Clinical profile and outcome of Wilson disease in Indian children: A single centre study

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Abstract

Background: Wilson disease is an inherited disorder of copper metabolism characterised by cirrhosis of the liver, bilateral degeneration of basal ganglia and pigmented rings in the periphery of cornea. The clinical features vary considerably. Early diagnosis and prompt treatment favours good prognosis.

Objectives: To study the clinical and biochemical features of children with Wilson disease and the outcome after therapy at one year follow up.

***Method*:** The study was carried out at a tertiary care centre in South India. From January 2001 to December 2017, 35 children were diagnosed with Wilson disease based on clinical findings along with two or more of the following criteria: low serum caeruloplasmin level, increased urinary copper concentration before or after penicillamine challenge and/or the presence of Kayser–Fleischer (KF) rings.

***Results*:** Presentation was hepatic in 18 (51.4%), neurological in 8 (22.9%), mixed hepatic and neurological in 3 (8.6%) and pre-symptomatic in 6 (17.1%). All 35 children had low serum caeruloplasmin (mean 9.29±5.37mg/dl) and elevated urinary copper (mean 172.8±118.8 µg/24hr). KF rings were seen in 16 (45.7%). The Ferenci score ranged from 3 to 8 (median 4). Zinc was started in 33 (94.3%) patients and penicillamine in 29 (82.9%) Three patients died within 2 months of diagnosis, all having hepatic presentation. About 32 children were followed up for a mean duration of 5.42 years. Among children with hepatic presentation 11 (61%) improved fully following treatment. Among children with neurologic onset 4 (50%) showed significant improvement, while the rest had persistent neurological deficits.

***Conclusions*:** In this study, presentation of Wilson disease was hepatic in 51.4%, neurologic in 22.8%, mixed hepatic and neurological in 8.6% and pre-symptomatic in 17.2%. Hepatic presentations had more mortality while neurological presentations had persistent abnormalities

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Introduction

Wilson disease is caused by mutations in the ATP7B gene leading to toxic accumulation of copper in the liver, nervous system, cornea, kidneys and heart[1]. Diagnosis is sometimes difficult and a scoring system can be useful. Ferenci scoring system has a sensitivity of 98.1% and a specificity of 96.6% in the diagnosis of Wilson disease[2].

Objectives

To study the clinical profile of children with Wilson disease and the outcome following therapy.

Method

A retrospective review was done of the files of 35 children presenting to our paediatric unit between January 2001 and December 2017, with a diagnosis of Wilson disease. An approval from Institutional ethics committee was obtained for the study (IEC: 146/2018). The diagnosis of Wilson disease was based on presence of liver disease or neurological manifestations and a minimum of two of the following criteria:

1. Wilson disease among first degree relatives.
2. Low serum caeruloplasmin (< 20mg/dl)
3. Elevated baseline 24-hour urine copper (>40 µg/24 hours),
4. Raised 24-hour urine copper excretion after administering two 500-mg doses of penicillamine (>200 µg/24 hours),
5. Presence of Kayser–Fleischer (KF) rings
6. Coomb's negative haemolytic anaemia.

Children having hepatitis B, hepatitis C or autoimmune hepatitis were excluded from the study.

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Ferenci Score[2] was calculated for each of the patients. Siblings of index cases were screened for Wilson disease. Patients with hepatic forms were treated with oral Zinc sulphate (150mg/day) and/or D-penicillamine starting at an initial dose of 1-10mg/kg/day and gradually increased to 20mg/kg/day. Patients with neurological forms received pyridoxine (100mg/week and dose titrated as per response) in addition to zinc and D-penicillamine. Patients were followed up every 3 to 6 months depending on the clinical condition. Side effects of therapy like skin rashes, gastritis etc. were closely monitored.

Outcome was measured in terms of free copper [=serum copper in µg/dl - (3 x caeruloplasmin in mg/dl)], urine copper and liver enzymes at one year follow up, time taken for normalisation of liver enzymes and clinical course of the disease. King Wilson's index as suggested by Dhawan et al[3] was calculated for each patient to predict the outcome of hepatic decompensation in the setting of Wilson disease.

