Clinical profile of Wilson disease in children between 1 and 12 years of age admitted at a tertiary care center

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ABSTRACT

Background: Wilson disease (WD) is a rare autosomal recessive disorder characterized by the accumulation of copper in the liver, brain, cornea, and kidneys. Asymptomatic nature of disease at earlier stages leads to diagnostic enigma. **Objective:** The objective of this study was to study the clinical, biochemical, and histological profile of WD in children between 1 and 12 years of age. **Methodology:** It was a hospital-based descriptive study. All children between 1 and 12 years of age who were admitted with symptoms of liver disease and neuropsychiatric symptoms were screened for WD. Low serum ceruloplasmin (<20 mg/dl) and presence of Kayser–Fleischer rings in cornea were the parameters for diagnosis of WD in the study. Clinical and laboratory data were collected from 32 children diagnosed with WD. Evaluation included detailed history and physical examination, ultrasound abdomen, upper endoscopy, laboratory examination, and liver biopsy. **Results:** The mean age of presentation was 9.2 years. Hepatic manifestations (53%) were the main presentation followed by neurologic (25%) and hepatocerebral (18.7%) manifestations. Predominant symptom was jaundice in 64.7% of children with hepatic manifestations. Speech disturbance was found to be the most common symptom in neurologic presentation. Ultrasound abdomen showed features of portal hypertension in 11 (34.7%) children. Different grades of esophageal varices were noted in 13 (40.5%) children. Histopathology of biopsied samples showed evidence of cirrhosis in 18 (56.2%) children and features of chronic active hepatitis in 14 (43.7%) children. **Conclusion:** Diagnosis of WD in children is obscure and this may invariably decelerate the diagnosis and prognosis of this malady. Therefore, children presenting with any form of liver disease and/or neuropsychiatric features, WD must be suspected and further investigations should be carried out.

Key words: *Hepatic manifestations, Jaundice, Neuropsychiatric manifestation, Wilson disease*

Wilson disease (WD) is an autosomal recessive genetic disorder of copper metabolism, characterized by liver disease and neurological symptoms with accumulation of excess copper in liver, brain, and other tissues [1]. The worldwide prevalence of WD is estimated to be 1 in 30,000 live births, a gene frequency of 0.58%, and a carrier frequency of 1 in 86 [2]. It is caused by mutation in the ATP7B gene encoding a copper transporter P-type ATPase, which results in decreased biliary copper excretion and diffuse accumulation of copper in liver. With increasing copper overload overtime, deposition of copper occurs in other organs such as nervous system, cornea, kidneys, and heart [3].

The clinical presentation of WD varies widely, a typically hepatic form which presents in the first decade of life is followed by neurologic symptoms and psychiatric symptoms which usually presents after the age of 20 years. Kayser–Fleisher (KF) ring is a brownish discoloration of outer margin of cornea due to deposition of copper in Descemet's membrane. KF ring is present in 95% of patients with neurological symptoms, in 50%–60% of patients without neurological symptoms. WD can present as Coomb's negative hemolytic anemia due to the release of large amounts of copper from damaged hepatocytes [4,5].

Laboratory parameters such as low ceruloplasmin and elevated 24-h urine copper and observation of KF rings in an ophthalmological examination carried out in combination direct toward the diagnosis [3]. Due to the lack of a single diagnostic test with adequate sensitivity, diagnosis should be based on the combination of clinical features, laboratory findings, and the results of mutation analysis in a patient with liver and/or neuropsychiatric manifestations [2].

Considering the rarity of disease, diagnosis has a great impact because a specific treatment of proven efficacy exists, and without timely management, the disease is invariably fatal. Limited studies are available that have described exclusively pediatric samples and those that have been published generally have small patient samples [6-9]. Hence, this study was undertaken to study the clinical, biochemical, and histological profile of WD in children between 1 and 12 years of age in our geographical area.

METHODOLOGY

A hospital-based descriptive study was conducted at a tertiary care teaching institute of Chennai for a period of 18 months. Ethical clearance was obtained from the institutional ethical committee and informed consent was taken from parents and children before recruitment. Children between 1 and 12 years of age, who presented with acute and chronic liver disease, extrapyramidal symptoms, speech disturbance, and gait disturbances, recent deterioration of school performance, and siblings of proven cases of WD, were subjected to preliminary screening. Children in whom liver biopsy was contraindicated were excluded from the study.

