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A study on clinical profile and therapeutic aspect of Wilson's disease

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***Abstract*---**Introduction: Wilson's Disease is an autosomal recessive disease. It is characterized by degenerative changes in the brain, liver and Kayser-Fleischer Rings in the Cornea. It is observed with the prevalence of approximately 1:3000 among all ethnic groups. Aims & Objectives: To study the clinical profile and therapeutic aspects of Wilson's Disease. Material and Methods: It was a prospective observational study conducted in the department of Hepatology of SCB Medical College & Hospital, in Cuttack city of Odisha. Patients were followed up after 6 month and response to treatment was observed. Results: Most patients were in age group 11-15 years (43%), male, female ratio being 2:1. 64% patients had hepatic presentations, 11% patients had neurological presentations and 25% of patients had both hepatic & neurological presentations. The hepatic presentations were jaundice in 79% of cases followed by Ascites and pedal edema in 75% of cases each, 29% patients were having UGI bleeding. Among the 28 patients 68% presented with KF Rings, 16% patients had child A, 28% had Child B and 56% patients had Child C cirrhosis. Conclusion: The commonest presentation of Wilson's disease was Chronic Liver Disease. Early and correct diagnosis with proper treatment & regular follow up can prevent devastating consequences as the disease is treatable. In child B and early child C, cirrhosis may proceed and requires liver transplantation and there is dramatic improvement in liver functions.

***Keywords*---**Wilsons disease, Kayser-Fleischer rings, chronic liver disease.

Introduction

Wilson's Disease (WD) is an autosomal recessive disease caused by mutations in the ATP7B gene. It is characterized by degenerative changes in the brain, liver disease and Kayser-Fleischer rings in the cornea[1]. It is observed with the prevalence of approximately 1:3000among all ethnic groups[2]. It is fatal if untreated. Specific treatment is available for this disease. Defective mobilization of copper from lysosomes in the liver cells for excretion into bile is the basis for the multi-organ damage in the patients with WD. Manifestations of WD are variable, with a tendency to having familial pattern.

Wilson's Disease can virtually involve any organ of body but brain, liver, eyes are the main targets[3]. The neurological disease usually present with movement disorders along with abnormalities of speech. It can manifest insidiously or precipitously with dystonia, drooling, tremors, dysarthria, and lack of motor coordination. Impairment or emotional disturbances are also frequent. Rare presentations include epileptic seizures and pyramidal signs. Hemiparesis can be the initial presentation in few cases.

Diagnosis of WD is often difficult and is formulated through, clinical, biochemical, imaging, histochemical and genetic evaluations. However in neurological presentations usually it is straight forward with presence of Kayser-Fleischer rings and urine copper of more than 100μg/day. In doubtful cases serum ceruloplasmin level, copper level and mutation analysis may be helpful. Wilson Disease is one of the few monogenetic hereditary diseases, which can be successfully treated with medical therapy. Supportive treatment consists of Ursodeoxycholic Acid, Sylimarin, S adenosine Methionine, Human Albumin, Diuretics,Propranolal / Carvedilol, Nutritionaltherapy, Specific treatment is done with Zinc, Penicilamine, Trientine and Tetra thiomolybdate but in case of progression of disease, not responding to chelating medications, resulting in acute liver failure, liver transplant is the last resort.

Objectives

To study the clinical profile and therapeutic aspects of Wilson's Disease.

Materials & Methods

It was a prospective observational study conducted in the department of Hepatology of SCB Medical College & Hospital in Cuttack city of Odisha. The data was collected over a 12 months period of August2020 to July2021. The study population included all the patients who fulfilled the diagnostic criteria of Wilson's disease presenting at OPD and admitted to the indoor of Hepatology department. Wilson's disease was diagnosed on the basis of the presence of atleast 2 of the following criteria[4].

- Family history of Wilson's disease
- KF ring by slit lamp examination
- Decreased serum ceruloplasmin level (<20 mg/dl)
- Increased 24-hour urinary copper excretion (>100 μg/24 hrs)

- Decreased serum copper level (<75 μg/dl)
- Liver copper gold standard (≥250 μg/g dry weight)

Exclusion Criteria

- Patients who were HIV positive or were having pulmonary tuberculosis
- Patients who were having malignancy
- Patients who were alcoholics

All the patients were subjected to a detailed general and systematic examination as per the standard protocol. The past history of hepatic or psychiatric illness and family history of similar illness were taken from all patients. An ophthalmological examination for the presence of Kayser-Fleischer Ring was carried out by examination with naked eye and by slit lamp evaluation in Ophthalmology department. The patients were subjected to routine blood counts, liver function test, estimation of total serum copper, serum ceruloplasmin and 24 hour urinary copper excretion. Neuroimaging (MRI/CT scan brain) was done. EEG was performed in cases that have manifestations of seizure disorder. Ultrasound abdomen and upper GI endoscopy was done. Serum ceruloplasmin was done by nephelometry method (normal value : 20-60 mg/dl.). 24 hour urinary copper by atomic absorption spectrometry (normal value: <40 μg/day). Serum copper estimation was done by spectrophotometry (normal value 75-150 μg/dl.). CT scan brain was done on light speed volume computer tomography version machine of 128 slice MSCT (Multi Slice Computer Tomography). MRI of brain was done by MRI machine of 1.5 tesla strength. Electroencephalography (EEG): Sixteen channels EEG recording was done and analysis software system as per international guidelines. UGI Endoscopy was done and USG abdomen was done using an ultrasonic transducer.

