Original Article

WILSONS' DISEASE: VARIOUS SHAPES OF ONE DISEASE

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ABSTRACT

Objective: To find out the various clinical and biochemical presentations of patients with Wilsons' disease.

Methodology: This descriptive case series study was conducted in department of medicine and pediatrics at Liaquat university hospital Hyderabad/ Jamshoro from July 2005 to October 2008.It included 24 consecutive patients below 35 years of age who presented with hepatic manifestations and/ or Neuropsychiatric manifestations and or family history suggesting features of Wilsons' disease. Patients with hepatitis B and C and those with history taking antipsychotic drugs were excluded from the study. Patients data was included in a well designed Performa. Blood complete picture, liver function test with Serum ceruloplasmin, 24 hour urinary copper, Serum copper were sent. Quantitative data such as age, hemoglobin etc were expressed as mean with ± SD and quantitative variables such as sex, movement disorders, hepatic involvement etc were expressed as frequency and percentage.

Results*:* This study included 24 cases 15(62.5%) male and 9 (37.5%) female with mean age 11.8±3.5 years**.** *Jaundice was found to be the most prevalent feature whereas stiffness of whole body was the most prevalent feature in central nervous system .*Kayser-Fleischer rings were positive on slit lamp examination in 17 of 24(70.8%) patients .The mean hemoglobin level were 9.45±3.29g/dl,Bilirubin1.9± 3.13 mg/dl,INR1.34±.35, Serum copper 63.68 ±18.68ug/dl, cerulopasmin0.136±0.075g/l. The diagnosis of wilsons' disease was made on Sternlieb's criteria in 70.8% of cases.

Conclusion: The wilsons' disease is rare but important cause of chronic liver disease. It needs high degree of suspicion because it can involve various organs and early treatment can have good outcome.

KEYWORDS: Wilsons' Disease, Parkinsonism, and Chronic liver Disease.

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INTRODUCTION

Wilson's disease (WD) is an autosomal recessive disease characterized by accumulation of intracellular copper in the liver and central nervous system.[1] Patients present with a spectrum of clinical syndromes according to the most severely affected organ (e.g., acute liver failure, cirrhosis, neurologic or psychiatric syndromes).[2,3] It most commonly affects children or young adults and runs an invariably fatal course if not adequately treated by decoppering

therapy.[4] Increased awareness, improved diagnostic facilities leading to earlier recognition even in the pre symptomatic phase, clear distinction from mimicking conditions, aggressive therapeutic approaches owing to effective treatment, and an overall reduction in the morbidity and mortality are some of the expected changes over a century. It is widely acknowledged that the disease is not as rare as once believed.[4]

The clinical manifestations of WD are extraordinarily diverse. In the first decade of life, WD presents more often with hepatic manifestations. After the age of 20 years, 75% of case s present with neurological manifestations and 25% with both hepatic and neuropsychiatric manifestations.[5]

The current study describes the clinical, and biochemical aspects of WD from a tertiary care Liaquat university hospital Hyderabad / Jamshoro.

METHODOLOGY

This descriptive case series study included 24 consecutive patients received at paedriatic and medical outpatient and emergency departments of Liaquat university hospital Hyderabad, Jamshoro from July 2005 to October 2008.The inclusion criteria were patients below35 years of age presenting with:

1. Hepatic manifestations such as asymptomatic hepatomegaly, acute hepatitis, acute fulminant hepaticfailure, chronic active hepatitisor cirrhosis of liver.
2. Neuropsychiatric manifestations such as juvenile Parkinsonism, dystonia, choreoathetosis.
3. Family history of features suggestive of Wilsons' disease.

Exclusion criteria: Patients with hepatitis B and C, those with history of drugs causing extraparmedial symptoms such as antipsychoticdrugs, metoclopramide, and history of chorea due to other causes were excluded from the study.

