfunction defined as, clinically, presence of stigmata of liver disease-jaundice, edema, ascites, HSM, etc., plus laboratory findings suggestive of deranged liver function tests:

- 1) Elevated liver aminotransferases: >2 x ULN
- 2) Deranged Prothrombin time international normalized ratio (INR) >1.5 not corrected with vit K
- 3) Hypoalbumenia: Serum albumin <3.5 g/dL
- 4) Hyperbilirubinemia: Serum bilirubin >1.5 mg/dL

### Acute Hepatitis

Presence of liver disease (clinically or biochemically) of duration less than 3 months.

### Acute Liver Failure (ALF)

Pediatric ALF defined as (a) evidence of liver dysfunction within 8 weeks of onset of symptoms, (b) uncorrectable coagulopathy with INR >1.5 in patients with hepatic encephalopathy, or INR >2.0 in patients without encephalopathy, and (c) no evidence of chronic liver disease either at presentation or in the past.<sup>17</sup>

### Chronic Liver Disease

Presence of liver disease (clinically or biochemically) of duration more than 3 months.

### Cirrhosis

Radiological (USG) findings of heterogeneous liver with coarse echo texture with nodule formation and irregular borders. Histopathologically, characterised by progressive hepatic fibrosis, distortion of hepatic architecture, and presence of regenerative nodule.

### Copper Study

#### Serum Ceruloplasmin

Done by immunoturbidometry by COBAS automated instrument. Normal values 20-60 mg/dL.

#### Urinary Copper

Done by DI-Br-PAESACOMPLEXONE/SPECTRO photometry. UV-1800 SPECTROPHOTOMETER INSTRUMENT was use. Normal values 0-40 µg/day.

We do not carried out liver copper estimation and genetic testing of patients due to non-availability of these investigations at our centre.

### Statistical Analysis

Statistical analysis was done using computer software (SPSS Trail Version 23 and primer). The qualitative data were expressed in proportion and percentages and the quantitative data was expressed as mean and standard deviations. The difference in proportion was analysed using the Student t-test. 5% probability level as considered as significant, i.e, p-value <0.05.

## Results

Total 50 patients were included in the study. Mean age at the time of diagnosis was 9.4 years with delay of 11

months after onset of symptoms. Male is to female ratio was 2/1 with 35 boys and 15 girls. Family history for liver disease was positive in 20 percent patients and history of consanguinity in 20%. Five patients diagnosed on family screening. Youngest patient was three-year-old presented with acute hepatitis with serum ceruloplasmin level of 19 mg/dL and 24-hour urinary copper was 934. Oldest patient was of 16 years admitted with decompensated chronic hepatitis.

Mode of presentation enumerated in **Table 1**. Among patients with neurological WD, 50% were older than 10 years. Two patients with hepatic WD presented with hemolytic anemia, two with effusion of knee joint. One patient was having hydronephrosis with renal calculus. He was also having neuroregression and history of jaundice in past. KF ring was positive in this patient and with serum ceruloplasmin 16 mg/dL. Baseline 24-hour urinary copper was elevated to 332 µg/day. USG abdomen showed coarse echotexture with micronodular cirrhosis. MRI brain showed hyperintensities in basal ganglia on T2 images.

**Table 2** shows the clinical and biochemical profile of patients. Twenty-one (61.7%) patients were having aspartate aminotransferase (AST) more than two times ULN whereas alanine aminotransferase (ALT) was

more than two times ULN in fourteen (41.1%) patients. AST/ALT ratio was more than two in eleven patients.

**Table 3** shows diagnostic indices and follow up of patients along with comparison of hepatic and neurological WD. KF ring was positive in 54% (27) of all patients. The baseline 24-hour urinary copper value

more than 100 µg/day was in 66% (n=33) patients and more than 2 times of ULN (>80 µg/day) in all. With PCT, it increased to more than 5 times ULN (200 µg/day) in 100% of patients. Sixty percent (30) of patients were having >1000 µg/day and 20% (10) >1600 µg/day.