Statistical analysis was done using IBM SPSS statistics version 23. Results were expressed as mean, median, range, standard deviation and percentage.

Results

The 35 children diagnosed with Wilson disease were offspring of 32 couples. Five (15.6%) couples were consanguineous. Symptomatic index cases were 29, three were asymptomatic with hepatomegaly incidentally detected on routine check-up and 3 were diagnosed during sibling screen. Males were 23 (65.7%) and females were 12 (34.3%). The clinical presentation is listed in Table 1, laboratory data in table 2 and ultrasound findings in table 3.

Table 1: ***Symptoms and signs at presentation***

Variable	Hepatic *(n=18)*	Neurologic *(n=8)*	Mixed *(n=3)*	Pre-symptomatic *(n=6)*
Age at onset in years (median/range)	11.5 (8-16)	11.7 (6-13.9)	09 (4-12)	12.2 (9-16)
Age at diagnosis in years (median/range)	11.5 (8-16)	13.0 (11.5-15.3)	10.3 (4-17)	12.2 (9-16)
Male/female	10/8	5/3	3/0	5/1
Consanguinity [n (%)]	03 (16.7)	0 (0)	02 (66.7)	0 (0)
Hepatomegaly [n (%)]	14 (77.8)	06 (75.0)	02 (66.7)	06 (100.0)
Splenomegaly [n (%)]	12 (66.7)	02 (25.0)	02 (66.7)	02 (33.3)
KF ring [n (%)]	10 (55.6)	03 (37.5)	02 (66.7)	01 (16.7)
Jaundice [n (%)]	09 (50.0)	0 (0)	01 (33.3)	0 (0)
Pedal oedema [n (%)]	08 (44.4)	0 (0)	01 (33.3)	0 (0)
Ascites [n (%)]	05 (27.8)	0 (0)	0 (0)	0 (0)
Haematemesis [n (%)]	03 (16.7)	0 (0)	0 (0)	0 (0)
Melaena [n (%)]	01 (05.6)	0 (0)	0 (0)	0 (0)
Decreased school performance [n (%)]	02 (11.1)	05 (62.5)	02 (66.7)	0 (0)
Dysarthria [n (%)]	0 (0)	02 (25.0)	02 (66.7)	0 (0)
Slurred speech [n (%)]	0 (0)	03 (37.5)	02 (66.7)	0 (0)
Abnormal gait [n (%)]	0 (0)	03 (37.5)	02 (66.7)	0 (0)
Behavioural problems [n (%)]	0 (0)	04 (50.0)	01 (33.3)	0 (0)
Tremors [n (%)]	0 (0)	02 (25.0)	01 (33.3)	0 (0)
Chorea [n (%)]	0 (0)	01 (12.5)	0 (0)	0 (0)
Seizures [n (%)]	0 (0)	02 (25.0)	0 (0)	0 (0)
Rigidity [n (%)]	0 (0)	07 (87.5)	03 (100.0)	0 (0)
Dystonia [n (%)]	0 (0)	02 (25.0)	01 (33.3)	0 (0)