Indicators such as slit-lamp examination for KF ring and serum ceruloplasmin level were assessed in all the patients. Patients with serum ceruloplasmin level <20 mg/dl and positive KF ring were diagnosed as WD. A total of 32 children diagnosed with WD were included in the study. Detailed medical and family history was taken. Thorough physical examination was conducted to assess the presence of jaundice, hepatosplenomegaly, ascites, and signs of liver failure. Neurologic and psychiatric assessments were done. Investigations such as complete blood count, liver function tests, renal function test, ultrasound abdomen, upper gastrointestinal (GI) endoscopy, and liver biopsy were performed.

RESULTS

The data obtained were tabulated and subjected to statistical analysis. Descriptive analysis was carried out to measure mean, standard deviation, and frequencies of the sample. A total of 32 children aged 1–12 years, diagnosed with WD, were included in the study. Of 32 children, 18 (56.2%) belonged to the age group of 10–12 years and only 2 (6.2%) children belonged to the age group of 3–5 years. The male-to-female ratio in the study population was 1.9:1 (Table 1).

A total of 7 of 32 children had family history suggestive of WD. Consanguinity of parents was found in 9 (28.1%) cases, of which four children were born to the 2nd degree consanguineous parents and five children were born to the 3rd degree consanguineous parents. Of 32 patients, 20 (62.5%) resided in rural and 12 (37.5%) resided in urban areas.

Hepatic presentations were noted in 17 (53.1%) of children, of which 8 (47%) belonged to the age group of 6–9 years followed by 7 (41.1%) in 10–12 years and 2 (11.7%) in 3–5 years of age. Among the 8 (25%) children who presented with neurological symptoms, 6 (75%) belonged to the age group of 10–12 years and 2 (25%) in the age group of 6–9 years. Hepatocerebral presentation was noted in 6 (18.7%) of children, of which 4 (66.6%) belonged to the age group of 10–12 years and 2 (33.3%) were in the age group of 6–9 years. One (3.1%) patient who belonged to the age group of 6–9 years presented with Coomb's negative hemolytic anemia (Table 2).

Table 1: Age and sex distribution of children with Wilson disease

Age group (years)	Male n (%)	Female n (%)	Total n (%)
1–2	0	0	0
3–5	1 (50)	1 (50)	2 (6.2)
6–9	9 (75)	3 (25)	12 (37.5)
10–12	11 (61.1)	7 (38.8)	18 (56.2)
Total	21 (65.6)	11 (34.4)	32 (100)

Of 17 children with hepatic manifestations, 2 (11.7%) children were asymptomatic, 4 (23.5%) children were initially diagnosed as acute hepatitis, and 11 (64.7%) children as chronic liver disease. Jaundice was the predominant symptom seen in 12 (70.5%) children, followed by abdominal distension in 10 (58.8%), fever in 7 (41.1%), and GI bleed in 3 (17.6%) patients. Of eight cases with neurological presentation, speech disturbance was the most common symptom seen in 6 (75%) children followed by gait disturbance in 5 (62.5%), involuntary movements in 4 (50%), poor scholastic performance in 3 (37.5%), and behavioral disturbances in 3 (37.5%) children.

Among six children with hepatocerebral presentation, speech disturbance was predominant symptom, seen in 4 (66.6%) children followed by gait disturbance in 3 (50%) children (Fig. 1).

Among the 17 children with hepatic presentation, jaundice 12 (70.5%) was the predominant sign, followed by ascites in 10 (58.8%), hepatosplenomegaly in 9 (52.9%), and anemia in 4 (23.5%) children. Isolated hepatomegaly and splenomegaly were seen in 2 (11.7%) children each. Among eight children with neurological presentation, dysarthria was the predominant sign in 6 (75%) children, followed by dystonia in 5 (62.5%) children, tremors in 4 (50%) children, while 2 (25%) presented with chorea. Of six children with hepatocerebral presentation, 4 (66.6%) children presented with jaundice, ascites, anemia, and isolated hepatomegaly and isolated splenomegaly in 1 (16.6%) child each (Fig. 2).

