STUDY OF CLINICAL PROFILE OF WILSON DISEASE IN A TERTIARY CARE CENTER

Gastroenterology

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ABSTRACT

Introduction and Aim: Wilson disease is one of the common metabolic liver diseases of the liver due to inborn error of copper metabolism with varied clinical manifestations. We conducted this study to analyze clinical profile of this disease which will help in early diagnosis and management.

Materials and Methods: The study was conducted in the Department of Medical Gastroenterology, Govt. Stanley medical college Chennai, from October 2017 to December 2018. 24 Patients diagnosed to have Wilson disease were taken into the study. Wilson disease was diagnosed based on modified Leipzig score. Patients were analysed based on their clinical features at the time of presentation.

Results: Majority of the patients were in the age group 15-30 years (56%). Male to female ratio was 15:9. Majority of the patients presented with hepatic manifestations (54%), jaundice was found in 50% patients and 41% patients had ascites. 16% patients had neurologic manifestations and 12.5% patients had both hepato-neurologic features. 16% patients were presymptomatic and was diagnosed on family screening. KF ring was present in 66% patients. 58% of patients were born out of consanguineous marriage.

Conclusion: Consanguinity plays an important role in high frequency of disease. Family screening is important for early diagnosis. Hepatic manifestations were found to be more common. Wide variety of clinical presentations emphasize the high index of clinical suspicion especially in young patients with hepatic manifestations. Further large scale follow up studies warranted in view of high degree of consanguinity in India.

KEYWORDS

Wilson Disease, Hepatic, Neurologic

INTRODUCTION

Wilson disease is an inherited disorder of copper metabolism which leads to impairment of cellular copper transport. It is transmitted in an autosomal recessive manner, caused by a defect in the ATP7B gene in chromosome 13 that results in a decreased transport of copper from the liver into bile. It is found worldwide, with a prevalence of approximately 1 case in 30,000 live births in most populations¹. Impaired biliary copper excretion leads to accumulation of copper in several organs, mainly in the liver, brain, and cornea, causing progressive neurologic dysfunction, chronic liver disease and a corneal abnormality, the Kayser-Fleischer (KF) ring.

The clinical manifestations of Wilson disease are predominantly hepatic, neurologic, and psychiatric, or with combination of symptoms in many patients². There are wide variability in the reported rates of the different clinical manifestations seen at the time of clinical presentation^{2,3}. Regardless of the clinical manifestations present initially, many patients often develop other clinical manifestations as the disease progresses.

Most common initial presentation in children is liver disease, which usually manifests at 9 to 13 years of age^{4,5}. Wilson disease account for 8 to 10 percent of chronic active hepatitis in children⁶. Children may be diagnosed through screening because of an affected sibling. Unlike children, older patients are more likely to present with neurologic manifestations. The mean age at presentation for patients with neurologic symptoms is between 15 and 21 years⁷.

Wilson disease can be diagnosed by characteristic clinical features with low serum ceruloplasmin, elevated 24-hour urinary copper excretion, slit-lamp examination for Kayser-Fleischer rings and liver biopsy to determine the hepatic copper concentration. Genetic testing for mutation analysis is usually reserved for those patients in whom a diagnosis cannot be established in other ways, or for screening family members when the mutation in the proband is known. Patients with Wilson disease require lifelong therapy with copper chelating agents like D- penicillamine and trientine or with zinc to decrease copper absorption from intestine.

This rare metabolic disorder with various clinical presentations have a

slightly higher prevalence in south India, but there are few studies which provide a lucid and elaborate account of various clinical presentations. Keeping this fact we conducted this study as our center is a referral center for liver transplantation under public sector and we are seeing more number of patients with Wilson Disease.

AIM OF THE STUDY:

This study was aimed at analyzing the clinical profile of the patients with Wilson disease.