KF: Kayser–Fleischer,

Table 2: ***Laboratory parameters at presentation***

Variable	Hepatic *(n=18)* median (range)	Neurologic *(n=8)* median (range)	Mixed *(n=3)* median (range)	Pre-symptomatic (n=6) median (range)
Hb g/dl	10 (7-15)	12.3 (10.4-13.7)	13 (13-13)	12 (10-14)
Total WBC count per µL	6100 (2200-17,200)	8000 (4300-10,400)	6100 (5800-9300)	5100 (2200-8100)
Platelet per µL	111,000 (20,000-404,000)	230,000 (68,000-295,000)	105,000 (64,000-236,000)	240,000 (49,000-282,000)
TB mg/dl	02 (0.2-27)	0.8 (0.2-3.0)	01 (1-33)	01 (1-2)
DB mg/dl	01 (0.1-21)	0.2 (0.1-1.5)	0.3 (0.3-23.3)	0.16 (0.2-1)
Total protein g/dl	7 (4-8)	7.9 (4.7-8.6)	7 (7-7)	8 (6-8)
Albumin g/dl	3 (2-5)	4.25 (1.9-4.6)	4 (2-4)	4 (3.8-4.1)
AST, IU/L	91 (11-982)	24.5 (19-63)	39 (29-618)	27 (20-125)
ALT, IU/L	57.5 (8-1322)	14.5 (5-54)	15 (13-110)	23.5 (12-143)
ALP, IU/L	227 (67-855)	145 (88-288)	286 (13-622)	149 (102-556)
PT seconds	19 (12-120)	14.4 (12.1-31.7)	23 (12-27)	13.5 (12-18)
INR	1.5 (1-9)	0.95 (0.8-2.23)	1 (1-1)	1 (0.8-1)
Caeruloplasmin mg/dl	12.5 (1.8-18.7)	13.5 (3.3-18.6)	5 (5.2-13.8)	17 (8-18.5)
Serum copper µg/dl	44.2 (23-135)	74.5 (44.4-98)	70.2 (22-80)	64.5 (23-162)
Free copper µg/dl	19.5 (0-102)	36.85 (0-78)	39 (6-58)	25.5 (0-112)
Basal urine Cu µg/24 hrs	247.5 (56-1324)	250.5 (81-489)	356 (242-514)	203.5 (137-416)
Ferenci score[1]	4 (2-6)	4.5 (2-8)	2.5 (2-6)	8 (2-8)
King's Wilson index[3]	4 (1-18)	2 (1-7)	4 (1-11)	1 (0-2)

TB: total bilirubin, DB: direct bilirubin, AST: aspartate transaminase, ALT: alanine transaminase, ALP: alkaline phosphatase, PT: prothrombin time, INR: international normalized ratio

Table 3: ***Ultrasound features at presentation (n=35)***

Variables	Hepatic *(n=18)*	Neurologic *(n=8)*	Mixed *(n=3)*	Pre-symptomatic *(n=6)*
Coarse liver echotexture [n (%)]	13 (72.2)	06 (75)	03 (100)	01 (16.7)
Surface nodularity [n (%)]	06 (33.3)	03 (37.5)	0 (0)	01 (16.7)
Portal Hypertension [n (%)]	05 (27.8)	0 (0)	0 (0)	01 (16.7)
Portal vein size [mm (median/range)]	09 (06-14)	08.8 (08.2-10)	09 (08-11)	10.5 (10-11)
Features of cirrhosis [n (%)]	05 (27.8)	03 (37.5)	01 (33.3)	01 (16.7)

Characteristics of patients presenting with liver disease

Four children presented with acute hepatitis, 11 with features of chronic liver disease and 3 with fulminant hepatic failure. The predominant symptoms were jaundice in 9 (50%) (duration < 1 month in 5, persistent jaundice between 3 to 6 months in 3 cases, intermittent jaundice since 2 years with episode at presentation less than one month duration in one patient), pedal oedema in 8 (44.4%), ascites in 5 (27.8%), haematemesis in 3 (16.7%) and melaena in one (5.6%).

Genetic tests were done in 3 children and mutations in the ATP7B gene were detected in one child (homozygous for stop codon replaces lysine at codon 910 [AAG>TAG]). Two children underwent splenectomy within 2 years of presentation in view of portal hypertension. One child progressed to decompensated liver cell failure. One child had symptomatic refractory anaemia despite multiple blood transfusions and oral/intravenous iron on several occasions. The work up had revealed reticulocyte count of 2.7%, c-ANCA weakly positive, normal vitamin B12 level and haemostatic

screen with negative stool occult blood and parasites.

In this group 16 (88.9%) received zinc, 14 (77.8%) received penicillamine and 6 (33.3%) received pyridoxine. Compliance to treatment was good in 12 (66.7%) patients. The outcome at one year follow up is presented in table 4.