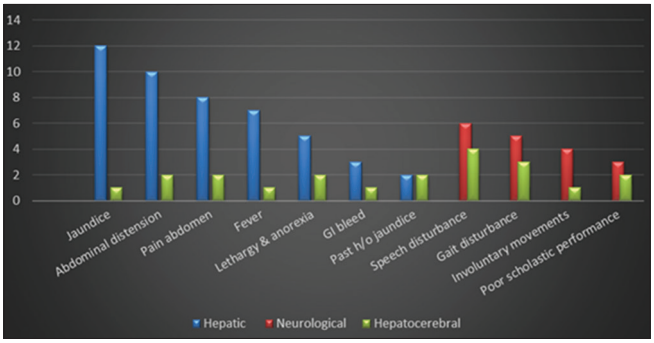

Fig. 1: Symptoms of Wilson disease in different presentations

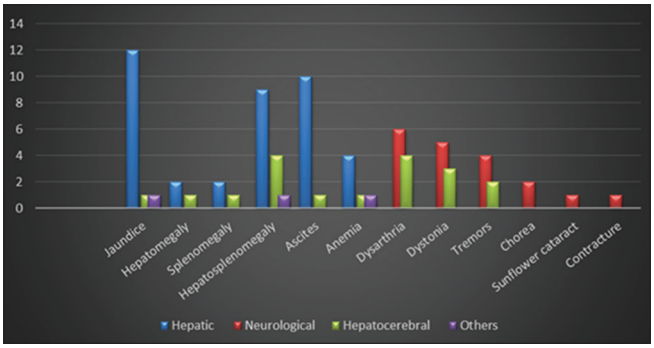

Fig. 2: Signs in Wilson disease with different presentations

Table 2: Age distribution among children with different presentations

Age (years)	Hepatic (%) n=17	Neurological (%) n=8	Hepatocerebral (%) n=6	Others (%) n=1
3–5	2 (11.8)	0	0	0
6–9	8 (47)	2 (25)	2 (33.3)	1 (100)
10–12	7 (41.1)	6 (75)	4 (66.6)	0

Liver function tests showed elevated serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase in 18 (56.2%) children, elevated serum bilirubin in 14 (43.7%) children, and prolonged prothrombin time in 4 (12.5%) children. Ultrasound abdomen showed portal hypertension in 11 (34.7%) children. Upper GI endoscopy showed different grades of esophageal varices in 13 (40.5%) children. Liver biopsy showed the evidence of cirrhosis in 18 (56.2%) children and features of chronic active hepatitis in 14 (43.7%) children.

DISCUSSION

Wilson's disease is one of the rare forms of liver disease in children. The first possible case of WD was described by Frerichs (1861) in a 9-year-old boy with movement and speech abnormalities, whose autopsy showed liver cirrhosis [10]. In India, among pediatric liver diseases, WD accounts for 7.6–19.7% in tertiary hepatobiliary centers. Fifteen to 20 new cases of WD are registered annually in referral neurology centers [11]. There are few studies that have described exclusively pediatric samples and those that have been published generally have small patient samples [6-9].

Important indicators of disease which help in diagnosis are the presence of KF rings, low serum ceruloplasmin, and increased 24 h urinary excretion. In our study, two parameters –positive KF ring and serum ceruloplasmin level <20 mg/dl were considered while screening of patients for WD [3].

A total of 32 children diagnosed with WD were included in our study. Majority of the children (56.2%) belonged to the age group of 10–12 years and only 6.2% of patients belonged to the age group of 3–5 years. The mean age of presentation in our study group was 9.2 years. Similar results were also noted in studies by Sánchez-Albisua *et al*. [12] (mean age=9.8±3.4 years), Yüce *et al*. [7] (10.1±2.5 years), and Kalra *et al*. [13] (7.2 years). The mean age of the onset of WD was 11.2 years and 12 years, respectively, in studies done by On *et al*., [14] and Saito [15] WD is asymptomatic in initial phases mainly due to ignorance of people; rarely, patients less than years are diagnosed; however, screening for the disease among the family members of patients may reduce this age by identifying asymptomatic patients earlier in life.