MATERIALS AND METHOD:

The study was conducted in the Department of Medical Gastroenterology, Govt. Stanley medical college Chennai, from October 2017 to December 2018. A total of 24 patients with Wilson Disease were included in our study after obtaining informed consent. All patients were aged 10 years or above. Prior approval for the study protocol was obtained from institutional ethical committee. Wilson disease was diagnosed based on modified Leipzig score. Detailed history, clinical examination findings and relevant investigations like complete hemogram, Liver function tests, Serum Ceruloplasmin, 24 hours urinary copper, Ultra sound abdomen with Doppler study and OGD were entered in study proforma and the results were analyzed. MRI brain & EEG were done in patients with neurological symptoms.

RESULTS:

A total of 24 patients including 15 males and 9 females were included in our study. Age distribution was between 11 and 61 years with 50% of the patients in the age group between 15-30 years. History of consanguinity was present in 13 patients (54%). 4 patients were asymptomatic and were diagnosed on family screening.

Majority of the patients presented with (table 1 & figure 1) hepatic manifestations (54%), with jaundice being the most common presenting symptom and was found in 50% patients. 41% patients had ascites and 25% patients had upper GI bleed. 16% patients had only neurologic features. 3 patients (12.5%) had both neurological and hepatic manifestations, with two of them presented with tremor, without any hepatic symptoms and found to have features suggestive of CLD on evaluation. Tremor was the most common neurological manifestation in our study. Dysarthria, muscular dystonia and ataxia

were the other neurological features. KF ring was found in 66% patients and all patients with neurological features had KF ring. 3 out of the 4 asymptomatic patients and 6 patients with only hepatic features had K F ring (figure 2). Sun flower cataract was seen in 1 patient.

patients had Coombs negative hemolytic anemia. Ultrasonography showed parenchymal liver disease in 8 patients. OGD showed esophageal varices in 6 patients, portal hypertensive gastropathy in 4 patients. 13 patients noted improvement with treatment. 2 patients with ESLD had undergone liver transplantation. One patient presented as ALF succumbed to the disease.

Table 1 Clinical Presentation

Presentation	No. of Patients	Percentage
Clinical type		
Hepatic	13	54
Neurologic	4	16.6
Hepato-neurologic	3	12.5
Presymptomatic	4	16.6
Clinical features		
Jaundice	12	50
Ascites	10	41
UGI bleed	6	25
Acute Liver Failure	2	8
Tremor	4	16
Ataxia	2	8
Psychiatric	2	8

Figure 1 : Clinical Types

Figure 2: Distribution of K F Ring

DISCUSSION

Wilson Disease can clinically present at any age, often between 3 to 55 years of age. Age distribution in our study was between 11 to 61 years. Clinical presentation of Wilson disease is variable. It may be hepatic, neurologic or psychiatric, with many patients having a combination of these symptoms.

In Wilson disease, liver is the usual initial site of copper accumulation and there are several different clinical manifestations of hepatic copper accumulation^{8,9}. Hepatic manifestations include acute liver failure, acute hepatitis, chronic hepatitis, cirrhosis, steatosis, and asymptomatic liver biochemical abnormalities.

In a study by Walshe et al⁵ hepatic presentation was the major presenting symptom in approximately 40% of patients followed by neurological manifestations. Similarly in our study we noted higher hepatic manifestations as compared to neurological features (54 vs 16%). Some degree of liver disease is usually seen at the time of diagnosis of liver disease regardless of the presenting symptoms¹⁰. In

our study we noted features of liver disease in 33% of patients presented with only neurological symptoms. However Brewer et al⁸ in their study observed higher incidence of neurological features (60%). Similarly Taly et al¹¹ noted higher prevalence of neurological features (69%) in their study, it could be due to the selection bias as the study was conducted in an apex center for neurological disease.

