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Clinical profile, prognostic indicators and outcome of Wilson's Disease in children: a hospital based study

Samanta Tryambak, Laha Sumanta, Purkait Radheshyam and Ganguly Sutapa

Department of Paediatric Medicine
NRS Medical College and Hospital
Kolkata

Correspondence:
Dr. Tryambak Samanta
Email: ts_ped@rediffmail.com

ABSTRACT

Background: Wilson's disease is a common metabolic disease of the tropics, which is treatable, if diagnosed early. In the paediatric group, the manifestations are mainly hepatic.
Aims: The objective was to study the varied presentations of the disease and to evaluate the diagnostic values of conventional tests in children. The prognostic importance of different indices in liver disorders was also assessed.
Method: The prospective work was carried out in the Paediatric Medicine Department of Nilratan Sircar Medical College & Hospital (NRSMCH) over a span of three years on children 1 through 12 years of age who fulfilled the prerequisite inclusion criteria.
Results: The mean age of the 34 children was 7.7 ± 2.13 years. Predominant liver involvement was seen in 17 patients, neurological disturbance in 7 and purely hematological manifestations in 2 cases; the remaining 8 children were incidentally diagnosed whilst screening the siblings of affected subjects. In our series the sensitivity of various diagnostic tests was: 24 hour urinary copper excretion - 100%, serum ceruloplasmin less than 20 mg/dL - 82.3%, K-F rings - 32.35%. Eighteen of the 23 followed up cases (78.2%) responded to medical treatment. The sensitivity and specificity of the new Wilson Index was more than the Nazer index in predicting mortality with liver involvement.
Conclusion: The superiority of the new Wilson Index over the Nazer index has to be validated on a larger scale. As the outcome of management was very promising, a high index of suspicion in pertinent cases can not only check mortality, but also prevent florid manifestations.

KEYWORDS: Wilson's disease (WD), ceruloplasmin, Nazer Index, new Wilson Index

Introduction

Wilson's disease (WD) is an inborn error of copper (Cu) metabolism and results in toxic accumulation of Cu in the liver, brain, cornea and other tissues. It occurs with an estimated occurrence of 1 in 500,000 to 1 in 100,000 in Western countries.[1] But in Southeast Asia, the prevalence is much higher (approximately 1 in 30,000 – 50,000) and is the leading causes of chronic liver disease in Indian children.[2] The manifestations are mainly hepatic, neurological, psychiatric and hematological. However, the wide array of clinical manifestations of Wilson's disease can lead to misdiagnosis with subsequent greater risk of irreversible damage to the liver and brain. With an aim to evaluate the clinical presentation and sensitivity of various diagnostic and prognostic parameters, a hospital-based prospective study was carried out.

Methods

The study was conducted over a span of three years on children 1 to 12 years of age in the Paediatric Medicine Department of Nilratan Sircar Medical College and Hospital (NRSMCH), Kolkata, India. All children presenting with all forms of liver disease were screened after exclusion of an infective etiology. Patients with regression of milestones, involuntary movement or psychiatric manifestations were also assessed. Children with acute hemolytic episodes were investigated, as and when necessary. All siblings of index cases were simultaneously evaluated. A pre-designed proforma was filled, which included a detailed history, neurological examination, systemic examinations, and ocular examination. All patients underwent specific diagnostic evaluation and investigations such as estimation of 24-hour urinary excretion of copper and level of serum ceruloplasmin along with ocular biomicroscopy of the cornea for the presence of Kayser-Fleischer (K-F) ring. For results and analysis, laboratory parameters only on first presentation were taken into account. As no single test is diagnostic by itself, only those patients who fulfilled 2 or more of the following criteria were enrolled: serum ceruloplasmin < 20 mg/dL, urinary Cu excretion > 100 mg/day, urinary Cu excretion > 1000 mg /day after penicillamine challenge and presence of the Kayser – Fleischer ring.[3] Penicillamine challenge test was done only in those subjects who had only