Table 4: ***Laboratory parameters at one year follow up (n=26)***

Variable	Hepatic *(n=14)* median (range)	Neurologic *(n=5)* median (range)	Mixed *(n=3)* median (range)	Pre-symptomatic *(n=4)* median (range)
Free copper µg/dl	24 (3-61)	22 (4-46)	38 (23-42)	18 (0-96)
Urine copper µg/24 hrs	200 (25-705)	201 (45-1323)	355 (49-355)	127 (59-248)
AST IU/L	25.5 (13-88)	26 (20-79)	36 (26-128)	30 (28-64)
ALT IU/L	18.5 (11-66)	18 (10-27)	14 (11-102)	19.5 (18-32)
Follow up period in years	4.1 (0-10.5)	2.2 (0.4-12.1)	2.3 (1.7-6.7)	3.3 (0-11.7)

AST: aspartate transaminase, ALT: alanine transaminase,

Elevation in AST was observed in 7 (38.8%) and ALT in 6 (33.3%) patients which normalised within a mean duration of 18.8±14.0 months and 16± 15.94 months respectively following therapy. Three children died within two months of presentation. Two had hepatic encephalopathy and one had intraventricular haemorrhage secondary to grossly deranged liver function tests and coagulation parameters. Eleven children had good response to treatment and remained asymptomatic.

Characteristics of patients presenting with neurological disease

The predominant symptoms and signs were decreased school performance in 5 (62.5%), dysarthria in 2 (25%), drooling of saliva in 2 (25%), slurred speech in 3 (37.5%), abnormal gait in 3 (37.5%), behavioural problems in 4 (50%), seizures in 2 (25%), tremors in 2 (25%), chorea in one (12.5%), rigidity in 7 (87.5%) and dystonia in 2(25%).

Genetic tests were done in two children of which mutation in the ATP7B gene was detected in one child (Homozygous for stop codon replaces lysine at codon 910 [AAG>TAG]. Another heterozygous substitution in codon 952 replaces lysine with arginine [AAA>AGA]).

In this group 8 (100%) received zinc, 7 (87.5%) received penicillamine and 7 (87.5%) received pyridoxine. Only 4 (50%) children were compliant with the treatment. Only 2 children had elevated AST and ALT at presentation, both of which normalised within a mean duration of 24.0±8.4 months and 12 months respectively following therapy. Good response with complete recovery of neuro-psychiatric manifestations was observed in 4 (50%) children while 3 (37.5%) had persistent neurological deficits

Characteristics of patients presenting with mixed hepatic and neurologic disease

The predominant symptoms and signs were jaundice in one (33.3%), dysarthria in 2 (66.7%), slurred speech in 2 (66.7%), abnormal gait in 2 (66.7%), rigidity in 3 (100%) and dystonia in one (33.3%). Genetic test was done in one child and no mutations were detected in the ATP7B gene. All 3 children received zinc, penicillamine and pyridoxine. One child had elevated AST and ALT at presentation both of which normalised by 48 months following initiation of therapy.

Characteristics of pre-symptomatic patients

These children were asymptomatic and were screened either in view of affected sibling or incidentally detected organomegaly. Hepatomegaly was found in 6 (100%), splenomegaly in 2 (33.3%) and KF ring in one (16.7%). Six (100%) children received zinc, 5 (83.3%) received penicillamine and one (16.7%) child received pyridoxine. One child had elevated AST and ALT at presentation, both of which normalised by 12 months following initiation of therapy.

There was no significant difference between age at onset, age at diagnosis, serum caeruloplasmin, free copper, basal urine copper, Ferenci score between the 4 groups at presentation. However King's Wilson index differed significantly between the 4 groups (p=0.04).

Discussion

There are limited data on Wilson disease that have exclusively described paediatric samples. Dhawan et al[3] studied 88 children, El-Karaksy et al[4] studied 54 children and Sintusek et al[5] studied 21 children. Wilson disease may manifest anytime between 3 to 74 years[6]. Mean age at diagnosis in our study was 11.3 years which is comparable to studies by Lin et al[6] (13.2 years) and Rukunuzzaman et al[7] (8.5 years).