Information regarding age, sex, mode of onset (e.g. hepatic, neurologic, psychiatric symptoms, other) was collected through a questionnaire and patients were classified as ''pure hepatic'', ''hepatoneurologic'', ''neurologic'', ''pure psychiatric'' and ''presymptomatic based on the mode of presentation''[6]

1. Pure hepatic when they had only liver dysfunction,
2. Hepato-neurologic when patients had hepatic and neurologic dysfunctions simultaneously or when the neurologic deficits evolved during ongoing hepatic manifestation,
3. Neurologic when they presented with only neurologic features with or without having suffered one or more episodes of jaundice in the past,
4. Pure psychiatric when patients had predominant psychiatric or behavioral manifestations with subtle or no neurologic features and with or without past history of jaundice.
5. Pre symptomatic when their diagnosis was established before the onset of any symptoms, during screening of siblings of index cases.[6]

Detailed family history was obtained along with pedigree pattern with emphasis on consanguinity. Biochemical investigations including liver function tests, prothrombin time and hematologic data including platelet count and peripheral smear examination and coombs' test were done in all cases. An abdominal ultrasound examination was done to look for hepatic changes, features of portal hypertension, and renal/gall stones. Serum ceruloplasmin, 24 hour urinary copper, Serum copper was sent to laboratory for analysis. The patients were sent to ophthalmology department of Liaquat university hospital Hyderabad for the presence of Kayser-Fleischer ring by slit lamp.

Diagnosis of WD was based on Sternlieb's criteria (at least two of the following findings present: Kayser–Fleischer rings by slit lamp examination, typical neurological symptoms, and/or low serum ceruloplasmin level).[7] Patients who did not fulfill these criteria, the nonclassic diagnosis of WD was based on clinical manifestations along with low ceruloplasmin,

increased24 hour urinary copper (>100ug/24hr), Serum copper > 60ug/dl, hepatic copper content > 250 mg/g dry weight liver tissue.[8]

Statistical Analysis: Quantitative variables such as age the hemoglobin levels, Bilirubin, INR, Serum copper, ceruloplasmin, urinary copper were expressed as Mean and Standard deviation. Qualitative variables such as sex, jaundice, movement disorders, pure hepatic involvement, hepato-neurologic presentation, pure neurologic presentation, presymptomatic, anemia, hepatomegaly, hepato-splenomegaly. Kayser-Fleischer rings were expressed as frequency & percent. Statistical analysis was performed by SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

This study included 24 cases of which 15(62.5%) were male and 9 (37.5%) were female. The mean age of patients at the time of presentation were11.8±3.29.In our cases 7/24(29.2%) patients presented with jaundice and 12/24 (50%) patients presented with movement disorders of which seven (29.3%) had juvenile Parkinsonism, three(12.5%) had dystonia and two(8.3%) had chorea. On clinical examination7/24(29.3%) were anemic, 16(66.7%) had hepatomegaly and nine (37.5%) patients had hepato-splenomegaly. Kayser-Fleischer rings were positive on slit lamp examination in 17/24 (78.8%) patients. The mean hemoglobin levels was 9.45+ 3.29g/dl, Bilirubin 1.9+ 3.13mg/dl, INR 1.34 ±0.35, Serum copper 63.68±18.68ug/dl, ceruloplasmin 0.136±0.075g/l ,24 hr. urinary copper 11.5± 44.4ug/24hrs. Table-I and II shows the baseline charectestics of patients. Pure hepatic involvement was seen in 6/24(25%), hepato-neurologic presentation in 8/24(33.3%), pure neurologic presentation in 4/24(16.7%) and 6/24(25%) were presymptomatic. Serum ceruloplasmin was <20 g/l in 19 (79.2%). Serum copper >60 ug/dl in14 (58.3%) and 24 hour urinary copper >100ug/24 hrs. in 15(62.5%) cases. Diagnosis was made on the basis of Kayser-Fleischer rings and ceruloplasmin levels in 17(70.8%)and 2(8.4%) cases had low ceruloplasmin levels and high levels of urinary copper and 5 (20.8%) patients had high levels of urinary copper and low serum free copper levels. Table-III shows the clinical and biochemical profile of the patients.