We started DP (mean dose of 20 mg/kg) in almost all patients along with zinc acetate (mean dose of 60 mg/kg/day). Symptoms managed accordingly. During the follow-up, monitoring was done for clinical and biochemical improvement, ensuring compliance and to identify adverse

effect. Five patients showed poor response to therapy with no improvement in liver function tests despite of good compliance. Two patients develop Stevens Johnson syndrome (SJS), one develop renal failure with rising creatinine. Twenty-seven (54%) patients showed improvement on chelation therapy with fall in hepatic enzymes and improvement in neurological symptoms. In two patient penicillamine was stopped

### Highlights

- Wilson's disease (WD) has considered as the common cause of metabolic liver disease in children above five years of age.
- Hospital based studies in India has reported WD to account for 7.6% and 19.7% of total patients of hepatobiliary disease.
- We reported the youngest patient presented at three years of age with acute hepatitis. Thus, age should be no bar to evaluate for WD.
- In this study, patient with hepatic WD has mean age at onset 7.5 years (delay in diagnosis of 7 months) and in neurological WD mean age was 10.5 years (delay of 12 months). All patients with neurological WD were more than 8 years except one was 4-year-old.
- The preferential standard treatment of WD is chelation therapy using D-penicillamine. Other drugs include trientine and zinc acetate. These drugs are highly efficient but have side effects so needs monitoring frequently.<sup>36</sup>

**Table 1. Clinical presentation**

Mode of presentation	Hepatic n=38/50 (76%)	Neuropsychiatric 12/50 (24%)	Others
Mean age	7.5 years	10.5 years	
Clinical forms (n)	Acute hepatitis (8) Acute liver failure (6) Chronic liver disease (24)	Choreoathetosis (10) Dystonic syndrome (9) Parkinson's syndrome (8) Neuroregression (8) Behaviour changes (7) Bulbar palsy (6) Tremors flapping (4) Cerebellar dysfunction (4) Abnormal Neuroimaging (8) Poor scholastic performance (7)	Both hepatic and neurological (4) Renal (1) Articular (2) Hemolytic anemia (2)

**Table 2. Clinical and biochemical profile of patients**

Jaundice	26 (52%)	Serum bilirubin mean (range) md/dL	4.2 (0.6-16)
Ascites with edema	20 (40%)	Serum albumin mean (range) gm/dL	2.9 (1.9-3.9)
Portal hypertension	17 (34%)	ALT mean (range) IU/L	158 (23-1848)
Variceal bleed	14 (28%)	AST mean (range) IU/L	216 (11-1708)
Coagulopathy not corrected with vitamin K	22 (44%)	PT INR mean (range)	2.44 (1.2-9)
Splenomegaly	20 (40%)	ALP mean (range) IU/L	240 (59-810)
Hepatomegaly	15 (30%)		

AST; Aspartate aminotransferase, ALT; Alanine aminotransferase, ALP; Alkaline phosphatase, PT INR; Prothrombin time international normalized ratio

**Table 3.** Comparison of hepatic form with neurological form of WD

S no.	Characteristics	Hepatic (38)	Neurological (12)	p-value
1	Mean age at onset (years)	7.5	10.5	p=0.710
2	Cirrhosis	19	6	p=0.303
	Micro nodular	13	6	
3	Macro nodular	6	0	p=0.248
	S.ceruloplasmin (mg/dL) (mean)	19	20.12	
4	<10	5	4	p=0.769
	24-hour urinary copper without challenge (mean)	170	208	
5	>100 µg	25	8	p=0.951
	24-hour urinary copper with challenge (µg) (mean)	1033	949	
6	>2 ULN	All	All	p=0.911
	>1000 µg	8	3	
7	>1600 µg	4	2	p=0.200
	Ferenci score ≥4	30/38 (78.9%)	12 (100%)	
8	KF ring positive	17/38 (44.7%)	10/12 (83.3%)	p=0.045
9	Mortality	7/38 (18.5%)	2/12 (16.6%)	p=0.769
10	Follow-up			p=0.989
	Improving clinical symptoms	20	7	
	Disappearance of KF ring	10	5	p=0.515

WD; Wilson's disease, ULN; Upper limit of normal, KF; Kayser Fleischer

after improvement and they were maintained on zinc acetate.