The male children predominated in our study with male-female ratio of 1.9:1 which was similar to a study done by Adhami and Cullufi, [16] and other studies documented in the Indian literature [17]. This could be due to society norm which pays higher attention to male children, which invariably increases the visits to hospital. In our study, the majority of our children were from rural areas. In contrary, Bhave *et al*. [18] noted in their study that 72.2% of children were from urban areas. As reported by Panagariya *et al*., [19] unrecognized environmental factors or habit of cooking food in copper utensils (in 40% of their cases) could have implicated the triggering events for the illness.

History of consanguinity was found in 28.1% of children. In other studies, it has been found consanguinity in 25.8% and 16.6% [18] of studied population, respectively, and mostly seen in Southern Indian population [20]. In our study, we noted family history suggestive of WD in 7 (21.8%) children. Similarly, positive family history has been documented by other previous studies [7,13,18]. This correlation helps to confirm the genetic nature of disease.

Among the many clinical presentations, hepatic form was most prevalent (53.2%) followed by neurologic presentation (25%) and hepatocerebral presentation (18.7%) and only 1 (3.1%) child presented with Coomb's negative hemolytic anemia. Similar records from the literature show, hepatic presentations as the most prevalent form in WD [18,21], except in one study by Kalra *et al.* [13] which showed predominance of hepatocerebal presentation.

Jaundice (70.5%) was the most common symptom among the hepatic form, followed by abdominal distension (58.2%), pain abdomen (47%), lethargy and anorexia (41.1%), fever (41.1%), GI bleed (17.6%), and history of jaundice in 11.7%. Similarly, jaundice was the predominant symptom noticed in studies done by Saito, [15] and Kalra *et al*., [13] whereas, abdominal pain (76.9%) was the predominant symptom in a study conducted by Yuce *et al.* [7].

The earliest symptoms of neurologic and hepatocerebral disturbances are speech disturbance, gait disturbances, involuntary movements, personality change, and scholastic backwardness [13,22]. In the present study, speech disturbances (71.4%) and gait disturbances (57.1%) were the predominant symptoms followed by involuntary movements (35.7%). Hepatocerebral presentation includes hepatosplenomegaly, ascites, and icterus, as the most common signs. In the present study, in children with hepatic and hepatocerebral presentation, hepatosplenomegaly was the predominant sign (56.5%), followed by ascites (47.8%), isolated hepatomegaly (13%), and isolated splenomegaly (13%). Our study correlated with previous literature studies [7,23].

In our study, liver enzymes were elevated in 56.2% of children. Hypoalbuminemia was seen in 28.1% of children and prolonged prothrombin time in 12.5% of children. Ultrasound abdomen showed features of portal hypertension in 34.3% of cases. UGI endoscopy showed various grades of varices in 40.6% of children. Yuce *et al.* [7] in their study, found elevated liver enzymes in 42.3% of cases and hypoalbuminemia in 38.5% of cases. Adhami *et al.* [16] in their study, found portal hypertension

in 42.5% of children. In our study, histopathologic evaluation of biopsy samples showed features of cirrhosis in 56.2% of children and chronic active hepatitis in 43.7% of children. This was similar to the study by Park *et al*. [24] (56%).

The results of the present study emphasize the importance of screening the patients with liver and/or neuropsychiatric symptoms and carrying out specific tests to increase the sensitivity of diagnosis of suspected cases. Limitations include small sample size and short duration of study which avert us from generalizing the results. We further recommend conducting a study in larger population, in a multi-institution setup which will help us to draw conclusions. Further, assessment of genetic and molecular changes will definitely aid in confirmation of the disease.

CONCLUSION

WD is a rare disease and diagnosis is a challenge for pediatricians and hepatologists since it can present in an oligosymptomatic form and test results may show little abnormalities. Although diagnosis depends on observing the clinical and laboratory data that provide evidence of abnormal copper metabolism, no single parameter is trustworthy in isolation. However, many pediatric patients do not exhibit all three. Therefore, maintaining a high index of suspicion, disease should always be considered in a patient of any age who exhibits hepatic and/or neurological abnormalities.

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