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Clinical Profile of patients with Wilson Disease – Our experience

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ABSTRACT **Aim**: To analyse clinical profile of patients with Wilson disease. **Materials and methods**: 20 patients diagnosed to have Wilson disease were included in the study. various clinical profile and investigation done were analysed. **Results**: Age distribution:13-30yrs; male;15, female:5; Born of consanguineous marriage:18 ; Clinical Presentation: Jaundice: 13, UGI bleed: 2; Neurological features:6 ; KF ring:18
Investigation: Serum ceruloplasmin <20mgs :17; AST and ALT were not significantly elevated; 24hrs copper excretion >100micrograms :4 . USG abdomen: CLD and Splenomegaly: 6, Coarse echo pattern of liver:7, Fatty liver :1 Gallstones:2 ; Normal liver:6 Upper GI endoscopy: GrIlesophageal varix:2; PortalHypertensive gastropathy :5 Normal OGD :13 ; Other findings: Short stature:1, ITP :1,Mitral valve prolapse: 2 Pulmonary tuberculosis:1 renal stones:2;Megaloblastic bone marrow:2.**Conclusion**: Consanguinity plays an important role in high frequency of the disease among the affected families. Extra hepatic manifestations of Wilson disease can also occur hence carefully analysed. Careful follow up of patients and appropriate treatment is mandatory for better outcome.

KEYWORDS : Wilsondisease, consanguinity, extrahepatic manifestation

Background: Copper, a component of several essential enzymes, is toxic to tissues when present in excess. *Menkes disease*, an X-linked defect in transportof copper from the intestine, and *Wilson disease*, autosomal recessive disorder deposition of excess copper in various tissues. Kinnear Wilson first described this disease in 1912. It is characterized by progressive, lethal neurologic dysfunction with chronic liver disease and a corneal abnormality, the Kayser-Fleischer (KF) ring[1].Impaired hepatic copper excretion leads to excessive copper deposition in the liver, brain, kidney, and cornea. The incidence of the disease in most populations is 1 in 30,000. Copper is incorporated into the protein apoceruloplasmin to formceruloplasminin liver. The normal serum concentration of ceruloplasmin in adults, as measured by immunochemical or enzymatic techniques, is 200 to 400 mg/L .Ceruloplasmin is an acute-phase reactant that is elevated by inflammation (including inflammatory hepatic disease), pregnancy, and the use of exogenous estrogen. Most of ingested copper is excreted in bile; a small portion is excreted in urine. Metallothioneins, a low-molecular-weight cysteine-rich proteins, are stimulated and convert copper into a nontoxic form if intestinal or liver cells are deposited with excess copper[2]. The classic patient with Wilson disease, whether displaying hepatic or neurologic findings, may be considered in 6 and 40 years of age with serum ceruloplasmin level less than 5 mg/dL (<50 mg/L) and definite Kayser-Fleischer rings. Otherwise, in the presence of chronic liver disease (indicated by hepatomegaly or biochemical abnormalities) or typical neurologic symptoms, the combination of a low serum ceruloplasmin level (less than 140 mg/dL) and elevated basal 24-hour urinary copper excretion (>40 µg/day) is highly suggestive of Wilson disease[3]. D-penicillamine challenge test by measuring 24-hour urinary copper excretion after administration of D.penicillamine may be so definitive. Typical ocular findings complete the clinical diagnosis but may be lacking. A percutaneous liver biopsy is useful for assessing the severity of liver damage and measuring parenchymal copper concentration, which is regarded by some to be the sine qua non for the diagnosis of Wilson disease. This procedure, however, may have to be delayed in patients with severe liver dysfunction. Other clinical entities in the differential diagnosis must be appropriately excluded. In the patient who does not have classic manifestations, extensive studies must be pursued meticulously; ultimately a gene mutation analysis may be the only convincing and reliable diagnostic procedure. The majority of mutations in *ATP7B* identified to date are missense mutations. Small deletions, insertions, nonsense, and splice-site mutations occur throughout the gene (Cox, Mutation Database).

Aim of the Study: This study was aimed at analysing the clinical profile of the patients who were already diagnosed to have Wilson disease

Materials and Method: Study Design: Descriptive study of case series.Twenty patients attending out patient department of Hepatologyin Government Rajiv Gandhi general hospital Chennai were included in the study. Study period : January 2008 to December 2011. Clinical examination with detailed history was conducted. Investigations like Completehemogram, Liver function tests, Serum Ceruloplasmin, routine urine examination,24 hours urinary excretion of copper excretion.Ultra sound abdomen, Chest Xray PA view, MRI brain were done.

Results: The age distribution of the selected 20cases : 13 to 30years . Sex distribution : Male 15 patients and female 5 patients. Number of cases born of Consanguineous marriage :18(90%). Siblings affected in the group :2 . Unknown cause of death in siblings:3

Mode of Presentation: (Table :1) Jaundice:13, UGI bleed: 2 Pain abdomen: 2, Ascites-2 Neurological: 6 K.F: 18(90%) Normal :1. Investigation: S.Ceruloplasmin <20mg/dl :17 . S.Ceruloplasmin <30 mg/dl -3 ALT marginally elevated . 24hours urinary copper excretion > 100micrograms noted in 4 patients.