Overall, nine patients died during the study period, among which three patients were having acute hepatic failure, four were in decompensated chronic liver failure and two were having neurological WD.

## Discussion

WD has considered as the common cause of metabolic liver disease in children above five years of age.<sup>18,19</sup> It account for 8-20% of cases with acute liver failure (ALF) similar to other etiologies.<sup>17</sup> The prevalence of WD in European population has reported between 10-30 per 100,000 and in Asian countries it is high and reported between 33 and 68 per 100,000.<sup>6,7</sup> In India, there are mainly hospital based studies with no community-based studies on epidemiology of WD. Hospital based studies in India has reported WD to account for 7.6% and 19.7 % of total patients of hepatobiliary disease.<sup>19</sup>

## Clinical Features

Patients usually become symptomatic between 5-35 years with wide range. In previous studies, youngest asymptomatic patient reported was 4 months, old diagnosed on family screening and youngest symptomatic patients was 3-year-old.<sup>20,21</sup> We reported the youngest patient presented at three year of age with acute hepatitis. Thus, age should be no bar to evaluate for WD. Studies reported mean age at onset of clinical feature between 7.7 to 9.2 years with mean delay in diagnosis of about 1.5 to 3 years.<sup>22</sup> We also reported similar findings with onset of symptoms at mean age of 8.3 years with lag of 11 months to diagnosis.

Some studies had reported male predominance.<sup>18,20</sup>

We reported the male: Female ratio of 2/1. However, some studies have shown, equal sex ratio<sup>11</sup> and others, few have shown female predominance.<sup>21</sup> Hence, there is no sex predilection for WD, although the clinical presentation of WD varies with age and gender.<sup>22</sup>

The younger children presented with mainly hepatic manifestations (<10 years: 83%; 10-18 years: 52% >18 years: 24%), while neurological presentations increases as age increases (<10 years: 17%; 10-18 years: 48%; >18 years: 74%).<sup>19,22</sup> Delay in the diagnosis of WD was more longer in neurological WD (18 months) as compared to hepatic WD (6 months).<sup>20</sup> In this study, patient with hepatic WD has mean age at onset 7.5 years (delay in diagnosis of 7 months) and in neurological WD mean age was 10.5 years (delay of 12 months). All patients with neurological WD were more than 8 years except one was 4-year-old.

Studies have shown that neurological features at diagnosis are more common in males and hepatic in females but in children, we did not observed such difference.

Manifestations in hepatic WD can vary from acute hepatitis to acute/fulminant hepatic failure, and there may be chronic hepatitis with compensated or decompensated cirrhosis.<sup>23</sup>

Neurological WD manifests as movement disorder like ataxia, dystonia, tremors or Parkinson's like an akinetic-rigid syndrome with or without bulbar involvement.<sup>24</sup>

Children mainly present with hepatic disease. In this study, hepatic manifestations were seen in 75% patients, neurological in 24% of patients. Studies from India reported isolated hepatic disease in 20-54% of pediatric patients, isolated neurological features in 8-22% of patients and combined neurohepatic disease in 11-36% with 15-35% of patients identified on family screening while asymptomatic.<sup>19-21</sup>

In this study, six patients presented with ALF with encephalopathy, eight with acute hepatitis (without encephalopathy). Rest patients presented with chronic liver disease. Studies have shown ALF constitutes 10 to 30 percent among all cases of WD, acute hepatitis 10 to 25 percent and chronic hepatitis in 10 to 30%. WD might be responsible for 9% of all ALF cases similar to other etiologies.<sup>19,21,23,25</sup>

Many patients with chronic liver disease had cirrhosis at the time of diagnosis. In this study, cirrhosis seen in 25 patients (50%) with majority having micronodular cirrhosis and portal hypertension was seen in 34%. Various studies reported cirrhosis in 30 to 60% patients.<sup>19,21,23,25</sup>

