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Profile of Wilson's disease Patients in a Tertiary Care Centre

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Abstract

Wilson's disease is an Autosomal Recessive disorder causing accumulation of copper in body. Disease is peculiar in that it can manifest at any age, has varied clinical presentations and is treatable if diagnosed at an early age before progressive liver damage sets in. Here we studied a profile of 10 patients. Patients were diagnosed based on biochemical and genetic studies. Including Serum ceruloplasmin <20 mg/ml, 24 hour urinary copper >100 microgram /24 hours, presence of a Kayser-Fleisher (KF) ring on slit lamp examination. We observed that gastrointestinal (GI) symptoms were most common in around 70% and 20% of patients had neurological (extrapyramidal) symptoms. Significant number of patients also had associated Anemia. Sibling screening revealed one asymptomatic patient while 3 were asymptomatic carriers. 40% succumbed to the disease. We conclude that Wilson's Disease should be considered as in the differential diagnosis in children presenting with any signs of liver disease. It may have varied presentations, significant mortality if undiagnosed and manifestations may be extrahepatic as well. Early diagnosis with timely treatment is essential to reduce mortality.

Keywords- Wilson's disease, Paediatric, Genetic Testing.

Aims and Introduction

Wilson's disease (WD) is a rare autosomal recessive disease that affects approximately 1:30,000 live births with a male predominance. It is characterized by a disturbance of copper metabolism that leads to accumulation of the metal in the various tissues of the body and is caused by a mutation of the ATP7B gene(1)

This defect results in progressive toxic accumulation of copper in the liver that begins in infancy, with increasing copper overload over time, deposition of copper in other organs, such as the nervous system, cornea, kidneys and heart occurs usually during the second decade or later(2). If Wilson's disease is not recognized and adequately treated, the progression of liver disease to cirrhosis and liver failure can be rapid or irreversible brain damage can occur (3).

The diagnosis of Wilson Disease rests on clinical suspicion in addition to appropriate laboratory tests that include low serum ceruloplasmin levels, increased 24 hour urinary Copper excretion, Kayser-Fleisher (KF) rings in the Descemet membrane of the cornea, and increased hepatic copper contents(4). With early diagnosis and treatment Wilson 's disease can be completely controlled,

however failure to management can lead to hepatic failure leading to death. However, the diagnosis of Wilson's Disease is very difficult particularly in paediatric age group due to atypical symptoms coupled with inconclusive findings of biochemical and clinical tests and for this precise reason, genetic testing is frequently warranted in this age group..

This study aims to analyse the clinical laboratory and evolutionary analysis of patients diagnosed with Wilson's disease at a tertiary care hospital

Methods

Retrospective analysis of 10 patients diagnosed with Wilson's disease during the year January 2016 to December 2018

The diagnosis of Wilson's disease were based on the following clinical and biochemical parameters

1. Serum ceruloplasmin <20 mg/ml

2.24 hour urinary copper >100 microgram /24 hours

3.presence of a KF ring on slit lamp examination,

We did genetic study of the patient if there was strong clinical suspicion of WD with inconclusive lab parameters which could not fulfil all set lab criteria for Wilson's disease.

Data from medical records included relevant history and complete examination findings including but not limited to presence of jaundice, hepatosplenomegaly, signs of liver cell failure and a KF ring on slit lamp examination.

Lab parameters assessed were Liver enzymes, coagulation profile (including Prothrombin time), serum ceruloplasmin levels, 24 hour urinary copper, slit lamp examination. Radiological assessment was done including Ultrasonography (USG) of abdomen, Upper Gastrointestinal scopy, and MRI of Brain. In addition Liver biopsy and/or genetic testing was done wherever deemed necessary.

Results

10 children were enrolled in the study. Youngest patient in the study was 8 years and oldest was 12 years with median age being 10 years. 7 males (70%) and 3(30%) females.

Most common clinical manifestation was ascitis and hepatomegaly (in 8 patients, 80%) while 7 patients (70%) had jaundice. Neurological symptoms like seizures and extrapyramidal symptoms were least common (20%).

Table 1- Clinical manifestations of symptomatic Wilson 's disease patients at diagnosis (n-10)

Jaundice	7(70%)
Hepatosplenomegaly	8(80%)
Ascites	8(80%)
Gastrointestinal (GI) bleeding	5(50%)
Abdominal pain	2(20%)
Pedal edema	7(70%)
Seizures and extrapyramidal symptoms	2(20%)

Lab parameters revealed low serum ceruloplasmin in 70% patients and high urinary copper in 70%, but most striking was KF ring which was found in 80% of patients, equal number of patients had deranged Liver Function Tests (LFTs). Most surprisingly 2 patients had normal lab parameters and their genetic study was done in view of the asymptomatic hepatomegaly which revealed ATPB7 mutation suggesting the diagnosis of WD.