Ultrasound abdomen: (Table:2)Features of Chronic Liver disease/Splenomegaly-6; Coarse echo of liver parenchyma:7; Fatty liver-1 ; Gall stone : 2 ;Normal liver :6 .Upper GI endoscopy: GrIlesophageal varices:2 ; Portal hypertensive gastropathy: 5; Normal OGD:13 Other findings: Short stature: 1 ; Idiopathic thrombocytopenic purpura:1 ; Mitral valve prolapse: 2 ; Gall stone disease: 2 ; Pulmonary tuberculosis: 1 ; Renal stones:2, Megaloblastic bone marrow:2. HBsAg, Anti HCVand HIV were negative in all patients. KF ring disappeared with treatment for 2 patients. Primary amenorrhea seen in one patient. Auto Immune Hepatitis was excluded. One patient got married and delivered a normal child, continuing d-Penicillamine. GIANT PANDA sign seen in MRI of one patient. Liver biopsy was done in 3 patients and they showed

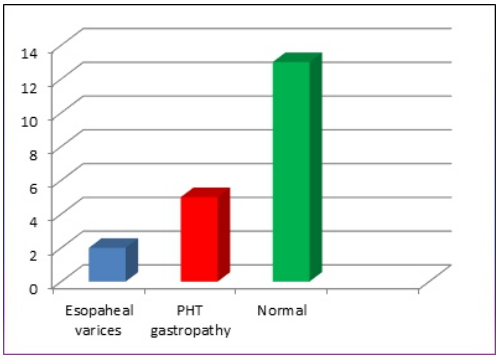
chronic hepatitis features and interface hepatitis with Kupffer cell hyperplasia.

Table :1

S.no	Presentation	Number of patients
1	Jaundice	13
2	UGI bleed	2
3	Pain abdomen	2
4	Ascites	2
5	Neurological	6
6	KF ring	18
7	Normal	1

Table:2

S.no	USG abdomen	Number of patients
1	CLD/Splenomegaly	6
2	Coarse echo liver	7
3	Fatty liver	1
4	Gall stone	2
5	Normal liver	6



Graph:1 Upper GI endoscopy

Discussion: Wilson disease can present as varied forms[4]. The age at onset of symptoms may range from 3 to 55 years. In our study the we have age group ranging from 13 to30 yrs. Chronic or fulminant liver disease, a progressive neurologic disorder without overt hepatic dysfunction, a haemolytic disorder, or psychiatric manifestation may be the presenting feature. The variable clinicalpresentation usually pose diagnostic difficulty.[4,5]

In a largest series of study group of patients inNational Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India from 1970 to 2000 there were 910 sibs in 262 families.Positive History of Consanguineous marriage among parents was noted in 144 of the 262 patients (53.7%). Sibs born of consanguineous parents had higher frequency of family history ($p = 0.042$) and duration of illness at presentation wasshorter ($p = 0.017$), and were significantly younger ($p = 0.002$) than patients without history of parental consanguinity[6].

Serum bilirubin level may be disproportionately elevated as a result of hemolysis. The combined feature of a less than 4 ratio of alkaline phosphatase and serum bilirubin and a ratio greater than 2.2 of the AST to ALT level will be helpful in diagnosis. The serum ceruloplasmin level alone is not useful in making diagnosis[7].In our study 17 out of 20 patients had ceruloplasmin values less than 20mg/dl. 40% to 60% of patients may not have Kayser-Fleischer rings even with liver involvement and in patients without symptoms. In our study 18patients (90%) had KF rings. Patients with neurologic or psychiatric manifestations usually have Kayser-Fleischer rings. Copper excretion in urine can be very high and in our group only 4 patients have elevated 24 hours urinary copper excretion. Histopathological examination of liver biopsymay show features such as interface hepatitis. Mallory bodies may be seen. Features of Cirrhosis may be seen along with parenchymal copper deposition visualised mainly in Kupffer cells .Hepatic mitochondrial changes identified by electron microscopy, are an important feature in Wilson disease.[8]The mitochondria vary in size, and the numbers of dense bodies in mitochondria may be increased. Dilatation of the tips of the mitochondrial cristae as a result of separation of the inner and outer membranes of the cristae resembling a tennis racquet is a striking feature[9]. In our group of patients liver biopsy was done in 3 patients and features of chronic hepatitis and interface hepatitis with kupffer cell hyperplasia were noted.Extra hepatic manifestations other than neurologic disease such as Hemolyti-canemia, Fanconisyndrome, Nephrolithiasis, Arthritis, Vitamin D–resistant rickets, Cardiomyopathy Hypoparathyroidism and Pancreatitis may be seen in wilsons disease. Amenorrhea and testicular dysfunction can occur due to Wilson disease not from cirrhosis[10]. Infertility or recurrent abortion may be a presenting feature. Renal stones were seen on one of our patients. Primary amenorrhoea seen in one patient and interestingly one patient in our group got married and delivered a normal child, continuing d-Penicillamine therapy.

Conclusions: 1. Consanguinity plays an important role in high frequency of the disease among the affected families. Hence cautious marriage counselling should be given against consanguineous marriage in affected families.2. Extra hepatic manifestations of Wilson disease can also occur hence carefully analysed to plan treatment for the same.3. Meticulous follow up of patients and appropriate treatment is mandatory for better outcome as evidenced by normal child birth in affected individual.

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