In our study, most common neurological presentation was movement disorder (90%) with dystonia, chorea athetosis, Parkinson's like presentation. Three patients also have seizures. Machado et al.<sup>24</sup> described dystonia in 69% of patients with neurologic presentations. A study from Bangalore reported Parkinsonism 62.3%, dystonia 35.4%, cerebellar 28%, pyramidal signs 16%, chorea 9%, athetosis 2.2%, myoclonus 3.4% and behavioural abnormalities 16% among various neurological features.<sup>15</sup> Deterioration of handwriting and school performance in older children, and dysarthria, and drooling of saliva in younger children may be the early neurological manifestations.<sup>24,26</sup>

Most patients with neurological WD had underlying hepatic involvement and 20-30% patients may have past history of jaundice.<sup>19</sup> In this study, most patients with neurological Wilson have normal liver function test but all have coarse echotexture of liver on ultrasonography and six were having micronodular cirrhosis. Neuroimaging was showing hyper-intensities in basal ganglia on T2 images in 8 patients, cerebral atrophy with gliosis in one. Nerve conduction study done in one patient showing pure motor axonal neuropathy affection. MRI features pathognomonic of WD are "face of giant panda" (14.3%), tectal plate hyperintensity (75%), central pontine myelinolysis-like abnormalities (62.5%), and concurrent signal changes in basal ganglia, thalamus, and brainstem (55.3%).<sup>27</sup>

Some other manifestations had been reported in literature like gigantism, renal abnormalities (8-10%) such as aminoaciduria, nephrolithiasis, hypercalciuria and nephrocalcinosis, coomb negative hemolytic anemia (7%) cardiomyopathy, myopathy, bone and joint manifestations, hypoparathyroidism, and pancreatitis.<sup>19</sup>

In this study, two patients present with direct Coombs test negative hemolytic anemia, one patient develops hydronephrosis with renal calculi. Osseo muscular symptoms may rarely be the presenting feature.<sup>19,28</sup> Our two patients presented with arthritis of knee with effusion. Investigations reveal chronic liver disease and WD was diagnosed later on.

In this study, KF ring are present in 44.7% of hepatic WD and 83.3% of neurological WD. Presence of KF ring is highly specific for WD. Studies had shown KF ring are always bilateral and seen in 50 to 60% of hepatic and 95 to 100% cases of neurological WD.<sup>29</sup> Younger patient may not develop KF ring at time of diagnosis. We have only two patients younger than 6 years with

positive KF ring on slit lamp examination. KF ring may also present in other diseases also such as biliary cirrhosis, cryptogenic cirrhosis, chronic active hepatitis, and neonatal hepatitis.<sup>19</sup>

Two patients were having sunflower cataract. Copper deposition in the anterior capsule of lens lead to sunflower cataract in 2-17% of patients.<sup>30</sup> Night blindness, exotropic strabismus, optic neuritis, and optic disc pallor are rarer ophthalmological manifestations.<sup>29,30</sup>

## Diagnosis

There is delay in diagnosis of WD due to variable clinical presentation. In addition there is no single reliable test easily available for diagnosing WD. After suspecting WD clinically, a wide range of test may be required to confirm the diagnosis. Over-reliance on specific test delays the treatment and leads to progression of disease.

The modified Leipzig scoring system incorporating routinely available laboratory tests has 98.1% sensitivity and 96.6% specificity for diagnosing WD.<sup>16,19</sup> In this study, we had use combination of various test for diagnoses of WD.