Table 2 - Diagnostic modalities used in the patients (n-10)

Low Serum Ceruloplasmin levels	7(70%)
KF ring on slit lamp	8(80%)
Portal hypertension on Ultrasonogram / Oral	5(50%)

Gastroduodenoscopy scopy	
Magnetic Resonance Imaging (MRI) brain	2(20%)
High 24 hour urinary.copper levels	7(70%)
Deranged LFT/jaundice	8(80%)
Cirrhosis on Ultrasonography / Biopsy	5(50%)
Genetic testing	2(20%)

Anemia was found in 7 patients(70%) mean Hemoglobin (Hb) being around 7.4 gm/dl (range- 4.5-10.6).

The median range of serum ceruloplasmin was 5.8(2.8-25.3).7 patients(70%) had significantly low levels <10 mg/ml and the remaining 3 patients had values between 20-30mg/ml highlighting the diagnostic significance of low ceruloplasmin levels.

24 hour urinary copper levels was 250 microgram (mcg) (107-474) done in 7 patients. 6 patients(85%) had values >250 mcg/24 hours.

Sibling screening was done in 8 patients -1 had asymptomatic Wilson's disease who later became symptomatic and 3 others had asymptomatic carriers (50%)

Table 3- Sibling Screening (Total – 8)

Asymptomatic Wilson's Disease (who later turned symptomatic)	1 (12.5%)
Negative Screening	5 (62.5%)
Asymptomatic Carriers	2 (37.5 %)
Total Siblings Screened	8

Discussion

We studied 10 patients, youngest one was 8 years with oldest one was 12 at the time of the diagnosis with mean age being 10 years. However, studies show that Wilson's can manifest at any age even in adulthood(5). In the present study 70% (7 patients) were males and 3 (30%) were females. All 10 patients(100%) included in the study were symptomatic at the time of diagnosis. 70% (7 patients)presented with the hepatic manifestations. In a study by Kalra et al out of 25 patients studied, 4 were asymptomatic whereas 20% patients (5 each) had hepatic and neurological symptoms at presentation(6). In another study in south India by Bincy Krishnan, out of 33 patients studied, 79% (26 patients), had initial hepatic manifestations and 7 (21%) had initial neurologic manifestations, no patient was asymptomatic(7). In patients presenting with hepatic manifestations, hepatosplenomegaly and ascitis were most common in 80% (8 patients) each, jaundice was the second most common. In a study of 100 patients of Wilson's in Bangladesh, most common presentation was of chronic liver disease followed by portal hypertension and 3.6% presented with fulminant hepatic failure(8). Interestingly 8 (80%) patients had Keyser Fleischer Ring, 7(70%) had Chronic Hemolytic Anemia. This clearly shows that clinical presentation of Wilson disease can be variable and may even be asymptomatic. For this very reason, genetic screening is recommended for asymptomatic siblings of the patients by both European and American guidelines(9).

Death occured in 4(40%) patients and all deaths occured within the first 6 months of diagnosis.all 10 patients were started on d-penicillamine therapy however compliance was an issue, lack of financial resources being the most important factor.

We encompass asymptomatic patients, patients presenting changes in biochemical tests only, and patients with acute liver failure, both with and without hemolytic anemia. The most common presenting complaints in our study were

abdominal distension and ascites(80%) followed by jaundice and pedal edema (70%). As per American Association for Study of Liver Diseases (AASLD) clinical manifestations are hepatic in first two decades and neurologic and psychiatric threreafter and an estimated 5% patients present with Acute Liver Failure(10). 2 children had features of neurological symptoms. MRI brain done was suggestive of wilson's disease (100%).We observed a low percentage of patients with neurological symptoms, which was expected because such characteristics are most commonly found in adults(10). For pediatric patients, deterioration in school performance, impulsive behavior, loss of motor coordination, dysarthria, dystonia, spasticity, tremor, depression, psychosis, and personality disorders have been reported(11).

The median range of serum ceruloplasmin was 5.8 (2.8-25.3) done in all 10 patients and 24 hour urinary copper levels was 250 microgram (107-474) done in 7 patients. The biochemically abnormal ceruloplasmin levels helped us to diagnose the disease, but normal values are frequently observed in some patients. In patients with normal ceruloplasmin values, the diagnosis was only possible based on the high levels of 24 hour urinary copper excretion. Sometimes, even with reduced levels of ceruloplasmin, the 24-hour urinary copper levels are not always elevated. When this happens, sensitization with d-penicillamine is one way to confirm the diagnosis. But all these methods have limitations and even with Genetic and chromosomal analysis and copper studies. In a study by Merle et al, only 57% and around 87-88% patients were diagnosed respectively. Whereas hepatic histological changes were observed in 73%, and they found 15% of patients had no mutations were detected(12).

Conclusion

Wilson's disease should be diagnosed by considering the family and clinical history as well as information from the biochemical laboratory tests because of the heterogeneity of the symptoms and the occurrence of asymptomatic patients.

Wilson's disease should be considered in the differential diagnosis in children older than 1 year presenting with any signs of liver disease ranging from asymptomatic increased serum transaminases to cirrhosis with hepatosplenomegaly with ascites or acute liver failure. Early diagnosis accompanied by the initiation of therapy with copper chelators, zinc salts, or even liver transplantation are essential for favorable outcomes.

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