ORIGINAL ARTICLE

A CLINICO-PATHOLOGICAL STUDY OF WILSONS DISEASE; 8 YEARS' EXPERIENCE OF A TERTIARY CARE HOSPITAL

Naurin Ali[1], Sahira Aaraj[1], Fareeha Farooqui[2], Munir Iqbal Malik[1]

[1]Department of Paediatrics, [2]Department of Surgery, Shifa Tameer e Millat University, Islamabad-Pakistan

Background: Wilson's disease is a genetically transmitted disease and has a variety of clinical manifestations. We evaluated the various clinical and biochemical presentations of Wilson's disease (WD) at different ages. **Methods**: This cross-sectional study was conducted in Shifa international hospital and Shifa Foundation Falahi Clinic (SFFC), Islamabad. Data from Jan 2010 to Dec 2018 was retrieved from hospital medical record on a structured proforma. All patients who had twenty-four hours urinary copper level of ≥100 mcg/day were included in the study. Their presenting symptoms, clinical signs and lab investigations were noted. **Results:** Mean age was 13±4.588 years. Male to female ratio was 1.5:1. Hepatic disease was seen in 35 (68.6%) patients mainly in <10 yrs age group. Pure neurological Wilson's was seen in 14 (27.45%) cases, which were >10 years of age while 18(35.3%) had hepato-neurological manifestations. Keyser Fleischer rings were present in 26 (51%) of total patients and 14 (100%) of neurological cases. Hepatic transaminases were elevated in 36 (70 %) patients. Low serum cerruloplasmin was seen in 37 (72.5%) cases. Mean value of haemoglobin was 10.38±2.772. Mean 24 hours urinary copper was 597.6±605.446. Consanguinity was seen among 33 (64.7%) families. Family history of WD was positive in 21 (41.2%) patients. **Conclusion**: Hepatic form of WD is more common, yet neurological presentation is seen in patients >10 years of age.

Keywords: Hepatolenticular degeneration; Keysher Fleischer rings; Neurological; Wilson's disease (WD); Copper metabolism

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INTRODUCTION

Wilson's disease (WD) is an autosomal recessive disorder of copper metabolism, with global prevalence of 1: 10,000 to 1: 30000.[1,2] There is a mutation in copper transporting gene resulting in decreased or absent transport of copper into bile leading to toxic copper accumulation in liver, resulting in hepatocellular injury. As the disease progresses, copper tends to deposit in other organs like brain, cornea and kidneys and heart.[2] Clinical presentation of disease correlates exactly with the site of copper accumulation and extent of tissue damage. Disease spectrum includes various clinical presentations, hepatic involvement being the commonest one in young patients less than 11 years of age.[1, 3] The hepatic disease ranges from asymptomatic children with incidentally noticed raised transaminases to fulminant hepatic failure or decompensated chronic liver disease (CLD), splenomegaly and liver cirrhosis.[4–6]

Neuropsychiatric manifestations are mostly seen in second or third decade of life or even later but they are fairly common in paediatric age group too.[1,7] Isolated neurological disease in paediatric patients is around 8–22%.[2] The presenting neurological symptoms tend to be wide and variable. Subtle neurological manifestations in young children include behaviour abnormalities, deterioration of school performance and of handwriting, dysarthria, and drooling of saliva. The classical dystonia involving the facial and mandible muscles produce a characteristic Wilson's facies. Wilson's facies are scored on the presence of vacuous smile, open mouth, hyper salivation, and dull look.[2,8] Common psychiatric abnormalities as depression, anxiety or even frank psychosis can also be associated.[9,10]

Wilson's disease with neurological manifestation may or may not have symptomatic liver disease.[2,11,12] Some odd presentations of the disease may include renal stones, early osteoporosis, cardiomyopathy, pancreatitis and hypoparathyroidism.[13,14]

Limited data is available from Pakistan regarding disease burden and various presentations of WD. This study was conducted to highlight the various presentations of WD in our group of patients and comparing it with international data. Hence, identifying the factors assisting in early diagnosis and prompt treatment, saving the patient from incapacitating brain damage and hepatic failures.