The reported neurologic manifestations of Wilson disease are broad, which include tremor, dysarthria, abnormal gait, abdominal distention seizures, dystonia, clumsiness, chorea and diagnosing neurologic Wilson disease may be challenging because of these myriad of symptoms. Tremor was the most common neurological symptoms in our study which was in consistent with other studies.

Behavioral and psychiatric symptoms are more common in patients with neurologic involvement than in patients with hepatic involvement⁶. In our study 2 patients presented with psychiatric symptoms in the form of irritable behavior and personality changes. Both of them had neurological features and one of them had deranged Liver function test without any other hepatic manifestations.

Prashanth LK et al¹² on their study on clinical profile of Wilson disease over three decades, observed some of the patients with hepatic Wilson Disease succumb to illness, while others developed neurological symptoms later in the course of the illness. In our study one patient presented as ALF succumbed to disease, two patients with ESLD underwent liver transplantation and doing well on follow up. 7 patients with ESLD are on liver transplantation work up and other patients have stable disease.

Hemolytic anemia can be seen in some patients, particularly among patients with acute liver failure causing disproportionate elevation in serum bilirubin. We noted Coombs negative hemolytic anemia in two patients, both of them presented as ALF. Ophthalmic manifestations include KF ring and sun flower cataract, and in our study we noted 66 % Kaiser-Fleischer rings, and all patients with neurological features and 46% patients with hepatic manifestations had KF ring. In a study¹² conducted at National Institute of Mental Health and Neurosciences Bangalore, India, history of consanguineous marriage among parents was noted in 144 of the 262 patients (53.7%). In our study we noted 56% consanguinity.

One limitation of our study is that many patients were referred because of their liver disease and therefore it does not represent the true distribution of Wilson disease in the community. Similarly our study was an observational study which could not find evolution of clinical features in presymptomatic patients.

CONCLUSION

Consanguinity plays an important role in the high frequency of disease among the affected family. Family screening is important for early diagnosis. Hepatic manifestations were found to be more common. The wide varieties of clinical presentations emphasize the high index of clinical suspicion, especially in young patients with hepatic manifestation. Further large scale follow up and population based studies are warranted in view of high degree of consanguinity in India.

REFERENCES

- Huster D. Wilson disease. Best Pract Res Clin Gastroenterol 2010; 24:531.
- Lorincz MT. Neurologic Wilson's disease. Ann NY Acad Sci 2010; 1184:173.
- Gollan JL, Gollan TJ. Wilson disease in 1998: genetic, diagnostic and therapeutic aspects. J Hepatol 1998; 28 Suppl 1:28.
- Saito T. Presenting symptoms and natural history of Wilson disease. Eur J Pediatr 1987; 146:261.
- Walshe JM. Wilson's disease presenting with features of hepatic dysfunction: a clinical analysis of eighty-seven patients. Q J Med 1989; 70:253.
- Gitlin JD. Wilson disease. Gastroenterology 2003; 125:1868.
- Oder W, Grimm G, Kollegger H, et al. Neurological and neuropsychiatric spectrum of Wilson's disease: a prospective study of 45 cases. J Neurol 1991; 238:281.
- Brewer GJ, Yuzbasiyan-Gurkan V. Wilson disease. Medicine (Baltimore) 1992; 71:139.
- Steindl P, Ferenci P, Dienes HP, et al. Wilson's disease in patients presenting with liver disease: a diagnostic challenge. Gastroenterology 1997; 113:212.
- Ferenci P. Pathophysiology and clinical features of Wilson disease. Metab Brain Dis 2004; 19:229.
- Taly, A. B., Meenakshi-Sundaram, S., Sinha, S., Swamy, H. S., & Arunodaya, G. R. (2007). Wilson disease: description of 282 patients evaluated over 3 decades. Medicine, 86(2), 112-121.
- Prashanth LK, Taly AB, Sinha S, Arunodaya GR, Swamy HS. Wilson's disease: Diagnostic errors and clinical implications. J Neurol Neurosurg Psychiatry 2004;75:907-9.