Male to female ratio of 2:1 in our study is similar to a large study from Bangladesh[7].

The hepatic form of presentation is the most common and is often limited to elevated serum transaminases[7] and our study showed similar findings. Neurologic or psychiatric manifestations usually develop during the second or third decade but studies by Noureen *et al*[8] and Kalra *et al*[9] have reported earlier presentation in the first decade. KF rings were seen in 45.7% of the patients in our study whereas 66.3% of patients had KF ring in a study by Merle *et al*[10] and was significantly higher in patients with neurologic presentation.

In children, the Ferenci score[2] has a high sensitivity (98.1%) and specificity (96.59%) in the diagnosis of Wilson disease. A score of 0-1 is unlikely, 2-3 is probable and ≥4 is highly likely of Wilson disease and in our study the mean Ferenci score was 4.86±1.86. In our study the mean serum caeruloplasmin was 9.29±5.37 mg/dl. The threshold of serum caeruloplasmin < 14mg/dl has a sensitivity and specificity of 93% and 100% respectively[11] and values <20mg/dl have a sensitivity and specificity of 95% and 84.5% respectively[12] in the diagnosis of Wilson disease.

The mean free copper (non caeruloplasmin bound) in our study was 17±15.51µg/dl. In most untreated patients it will be more than 20µg/dl[13]. The mean basal urine copper in our study was 172.86±118.85µg/24 hours. The basal urine copper cut off value of 40µg/24 hours has a sensitivity and specificity of 78.9% and 87.9% respectively[12], whereas increasing the cut off value to 100µg/24 hours decreases the sensitivity to 65.8%[12] in the diagnosis of Wilson disease. In our study, post penicillamine challenge urine copper levels were assessed in 13 patients and the mean value was 985.86±643.33µg/24 hours. Considering the cut off value to be 5 times the upper limit of basal urinary copper values, the test has a sensitivity of 88% but a low specificity of 24.1% in the diagnosis of Wilson disease[12].

Three children in our study were diagnosed as Wilson's disease on sibling screening. Both American and European guidelines[13,14] recommend screening of first degree relatives of patients with Wilson disease, as they have a 25% chance of being a homozygote and develop the clinical disease.

In our study Zinc was used as first line therapy. D-penicillamine was added in most of the hepatic forms and pyridoxine in neurologic forms. All patients were advised a copper restricted diet. No adverse drug reactions were documented. Studies have shown that both Zinc sulphate and D-penicillamine are effective as first line therapy in Wilson disease and neither therapy is superior[15]. A good response to treatment is defined as when the serum transaminases return to normal[16]. In our study the median duration of normalisation of AST and ALT following therapy was 18 months and 12 months respectively. In a Brazilian study[16] the median time taken to achieve a clinical response after starting D-penicillamine was 10.7 months.

The King's Wilson index (KWI) proposed by Dhawan et al[3] is a useful marker to predict the outcome of children with hepatic decompensation. In our study, KWI was assessed for each of the patients and the mean value was 4.57±4.31. Eleven points and above indicates urgent need for liver transplantation. The KWI has a sensitivity and specificity of 93% and 98% respectively and a positive predictive value of 93%[3].

The possibility of Wilson disease should be considered in any child more than one year old presenting with any form of liver disease ranging from asymptomatic with raised liver enzymes to decompensated cirrhosis. Appropriate evaluation and the Ferenci scoring system should be applied to make a diagnosis of Wilson disease. The King's Wilson index should be monitored for prognostication and timely referral for liver transplantation.

Conclusions

In this study, presentation of Wilson disease was hepatic in 51.4%, neurologic in 22.8%, mixed hepatic and neurological in 8.6% and pre-symptomatic in 17.2%. Hepatic presentations had more mortality while neurological presentations had persistent abnormalities

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