MATERIAL AND METHODS

This cross-sectional study was conducted in Shifa International Hospital and Shifa Falahi Foundation clinic, Islamabad. All patients who had 24 hour's urinary copper level of ≥100 mcg from Jan 2010 to Dec 2018 were retrieved from the laboratory data and included in the study. Total of 180 patients were retrieved with 24 hours urinary copper ≥100 mcg in the

defined period. Patients on antipsychotic drugs, having known seizure disorder or having hepatitis B or C disease were not included in the study. So, as to clearly see and document the various presentations of the WD and rule out the effect of other morbidities. Study was approved by the hospital ethical and research committee. Data was recorded on a predesigned *Proforma*. Demographic data (age and gender), history of consanguinity among parents (first cousins) were recorded. Positive family history of similar illness, i.e., history of Wilson's disease in a sibling or first degree relative was recorded. Death of a sibling/1st degree relative with unknown /undiagnosed liver disease was not considered as positive family history. Details of hepatic symptoms (jaundice, ascites, clubbing, palmer erythema, hepatosplenomegaly), neurological and psychiatric symptoms (progressive dystonia, tremors, gait problems, cognitive decline, seizures, dysarthria, dysphagia and drooling of saliva) were also recorded along with slit lamp examination for KF rings. Biochemical parameters (haemoglobin, hepatic transaminases, direct coomb's test, serum copper level, serum cerruloplasmin level, and total bilirubin) were recorded. Statistical analysis was done using SPSS version 23. Frequencies, percentages, means and standard deviations were calculated for all the variables defined.

RESULTS

Total number of Wilsons disease patients recorded were 180 based upon 24 hours urinary copper levels of more than 100 mcg, out of which only 51 cases met the inclusion criteria (N=51). Males were 31 (60.8%) and 20 (39.2%) were females with male to female ratio of 1.5:1. Youngest patient was 5 years old while maximum age at diagnosis was 24 years. Mean age was 13.01±4.588 years. Consanguinity was seen among 33 (64.7%) cases. Family history of Wilson's disease was positive in 21 (41.2%). Overall hepatic symptoms were found in 35 (68.6%) cases. Out of these jaundices was positive in 30(85.7%) cases. Pure hepatic WD cases were 17 (33.3%) out of which 11 (64.7%) had KF rings. Overall neurological presentation of WD was seen in 32 (62.7%). Pure neurological WD was seen in 14 (27.45%) patients and all of them had KF rings on slit lamp examination (100%). Overlap of Hepatoneurological symptoms was seen in 18 (35.3%) cases. Frequency and Percentage of various hepatic and neurological symptoms is given in table 1. In patients older than 16 years of age (12), mixed disease was seen in 6 (50%) of cases. The frequency of Hepatoneurological symptoms with respect to age is shown in figure 1. Psychiatric involvement was seen in 9(17.6%) cases. Hepatomegaly documented on abdominal ultrasound was seen in 21 (41.2%) cases. Other ultrasound findings included were ascites in 6 (11.8 %), liver cirrhosis in 5 (9.8%) and cholelithiasis in 2 (3.9%) of the cases. Mean value of 24 hours urine copper was 593.7±605.445 ranging from 103.7–3543 micrograms. Laboratory values of various liver function tests and haemoglobin levels are mentioned in table 2. Direct coombs test was negative in 35(68.6%) cases. Serum copper level was raised in 6 (11.8%) patients. Serum ceruloplasmin was low in 37 (72.5%) and normal in 12 (23.5%) cases while it was raised in 2 (3.9%) cases.