one of the first two criteria positive. Since few patients had involvement of more than one system, they were classified according to the main system involved. All were put on supportive measures, including dietary restrictions. Children with hepatic presentation were given zinc acetate during the decompensated state along with penicillamine. These drugs were given six hours apart to avoid chelation of zinc by penicillamine. Due to non-availability of trientine, all patients with neurologic manifestations were also treated with zinc and penicillamine. The cases as well as asymptomatic siblings were maintained on zinc. Those patients who responded to treatment were discharged and then followed up initially at intervals of 1 week for the first month and then monthly. A positive response was noted as clinical improvement along with either normalisation of biochemical or ophthalmologic markers or both wherever applicable. Clinical improvement was judged by subjective and objective wellbeing. The biochemical response in liver disorders was defined as lowering of serum transaminase to less than twice the upper limit of normal. Monitoring of serial urinary excretion of copper was done to monitor compliance to therapy as and when necessary. To keep a minimum window of 180 days for follow up of compliant patients, we did not include any case 6-months prior to completion of the study. So, depending on the time of enrollment of the patient, the followup period varied between 6 and 29 months. To predict the outcome of WD patients with liver disease, Nazer, *et al*[4] developed a prognostic score to be used at presentation. Dhawan, *et al*[5] reevaluated and proposed a new Wilson Predictive Index for paediatric patients. **Tables 1 and 2** describe the Nazer and new Wilson Predictive Index, respectively. We evaluated the significance of both the indices in our series.

Results

A total of 34 children were included in the study during a period of 3 years from December 2005 to November 2008.The mean age of the subjects was 7.7 ± 2.13 (range 3 years 2 months to 12 years). The male: female ratio was 19:15, most were Muslims (n=20), the rest Hindus. History of consanguinity was present in 18 cases. Predominant liver involvement was seen in 17 patients, neurologic disturbance in 7 and purely hematological manifestations in 2 cases, the remaining 8 children was incidentally diagnosed during the part of routine screening of the siblings of affected subjects.

Most cases with hepatic involvement (n=10) had manifestations of chronic liver disease, 4 had associated hemolysis (Coomb's negative hemolytic anaemia). Of these subjects, 5 had past history of jaundice, 2 had multiple episodes of the same. Four children presented with acute hepatitis like manifestations, 2 of them were relapsed cases. One relapsed patient had a protracted course with jaundice lasting greater than 12 weeks. Three children presented with acute liver failure, in all these cases the course of disease was very stormy. All of them succumbed, inspite of vigorous supportive management. **Table 3** compares the clinical features and biochemical parameters of patients with different forms of liver presentation. Of the 7 cases with neurologic manifestations, most presented with a combination of dystonia and involuntary movement (n=3). Purely dystonia and involuntary movement (in the form of chorea) were present in 2 and 1 child, respectively. Emotional lability as the sole presentation was seen in 1 subject. Among those with neurological manifestation, there was a past history of jaundice in 3 children. One of these patients died during the very first stay in hospital. However, that patient had concomitant features of chronic liver disease on presentation. Only 2 children presented with hemolysis as the only manifestation. Both had previous history of jaundice. The mean age of the asymptomatic children was much less, 5.46 ±1.8 years, the youngest being 3.2 years of age. **Table 4** compares the profile of patients with predominant hepatic, neurologic, and hematologic affection along with asymptomatic subjects. As far as individual diagnostic tests are concerned, 24-hour urinary copper excretion (without penicillamine challenge) had a sensitivity of 100%. But serum ceruloplasmin less than 20 mg/dL was present only in 28 cases (14 hepatic, 7 neurologic, 2 hematologic and 5 in asymptomatic cases) resulting in a sensitivity of 82.3%. K-F rings were present in 5 children with liver involvement and 6 patients with neurologic manifestations (overall sensitivity of 32.35%).

The Nazer Index was developed using a mixed population of adults and children and was based on simple laboratory parameters. When the score was used in other centres, however its utility was questioned.[6] Using more sophisticated statistical methods in a relatively large series of exclusively paediatric patients, Dhawan, et al[5] improved the original score and offered a new Wilson Predictive Index for children. Of the 5 parameters, total bilirubin (TSB), Internationalised Normal Ratio (INR), serum aspartate aminotransferase (AST), serum albumin and white blood cell count (WBC), the first four are conventional measures of liver function and provide for simple realisation of the severity of liver disease. Elevated WBCs may be a marker of occult infection or a surrogate marker of an as yet unidentified factor that predicts the severity of liver failure irrespective of the aetiology of liver disease. At the end of our study period, the sensitivity, specificity, positive predictive value and then negative predictive value of the Nazer Index to predict mortality was found out to be 80, 75, 57.1 and 90 %, respectively. But the corresponding values for the new Wilson Index were 100, 91.6.83.3 and 100.