## Serum Ceruloplasmin

Serum ceruloplasmin levels less than 20 mg/dL are seen in WD with values lower 10 mg/dL are highly suggestive. This test is use for patient more than 1 year of age. Values between 10-20 mg/dL are seen 20% of in heterozygotes.<sup>19</sup> However, levels are falsely elevated in presence of acute inflammation and low normal values are seen in 50% of patients with acute liver disease.<sup>33</sup> Upto 40% of patients with hepatic and 15% of neurologic WD have normal levels.<sup>32</sup> Serum ceruloplasmin is typically lower in neuropsychiatric disease compared with liver disease. Studies have shown that low serum ceruloplasmin has sensitivity of 21-56% and specificity of 63-84% for diagnosis WD in presence of hepatic disease.<sup>32</sup>

In this study, mean serum ceruloplasmin level was lower in neurological WD (18 mg/dL) than hepatic (25 mg/dL) WD. All patients with neurological WD were having serum ceruloplasmin level less than 20 mg/dL but with hepatic WD 32% were having serum ceruloplasmin values in normal range. Most of them have acute hepatitis.

## 24-hour Urinary Copper Assay

Level of more than 100 mcg/24-hour are diagnostic for symptomatic WD.<sup>31,33</sup> For asymptomatic patients lower value of cut off levels of 40 mcg/24-hour increases the sensitivity of test.<sup>19,31</sup> Our all patients have values more than 2 times of upper limit of normal. PCT had been consider useful in past but now it is not recommended because of high false positive results.<sup>34</sup> This test should be perform in equivocal cases only.

## Hepatic Enzymes

Previous studies reported that low level of serum alkaline phosphatase (ALP) with low ALP to serum bilirubin ratio or high value of aspartate aminotransferase as compared to ALT should also raise suspicion of WD. A ratio of more than 2.2 between AST and ALT may have a sensitivity of 94% and a specificity of 86% for WD.

However, these findings are not seen in all cases.<sup>32,33,35</sup> We observed AST to ALT ratio more than 2 in eleven patients.

### Treatment and Follow-up

The preferential standard treatment of WD is chelation therapy using DP. Other drugs include trientine and zinc acetate. These drugs are highly efficient but have side effects so needs monitoring frequently.<sup>36</sup>

In neurological WD, there may paradoxical deterioration of symptoms after starting DP. Studies had reported an incidence of 10% for such deterioration but one study by Brewer et al.<sup>36,37</sup> reported it as high as 50%. In our study one patient with neurological WD, develop mild neurological deterioration with increasing dose of penicillamine after 1 year of good improvement. Therefore, we must start DP at the lowest possible dose in neurological WD. The dose is slowly increase with regular clinical and biochemical monitoring. Significant other adverse effects reported in 10-30% of patients on DP therapy.<sup>19</sup>

Our two patients develop SJS, one develop renal failure with rising creatinine. The drug should stop immediately, if early hypersensitivity reactions occur. Clinical improvement in hepatic WD in response to chelation therapy is shown by decreasing level of jaundice, ascites, and portal hypertension. Studies had shown clinical response to treatment of around 90% in hepatic and 55% in neurological disease.<sup>19</sup> In our study after follow-up of 3 years, 27 patients showed clinical improvement on chelation therapy.

Reappearance or appearance of KF ring in whom it was absent should suspect the possibility of non-compliance of drugs or failure of therapy. Fulminant hepatic failure has 100% mortality in absence of liver transplantation.<sup>38</sup> We noticed 20 percent mortality in hepatic WD and 18 percent mortality in neurological WD. Overall, nine patient died during the study period, among which three patients were having acute hepatic failure, four were in decompensated chronic liver failure and two were having neurological WD.

### Conclusion

Children with WD may present with varied and unusual clinical manifestation. Therefore, early suspicion and prompt diagnosis is necessary for good prognosis. Family screening should be performed for every diagnosed patient. It requires wide range of tests as genetic testing is not easily available. Acute liver failure has high mortality. Early chelation therapy reverses the clinical and biochemical abnormalities.

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**Ethics Committee Approval:** Office of the Ethics Committee Sawai Man Singh Medical College and Attached Hospitals, Jaipur (decision no: 814, date: 26.08.2021) approved the study.

**Informed Consent:** Patients visiting the outpatient department or admitting in wards with clinical presentation suggestive of WD were enrolled in the study after obtaining a valid informed written consent.

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