Table-1: Frequency and percentages of Hepatic and Neurological Symptoms of Wilson's Disease

Symptoms and clinical signs		Frequency and percentages
Hepatic Symptoms	Hepatomegaly	25 (71.42%)
	Jaundice	30 (85.7%)
	Digital clubbing	13 (37.14)
	Palmer Erythema	5 (14.28%)
	Splenomegaly	17 (48.57%)
	Ascites	21 (60%)
Neurological Symptoms	Tremors	18 (56.25%)
	Drooling	3 (9.37%)
	Dysarthria	13 (40.6%)
	Seizures	17 (53.12%)
	Ataxia	7 (21.87%)
	Cognitive Decline	12 (37.5%)
	Personality Changes	14 (43.75%)
	Dystonia	14 (43.75%)
Kaiser Fischer ring		26 (51%)

Table-2: Laboratory values of various Liver Function Tests and haemoglobin in Wilson Disease

Laboratory parameters	Mean and SD	Median (maximum-minimum
ALT (15–40 U/L)	207.45±429.014	70 (2099–10)
AST (15–37 U/L)	132.9±138.274	74 (556–18)
Bilirubin (0.3–1.1mg/dl)	13.84±24.119	3.5 (142–0.2)
Haemoglobin (11–14)	10.38±2.772	10.5 (16.1–3.2)

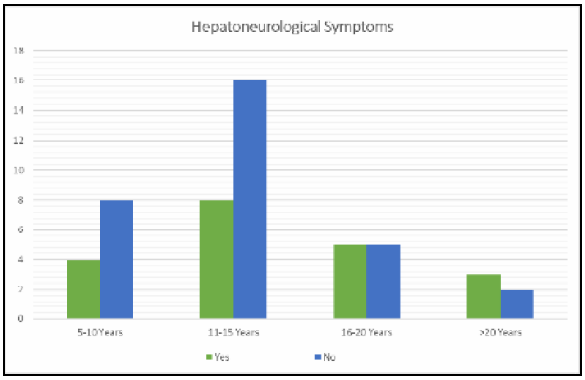

Figure-1: Hepatoneurological Symptoms

DISCUSSION

Wilson's disease is a rare metabolic disease which may become symptomatic at any age.[15] Majority presents between 5–35 years of age.[16] Only 3% of patients present beyond the fourth decade, either with hepatic or neurologic disease .[17] The oldest patients diagnosed were in eighth decade of their life.[18] Our hospital record showed WD patients between 5–36 years of age similar to the international data.[16]

Clinical presentations vary widely therefore, diagnosis is not always straight forward. Most of the times the disease goes undiagnosed until it is fairly advanced. To overcome the diagnostic challenge the Leipzig score is calculated based upon clinical signs (Kayser-Fleischer rings and neurologic symptoms) and laboratory features (copper in serum, urine, liver; serum ceruloplasmin; genetic testing).[19] Score ≥4, is highly diagnostic for Wilson disease.[19] The score also requires liver biopsy and mutational analysis for diagnosis, the data of which were lacking in most of our patients as mutational analysis was not performed for any of our patients and hardly a few had liver biopsies. Our group of patients were diagnosed only on the basis of 24 hours urinary copper. This was a big limitation in confirmation of diagnosis in our group of patients.

Clinically evident liver disease can be of any type and it may precede neurologic manifestations by as much as 10 years.[20] While most of the patients with neurological symptoms have some degree of liver disease as well at presentation.[15,16] We observed pure hepatic disease in 33.3% of our patients which were mainly under 10 years of age, which is comparable with Li Ching et al. They observed liver disease in 54.5% in their patients with mean age of 10 years.[21,22]