Of the 30 children who were discharged after their first

Table 1: Showing the Nazer Index

Lab Measurement	Normal Value	Score (in points) 0	1	2	3	4
Serum bilirubin	0.2-1.2mg/dl	<5.8	5.8-8.8	8.8-11.7	11.7-17.5	>17.5
Serum AST	10-35IU/L	<100	100-150	151-200	201-300	>300
Prolongation of prothrombin time (seconds)		<4	4-8	9-12	13-20	>20

≥ 7 lindicates poor prognosis and mortality in liver disorders

Table 2: Showing the new Wilson Index

Score	Bilirubin (µmol/L)	INR	AST IU/L	WBC 10^9/L	Albumin (g/L)
0	0-100	0-1.29	0-100	0-6.7	>45
1	101-150	1.3-1.6	101-150	6.8-8.3	34-44
2	151-200	1.7-1.9	151-300	8.4-10.3	25-33
3	201-300	2.0-2.4	301-400	10.4-15.3	21-24
4	>301	>2.5	>401	>15.4	<20

≥ 11 Indicates poor prognosis and mortality in liver disorders

Table 3: Comparing the clinical features and biochemical parameters of the children with different forms of liver presentation

Parameters		ALF (n=3)	CLD (n=10)	AH (n=4)
Age (years)	Range	7.1 - 8.2	5.3 - 11.1	5.8 - 9.1
	Mean±SD	7.7 ± 0.6	8.0 ± 2	7.3 ± 1.5
Male : Female		2:1	3:2	1:3
Ascites (n)		3	4	1
TSB (mg/dl)	Range	14.2 - 22.5	0.8 - 8.2	5.8 - 17.6
	Mean ± SD	18.5 ± 0.2	3 ± 2.6	12.6 ± 5.5
Serum Alanine aminotransferase (IU/L)	Range	302 - 611	56 - 268	596 - 1023
	Mean ± SD	457 ± 155	134.5 ± 67.1	786.5 ± 188
Serum Aspartate aminotransferase(IU/L)	Range	496 - 701	82 - 337	443 - 792
	Mean ± SD	573 ± 111.4	611.7 ± 147.5	134.5 ± 102.3
INR	Range	3.8 - 8.0	1.0 - 2.1	1.2 - 1.9
	Mean ± SD	5.4 ± 2.3	1.4 ± 0.4	1.5 ± 0.3
Serum albumin (g/dl)	Range	2.5 - 2.8	2.3 - 3.6	2.8 - 3.8
	Mean ± SD	2.6 ± 0.2	3 ± 0.4	3.1 ± 0.5
WBC count	Range	6900 - 12100	4500 - 21600	2250 - 8150
	Mean ± SD	9100 ± 2690.7	10715 ± 4580.5	5293 ± 3038.6
Serum ceruloplasmin (mg/dL)	Range	14 - 45	4 - 31	10 - 18
	Mean ± SD	26 ± 16.6	14.4 ± 8.3	13.5 ± 3.4
24-hour urine Cu excretion (without penicillamine challenge) (µg/d)	Range	164 - 323	170 - 711	298 - 489
	Mean ± SD	223 ± 87.1	381.5 ± 192.9	360.25 ± 87.8
K-F ring (n)		-	4	1

ALF = Acute Liver Failure, CLD = Chronic Liver Disease, AH = Acute Hepatitis, SD = Standard Deviation

Table 4: Showing comparison of the profile of patients with predominant hepatic, neurologic, hematological involvement along with asymptomatic subjects

Parameters		Hepatic involvement (n=17)	Neurological involvement (n=7)	Hematological involvement (n=2)	Asymptomatic siblings (n=8)
Age (years)	Range	5.3 - 11.1	7.6 – 12	6.8-7	3.2– 8
	Mean ± SD	7.8 ± 1.7	9.7 ± 1.54	6.9 ± 0.2	5.46 ± 1.79
Male : Female		9:8	5:2	0:2	1:1
Serum Ceruloplasmin (mg/dl)	Range	4 - 45	3 - 18	16 - 18	3-41
	Mean ± SD	16.2 ± 9.9	11.4 ± 5.4	17.0 ± 1.41	17.5 ± 12.4
24 hr urine Cu excretion (µg/d)	Range	164 - 711	211 - 584	161 - 212	133 - 301
(without penicillamine challenge)	Mean ± SD	348.5 ± 164.3	375.8 ± 151.6	186.5 ± 36.0	217.6 ± 51.75
K-F ring(n)		5	6	Nil	Nil
Died at 1st visit (n)		3	1	Nil	Nil
Regular follow up (n)		12	5	1	5
Improvement/healthy (n)		10	2	1	5
Non responder /deterioration /Expired (n)		2	3	0	0