Observations and Discussion

Age distribution of patient

Age	Male	Female	Total	Percentage	Mean + SD	Range
6 -10 Years	4	2	6	21	14.28 ± 4.79	6 to 25 yrs.
11-15 Years	9	3	12	43		
> 15 Years	6	4	10	36		
Total	19	9	28	100		

Presenting symptoms of the studied cases (n=28)

Symptoms	No. of patients	Percentage
Jaundice	22	79
Anorexia	22	79
Weakness	22	79
Abdominal distension	21	75
Pedal Edema	21	75
Vomiting	15	54
Pain abdomen	10	36
UGI bleed	8	29
Dystonia	5	18

Clinical signs of the studied cases (n=28)

Signs	No. of patients	Percentage
Jaundice	22	79
Ascites	21	75
Pedal Edema	21	75
K-F Ring	19	68
Splenomegaly	13	46
Hepatomegaly	12	43
Encephalopathy	3	11

Modes of presentation of Wilsons disease in different age group

Age (Yrs)	Hepatic only	Neurological only	Both hepatic & neurological
6-10	6	0	0
11-15	8	1	3
>15	4	2	4
Total	18 (64%)	3 (11%)	7 (25%)

Kayser-Fleisher (KF Ring)

Presentation	No. of patients	KF Ring Positive
Hepatic	18	9
Neurological	3	3
Mixed	7	7
Total	28	19 (68%)

Liver Function Test

Parameter test	Mean + SD
Total bilirubin (mg/dl)	5.78 ± 2.28
Direct bilirubin (mg/dl)	3.40 ± 2.60
SGOT (IU/L)	181.42 ± 154.41
SGPT (IU/L)	152.85 ± 125.51
ALP (IU/L)	188.5 ± 52.69
Sr. Protein (gm/dl)	6.37 ± 0.98
Sr. Albumin (gm/dl)	2.9 ± 0.69
PT (Sec.)	13.18 ± 3.51

Serum Ceruloplasmin

Serum Ceruloplasmin	No. of patients	Percentage
<20 mg/dL	22	79
> 20 mg/dL	6	21
Total	28	100

24 hr. Urinary Copper

24 hr. Urinary Copper	No. of patients	Percentage
40 – 100 μg/day	3	11
> 100 μg/day	25	89
Total	28	100

Serum Copper

Serum Copper	No. of patients	Percentage
<75 µg/dl	21	75
> 75 µg/dl	7	25
Total	28	100

USG Abdomen

USG Abdomen	No. of patients	Percentage
Altered echotexture	25	89
Ascites	21	75
Dilated Portal Vein	14	50
Splenomegaly	13	46
Hepatomegaly	12	43
Normal	3	11

UGI Endoscopy

UGI Endoscopy	No. of patients	Percent
Esophageal varices only	9	32%
Esophageal Varices + PHG (Portal Hypertensive Gastropathy)	5	18%
No Varix/PHG	14	50%

Child Turcotte Pugh Score (CTP Score)

CTP Score	No. of Patient	Percent
A	4	16
B	7	28
C	14	56
Total	25	100

Follow up study at 6 month

Parameter	At Presentation	At 6 month
CLINICAL		
Jaundice	22	17
Ascites	21	15
Pedal Edema	21	13
KF Ring	19	18
LABORATORY		
Total Bilirubin	5.78 ± 2.28	4.12 ± 2.17
SGOT	181.42 ± 154.41	126.57 ± 94.44
SGPT	152.85 ± 125.51	110.28 ± 79.16
Sr. Albumin	2.9 ± 0.69	3.1 ± 0.65
PT/INR	13.18 ± 3.51	11.62 ± 3.28
24 hr Urinary copper	588.90 ± 158.01	278.22 ± 159.06
ULTRASOUND	Ascites-21	Ascites-15
ENDOSCOPY		
Esophageal varices + PHG	14	13
CTP SCORE		
A	4	4
B	7	7
C	14	13
MELD SCORE		
<15	8	9
>15	20	19