Whereas, overall hepatic involvement was seen in 72.5% of our patients which is a bit higher as compared to Samiullah *et al*, who noted 58.3% of overall hepatic involvement.[7] The reason for such a large number of hepatic presentations in our study can be that our hospital is a referral centre for liver transplant from all over the country so, more of the hepatic presentations reported to our centre. Chief hepatic symptoms observed in our patients were jaundice, hepatomegaly and ascites which are similar to as reported in other national and international studies.[22,23] Neurological Wilson's is the next most common clinical presentation in 10–15 years of age. It is observed as initial symptom in 40–60% of WD patients as mentioned by certain studies.[24] In our study we found 27.5% patients were of 11–15 years of age with pure neurological WD while overall CNS involvement in 66.7% which is a bit higher as compared to other studies which mention 50%, 60% and 36.2% neurological disease.[2,7,11] One of the reasons could be a center-oriented bias in reporting depending on the facilities available. Subtle personality changes to gross CNS involvement can be seen in neurological Wilson's.[23] In our study we noticed tremors and seizures as the most frequent presentation (35.3% and 33.3% respectively). Similar frequency of tremors was observed by Nagral *et al*, i.e., 31.6%. 25 Dystonia and personality changes were 2nd frequent findings (27.4 % and 27.5% respectively), which are same as narrated by Dziezyc *et al*.[24] while Nuzhat and Ather *et al* observed dystonia, dysarthria and cognitive decline as 92% and 75% frequency respectively.[2,23] Samiullah *et al* observed juvenile Parkinson's as the most frequent finding which we were unable to observe. The reason could be that our study was a chart review of the patients who were referred for hepatobiliary review and maybe they were following other centers for other symptoms. Patients with mixed hepatic and neurological symptoms were 39.2% which is comparable to Medici *et al* who observed a number of 34.3%.[15] Whereas Rukunuzzaman and El Karasky described about 14% patients with both systems involvement,[1, 23] As different symptoms are prevalent in different age groups but in our study age range was very wide (5–36 years) so this explains the high percentage of mixed disease in our patients. Male predominance of 60.8%, observed in our study was similar to many of the other studies.[1–4] One of the clinical hallmarks of WD is the Kayser–Fleischer ring, which were seen in 100% of our patients with neurologic symptoms, while Taly *et al* observed 97.1% in their study. [22]

In 51% of our total cases, KF rings were noticed which is due to the fact that many of our patients were of hepatic WD. A positive family history for Wilson disease was noted at much higher frequency in our study than mentioned in literature (41.2% vs. 25%).[17] Consanguinity was seen in 33% families which is similar to Rukunuzzaman, i.e., 30%.[1] We have observed low ceruloplasmin in 72.5% cases while others observed high percentage (up to 97%) of low ceruloplasmin.[24] But ceruloplasmin level is modifiable by many factors like other causes of cirrhosis, malabsorption and renal disease. Low serum ceruloplasmin levels alone cannot be relied upon to make a diagnosis of WD.[2]

Coombs-negative haemolytic anaemia may be the only initial symptom of Wilson's disease although it is not very common, i.e., 10–15% cases. In our study we have 68.6% coombs test negative. This study regarding spectrum of presentation at different ages is very important especially in Asian population as many of our observations are different from international data based upon demography. We can reduce complicated disease burden with prompt diagnosis based upon symptoms, of high suspicion index and biochemical tests. This would further reduce requirement of costly treatments like liver

transplant and would reduce the irreversible damage. Our study had few limitations as our data was retrospective chart review of the patients mainly referred for hepatobiliary consult and liver transplant. So, the spectrum we observed was mainly hepatic or mixed one. Further multicenter studies should be carried out to analyse the wide spectrum of presentations in our group of patients.

CONCLUSION

Hepatic form of Wilson's disease is more common in younger age group with jaundice being most frequent presentation. Neurological form is seen mostly in >10 years age group with tremors as most common symptom. Early diagnosis can save the patient from permanent hepatic and neurological damage.

AUTHORS' CONTRIBUTION

NA: Data collection and manuscript writing. SA: Drafting, write-up, statistical analysis. FF: Statistical analysis, review. MIM: Concept, review.

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Address for Correspondence:
Sahira Aaraj, Department of Paediatrics, Shifa Tameer e Millat University, Islamabad-Pakistan
Email: sahiraaaraj74@gmail.com