Table-I: Baseline Characteristics of the Patients (n=24)

Quantitative Variables	*Mean*	*SD±*
Age(yrs)	11.8	3.29
Hemoglobin(g/dl)	9.45	3.29
Bilirubin mg/dl	1.9	3.13
Serum copper ug/dl	63.68	18.68
cerulopasmin(g/l)	0.136	0.075
24 hr urinary copper ug/24hrs	115.4	44.4

DISCUSSION

Wilson's disease is an autosomal recessive inherited disorder of hepatic copper metabolism resulting in the accumulation of copper in many organs and tissues. In our patients the mean age of presentation was 11.8 years ±3.29 years in accordance with a study by Schoen RE etal.[9] Sinha et al[10] also had reported an early age of onset at 11.13 years in 49 patients with WD .In our study Wilson's' disease was present in 62,5% of male patients. Similar observation of two-thirds being male was made by Dastur et

Table-II: Baseline characteristics of the patients (n=24)

Qualitative Variables	*Frequency*	*%*
Sex		
Male	15	62.5
Female	9	37.5
Anemia	7	29.3
Jaundice	7	29.2
1.Pure hepatic	6	25
2.Hepato-neurologic	8	33.3
3.pure motor	4	17.6
4.presymtomatic	6	25
Hepatomegaly	16	66.7
Kayser-Fleischer	17	78.8

Table-III: Clinical and Biochemical Profile of patients with Wilson Disease (n = 24)

Variables	*Number (%)*
Hepatic:	
Jaundice	7(50)
Fulminant Hepatitis	2(14)
Ascites	2(14)
Hepatomegaly	6(100)
Hep-speomegaly	09(64.2)
Neurological:	
Juvenile	
Parkinsonism	7(58.3)
Dystonia	3(25)
Chorea	2(16.7)
Presymtomatic:	
Asymtomatic	4(66.6)
Hepatomegaly	2(33.3)
kayser-Fleisherring	17(78.8)
S.Ceruloplasmin g/l	
< 20	19(79.2)
>20	5(20.8)
Urinary Copper ug/24hrs	
>100	15(62.5)
<100	9(37.5)
S.copperUg/dl	
>60	14(58.3)
<60	10(41.6)
Diagnosis	
1.Kayser-Fleischer ring+S.ceruloplasmin.	17(78.8)
2. Low S.ceruloplasmin +high urinary copper.	2(8.3)
3. High urinary copper + low serum free copper	5(20.8)

al[11] in a major Indian series, while 20 of 22 cases reported by Jha et al were male.[12]

Wilson's disease may present with a variety of clinical conditions, the most common being liver disease and neuropsychiatric disturbances. Wilson's disease may also present with a clinical syndrome indistinguishable from chronic hepatitis or cirrhosis of other etiology.[13] In our cases liver involvement was present in nearly 60% of cases whereas neuropsychiatric symptoms were present in 50% of cases which is similar to the study conducted by Yarze JC et al.[14] Neurological symptoms usually develop in the mid-teenage years or twenties.[6] However, there are well-documented cases of late (45-55 years) neurological disease The initial symptoms may be very subtle, such as mild tremor and speech and writing problems, and are frequently misdiagnosed as behavioral problems associated with puberty. Patients presenting with neurological symptoms may also suffer from significant liver disease. In a substantial proportion, asymptomatic liver disease predates the occurrence of neurological signs. In many patients with neurological disturbances, asymptomatic liver disease can only be diagnosed by liver biopsy.[15]

The diagnosis of neurological Wilson's disease is usually made on the basis of clinical findings and laboratory abnormalities. Traditionally, a diagnosis of Wilson's disease was made based on Sternlieb's criteria, which required two or more of the following to be present: Kayser Fleischer rings, typical neurologic symptoms, or low serum ceruloplasmin levels.[7,16] Kayser-Fleischer rings were present in 70.8% of our cases as seen by Brewer GJ et al.[17] However, there are a few well-documented cases of neurological Wilson's disease without Kayser-Fleischer rings.[18] The cerulopasmin levels< 20 g/l was present in 79.2% our cases in accordance to that documented by Gaffney D et al.[19] Another important indicator o f the disease is urinary copper excretion and serum free copper level. Basal measurement can provide useful diagnostic information.[20] The conventional level taken as diagnostic for W D is greater than 100 m g in symptomatic patients. In the present series, two of 7 patients who had nonclassic features were diagnosed on the basis of low ceruloplasmin levels and high levels of urinary copper and 5 remaining patients on the basis of high levels of urinary copper and low serum free copper levels in accordance to liana gheorghe et.al.[21]

Wilsons' disease is rare but important disorder involving multiple organs. It needs high degree of suspicion because early diagnosis and treatment can ensure a good outcome.