Discussion

Most of the patients were in the age group of 11 to 15 years (43%), followed by >15 years (36%).The mean age was 14.28 ± 4.79 years.Stephania et al in their study on Wilson's disease observed that patients were 2.8 to 15.1 years old, with a mean age of 8.8 ± 0.9 years. Age at diagnosis in the sample described by Sanchez-Albisua et al. was 9.8 ± 3.4 years in Yuce et al was 10.1 ± 2.5 years. Panagariya A et al in their study found the mean age of onset of Wilson's disease to be 13.2 years. M Seyhan et al in their study observed the mean age to be 11.5 ± 3.3 years

(range, 4 - 17 years). Niraj Kumar et al in their study found the mean age of onset of Wilson's disease to be 12.41 ± 4.41 years (range 7 - 21.5 years). Thus the mean age of onset of the disease of 14.28 years (range6 - 25 years) in our study correlated with the other studies mentioned with greater proportion of patients in the 11-15 years age group. Thus it is believed that Wilson Disease is a disease of children, adolescents and young adults[5'6].

In our study of 28 patients, 68% (19) males and 32% (9) females. M:F = 2:1.These male predominance could be due to male child getting more attention than female child in society[7,8].Panagariya A et al. noted a male preponderance (67%) in their study, which has earlier been documented in the Indian literature. M. Seyhan et. al. in their study found that among the 37 children with Wilson's disease 11(29.7%) were girls and 26 (70.3%) were boys. Out of 28 patients, 21% (6) patients had family history of WD. Screening of 1st degree relatives and all asymptomatic siblings is a very important issue and must be carried out[5,9]. Stephania et. al. in their study too found that 6 patients (35%) who had positive family history were identified by family screening. Thus family screening should be emphasized.

In our study 64% (18) patients had hepatic presentation, 11% (3) patients had neurological and 25% (7) patients had mixed presentation.Most of our cases presented with hepatic problems because those cases were referred to our Hepatology department as acute or chronic liver disease.This was in concordance with other study that hepatic presentation was most prevalent. M Seyhan et al in their study found that out of 37 Wilson's Disease patients 22 (59.6%) has hepatic presentation. Stephania et. al. in their study observed that the hepatic form was the most prevalent (65%) as observed in our study. Raiamani et al. in their study found that 11 patients has hepatic form[14]. Yuce et al observed six cases of fulminant hepatitis in a sample of 33 children with Wilson's Disease.

Among the 28 patients, KF ring was found in 68% (19) cases. Out of 18 hepatic presentation cases, 9 had KF ring. KF ring positive in all neurological (3) and Mixed (7) (both hepatic and neurological presentation) cases.Development of this KF Ring is primarily related with the time passed from the onset of accumulation of copper in cornea. Observation of KF Ring more frequently in patients with neurological findings may be related with the fact that neurological findings emerge at more advanced ages[10,11]. In our study, 79% (22) patients had serum ceruloplasmin levels less than 20 mg/dl and 21% (6) patients had levels more than 20 mg/dl. In our study, 24 hour urinary copper was found to be > 100 μg/day in 89% (25) patients and between 40 - 100 μg/day in 11% (3) patients. Other study also reported 24 hrs urinary copper >100 μg/day in 90% -100% patients[12].

In 11% (3) patients who had levels between 40 - 100 μg/day, penicillamine challenge test was done and 24 hour urinary copper was found to be > 1600 μg/day. Follow up study was done after 6 month of initial presentation. Improvement was noticed in the form of decrease in jaundice, ascites, pedal edema, total bilirubin, SGOT, SGPT, PT/INR, 24 hours urinary copper and increase serum albumin. In a study by *Beinhardt et al. 2014*[13], out of 162 patients, 85% improved and 15% deteriorated despite therapy.In follow up studies

by *Socha et al. 2018*, adequacy of treatment was monitored by measuring 24-hour urinary copper excretion while on treatment. It was highest immediately after starting treatment. With chronic (maintenance) treatment, urinary copper excretion was in the vicinity of 200 - 500 μg/day.In a study by *Suraj et al., 2004*, in 19 cases of WD, KF ring disappeared either completely or partially in 38.8% (7/18) patients at 6 months follow up and disappearance was noted in 14 cases in a year's time.

Summary & Conclusion

In our study most of the patients were in the age group of 11 - 15 years (43%). Male : Female = 2:1.64% patients had hepatic presentation, 11% patients had neurological presentation and 25% patients had mixed (hepatic + neurological) presentation.Commonest hepatic presentation were Jaundice in 79% followed by Ascites and Pedal Edema in 75% patient each. 29% patients had UGI bleeding.Among the 28 patients, 68% of them presented with KF ring.In our study, 16% patients had Child-A, 28% of patients had Child-B and 56% patients had Child-C Cirrhosis. Patients were followed up after 6 months and response to treatment was observed.

It has been concluded that commonest presentation of Wilson's disease was CLD. Early and correct diagnosis with proper treatment & regular follow up can prevent devastating consequences as the disease is treatable. In child B and Early Child C cirrhosis may proceed for liver transplantation and dramatic improvement in liver function.

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