hospital visit, 23 subjects were on regular (6 months) follow up. After showing initial signs of improvement, 2 of the 12 followed up cases with liver involvement deteriorated. Both were readmitted, and finally expired. Five patients with neurologic manifestations were drug compliant, but most (n=3) had not improved on medical treatment, one had already died and the other 2 were in a very moribund state. The other two children responded well following the disappearance of the K-F ring. All siblings (n=5) of affected subjects are however well on maintenance zinc therapy. In our study, the mean (± SD) age of responders and nonresponders (7.8 ± 2.35 vs. 8.4 ± 1.6 years respectively) was not significant. Similarly serum ceruloplasmin (15.4± 9.4 vs. 16.4±11.6 mg/day in that order) and 24 hour urinary copper excretion (351.9±168.7 vs. 311.4±132.3 mg/day, respectively) did not vary statistically between these two groups.

Discussion

The clinical presentation of WD in this retrospective study reflects the referral pattern of a specialised tertiary centre. There is no difference in the disease prevalence in males and female patients.[7] However, our series has shown a higher prevalence of disease in male cases than in their female counterparts. In our study, hepatic disorders were the commonest form of presentation. This has been corroborated in other reports, carried out on the paediatric population.[8,9] Giacchino, et al,[10] in Italy reported almost the same incidence

of liver disease (50%) just as we did. The pattern of neurological involvement is similar to other reports that have quoted the same in adults with WD.[11] As previously reported in various literature, we confirm that the diagnosis of WD is not always easy, particularly in patients who present at a young age. Ceruloplasmin is an acute phase reactant and is a reflection of hepatic inflammation.[12] It has been shown to have sensitivity and specificity rates of 82.4% and 94.4%, respectively. In the present series, 17% of patients had a normal ceruloplasmin level, a figure similar to previous reports.[13] The urinary copper excretion was also developed as an aid to confirm the diagnosis and was shown to be 88.2% sensitive and 98.2% specific.[14] It was interesting to note that in our study, this was the only test that was 100% sensitive. Although helpful, the examination is cumbersome and difficult to perform in severely ill patients. However, we were able to do this investigation in all the children who died, as their hospital stay was more than a day long. Serum copper has been shown to have a sensitivity and specificity of 50% and 88.4%, respectively, and liver copper (with values usually over 250mg/g dry weight) of 75% and 61.5%, respectively[14], but both these studies were beyond our scope. A complete Kayser-Fleischer ring indicates long standing disease and is visible in some children as early as 5 years of age.[3] The rings are the best sign for diagnosis but unfortunately they are uncommon in the pediatric series, and were absent in 67% of the children in the present series. Surprisingly, a remarkably high incidence of K-F rings was reported by Bavdekar, et al[3], i.e. 78% (96% of neurological and 72 %of hepatic) of the children with WD who were evaluated. According to some authors, the combination of Kayser-Fleischer rings and low ceruloplasmin is probably the best guide towards a rapid diagnosis, however it is yet to be substantiated on a larger scale.[12,15] Due to the difficulty in reaching the diagnosis of WD, a number of other laboratory parameters have been developed. A ratio between alkaline phosphatase and serum bilirubin of <2.0 has been shown to differentiate WD from other causes of liver disease in adults,[16] but it is not always helpful in children, probably because of the effect of bone-derived alkaline phosphatase.[17] Petrasek et al[18] validated 3 scoring systems, Model For End-Stage Liver Disease (MELD) Score, WD Prognostic Index (WPI) and its recently revised version (RWPI) for deciding between chelation treatment and liver transplantation in patients with chronic decompensated and fulminant WD. But this study was solely done in the adult population. Literature exclusively on the paediatric age group in this subject is quite scant.

Conclusion

Wilson's disease is a rare instance of a common metabolic disorder, where treatment is cost effective. So, there is a need to be 'Wilson's minded' in relevant cases. Screening of siblings of index subjects is a must. Diagnostic limitations of all conventional tests have also to be borne in mind. As far as prognostication of liver disease in WD is concerned, the new Wilson Index has been validated and found more useful than the Nazer Index by our small prospective cohort. But the new scoring system, with its important clinical implications should be established by a multicenter study involving a large number of patients.

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