REFRENCES

1. Sarkar B. Copper transport and its defect in Wilson's disease: Characterization of the copper-binding domain of Wilson disease AT Pase. J Inorg Biochem 2000;79(1–4):187–191.
2. Cuthbert JA. Wilson's disease: Update of a systemic disorder with protean manifestations. Gastroenterol Clin North Am 1998;27(3):655–681.
3. Borjigin J, Payne AS, Deng J. A novel pineal night-specific AT Pase encoded by the Wilson disease gene. J Neurosci 1999;19(3):1018–1026.
4. Walshe JM, Vinken PJ, Bruyn GW, Klawans HL, eds. Wilson's disease. In: Handbook of Clinical Neurology, Vol. 49. Amsterdam: Elsevier; 1986:223–238.
5. Riordan SM, Williams R. The Wilson's disease gene and phenotypic diversity. J Hepatol 2001;34:165 –71.
6. Arun B, Taly S. Meenakshi-Sundaram, SanjibSinha, H. S. Swamy, and G. R. Arunodaya. Wilson Disease: Description of 282 patients evaluated over 3 decades. Medicine 2007;82(2).
7. Sternlieb I. Perspectives on Wilson's disease. Hepatology 1990;12:1234–1239.
8. Gow PJ, Smallwood RA, Angus Pw. Diagnosis of Wilsons' Disease: an experience over three decades. Gut 2000;46:415-419.
9. Schoen RE, Sternlieb I. Clinical aspects of Wilson's disease. Am J Gastroenterol 1990; 85: 1453-57.
10. Sinha S, Taly AB, Ravishankar S, Prashanth LK, Venugopal KS, Arunodaya GR, et al. Wilson's disease: cranial MRI observations and clinical correlation. Neuroradiology 2006;48:613–621.
11. Dastur DK, Manghani DK, Wadia NH. Wilson's disease in India. I. Geographic, genetic and clinical aspects in 16 families. Neurology 1968;18:21–31.
12. Jha SK, Behari M, Ahuja GK. Wilson's disease: clinical and radiological features. J Assoc Physicians India 1998;46:602–605
13. Scott J, Gollan JL, Samourian S, Sherlock S. Wilson's disease, presenting as chronic active hepatitis. Gastroenterology 1978;74: 645-51.
14. Yarze JC. Wilson's disease: current status. Am J Med 1992;92:643-54.
15. Scheinberg IH, Sternlieb I. *Wilson's Disease*. Vol. 23.Major Problems in Internal Medicine. Philadelphia Saunders, 1984.
16. Roberts EA, Schilsky ML.A practice guideline on Wilson disease. Hepatology 2003;37:1475 –92.
17. Brewer GJ. Does a vegetarian diet control Wilson's disease? J Am Coll Nutr 1993;12:527-30
18. Demirkiran M, Jankovic J, Lewis RA, Cox DW. Neurologic presentation of Wilson disease without Kayser-Fleischer rings. *Neurology* 1996; 46: 1040-3.
19. Gaffney D. Wilson's disease: acute and presymptomatic laboratory diagnosis and monitoring. J Clin Pathol 2000;53:807-12.
20. Steindl P, Ferenci P, Dienes HP, et al. Wilson's disease in patients presenting with liver disease: A diagnostic challenge. Gastroenterology 1997;113:212 – 8.
21. Liana Gheorghe, Irinel popescu, Speranta Iacob,Cristian Gheorghe,Roxana Vadan,Alaxendracon Stantinescue et.al. Wilsonâ•™s disease: a challenge of diagnosis. The 5-year experience of a tertiary centre.Romanian journal of Gastroenterology 2004.vol.13 No:3,179-185.

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