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CLINICAL PROFILE OF WILSON DISEASE IN CHILDREN IN A TERTIARY CARE CENTRE IN SOUTH INDIA

Gastroenterology

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ABSTRACT

Background: Wilson disease (WD) is the most common metabolic liver disease in Indian children with late presentation mandating early identification and treatment to prevent disease related morbidity and mortality. **Aim:** To study the clinical profile of Wilson disease in a tertiary referral care centre for children in South India. **Material & Methods:** Retrospective descriptive analysis of medical records of children with Wilson disease over five years from January 2014 to January 2018 admitted in Paediatric Gastroenterology department, Institute of child health & Hospital was done. **Results:** There were 75 children, 36 male 39 Female (1:1.08) with age ranging from 4 to 12 years. Clinical features include asymptomatic stage 7(9.3%). hepatic phenotype in 53 (70.6%) and neurophenotype in 15 (20%) children. Growth retardation was observed in 64 (85%), Kayser Fleischer ring in 30 (40%), Jaundice in 45 (60%), chronic liver disease in 40 (65.3%) out of which 21 (52.5%) children presented with decompensated liver disease and 14 children died during the study period with 18.7% mortality. Laboratory tests showed mean Hb 9.8 gm/dl SGOT 254 IU/L, SGPT 154 IU/L, albumin 2.2 gm/dl, low serum ceruloplasmin < 20mg/dl in 49 (65.3%), 24 hours urinary copper after D. Penicillamine challenge 680.4 µgm /day. Majority tolerated oral chelation therapy with D. Penicillamine except in 3. **Conclusion:** WD is the most common metabolic liver disease in children with chronic liver disease with 18.7%h mortality rate.

KEYWORDS

Wilson Disease Children

INTRODUCTION:

Wilson disease (WD) is an inherited disorder of copper metabolism due to defect in ATPase, encoded by the gene ATP7B. Young children often present with varied clinical features ranging from asymptomatic stage to end stage liver disease. Although hepatic manifestations are common in younger age, adolescents can present with neurologic, psychiatric, and hematologic manifestations.[1] Early diagnosis, with prompt treatment is likely to result in near-normal life. Low serum ceruloplasmin, and basal 24-hour urinary copper excretion and genotype determination are key to diagnosis.[2]

Pathogenesis

WD is due to defective incorporation of copper into serum ceruloplasmin and its excretion though bile caused by gene mutation with excess accumulation of copper in various tissues like hepatocytes,eye and brain. Toxic copper deposits cause oxidative stress and impair mitochondrial function with hepatic, neuropsychiatric, renal, musculoskeletal, and other symptoms involvement. Copper deposition in liver can present as fatty liver, acute liver failure, hepatitis, fibrosis and cirrhosis. Deposition of copper in astrocytes, leads to impairment of the blood–brain barrier with resultant damage to neurons and in basal ganglia with extra pyramidal and neuro psychiatric symptoms. Deposition of copper in descemets membrane on posterior surface of cornea is the reason for KF ring that is best demonstrated by slit lamp examination. Hematological features include negative Coomb's test haemolytic anaemia. Renal involvement include proximal renal tubular defects presenting as proteinuria, glycosuria and aminoaciduria. Children can present with delayed secondary sexual characters and features of hypopara thyroidism.

Aim: To study the clinical profile of Children with WD in children in a tertiary referral center

Study Design: Retrospective descriptive study
Duration: Five years from January 2014 to January 2018

MATERIAL & METHODS

Retrospective descriptive analysis of case records of children with WD from January 2014 to January 2018 at Institute of Child Health & Hospital for Children, Chennai a large referral public health center were analysed. All children diagnosed as Wilson disease based on clinical history, lab values were analysed for demography, clinical features and lab parameters. Disease frequency was measured as percentage and mean value was arrived for haemoglobin, transaminases, serum albumin and 24 hours urinary copper.

RESULTS

There were 75 children totally with 36 male and 39 female with age ranging from 4 to 12 years. Majority were referred from rural area. Positive family history in siblings was observed in 31 (41%) with a high rate of consanguineous parents.

Clinical Features

Clinical features include hepatic phenotype in 53 (70.6%) followed by neurological involvement predominantly presenting with extra pyramidal symptoms in 15 children (20%) and asymptomatic in 7 (9.3%). Growth retardation was observed in 64 (85%). Presence of Kayser Fleischer ring was noticed in 30 (40%) children, Jaundice in 45 (60%) Evidence of chronic liver disease was observed in 40 (65.3%) out of which 21 (52.5%) children presented with decompensated liver diseases and 14 children died during the study period with a mortality rate of 18.7%.

Laboratory tests showed mean Hb of 9.8 gm/dl mean SGOT 254 IU/L, SGPT 154 IU/L, albumin 2.2 gm/dl, Low serum ceruloplasmin was observed in 49 (65.3 %) with mean 24 hours urinary copper after D. Penicillamine challenge of 680.4 µgm /day. Most of the children tolerated oral chelation therapy with D. Penicillamine except in 3 children who were treated with zinc due to worsening of dystonia. Majority of children tolerated oral chelation with D. Penicillamine and Zinc was required in 4% of study subjects

Table 1 shows demography, clinical features and laboratory values in Wilson disease

Clinical Features (Cases 75)	Result
Demography	
Urban (11), Rural (64)	1 : 5.82
Male (36), Female (39)	1 : 1.08
Age range	4 yrs. - 12 yrs.
Growth Retardation	64 (85.3%)
KF ring	30 (40%)
Hepatic	53 (70.7%)
Jaundice	30 (40%)
Chronic liver disease	40 (53.3%)
Neurologic Type	
Extra pyramidal -10 & Seizure - 5	15 (20%)
Mortality	14 (18.7%)
Lab Parameters (mean)	
Hb	9.8 gm/dl
SGOT	254 IU/L
SGPT	154 IU/L
Albumin	2.2 gm/dl
24 hours urinary Copper D. Penicillamine challenge	680.4 µgm /day

** Lab values In children who died Mean value : Hb 9.2 gm/Dl, SGOT 247IU/L, SGPT 169IU/L, Alb 2.9gm/dl, Cerulo12.6, Urine Copper 942.5 µgm /day*

DISCUSSION

The clinical presentation of WD in this retrospective study reflects the referral pattern to a specialised tertiary centre. WD is the most common metabolic disease in our country but limited data is available in children. Though any age can be affected, it is commonly seen in children above 5 years of age. Our study showed age ranging from 4-12 years with slight female preponderance of 1:1.08 as compared to Bangladesh study with a mean age of 8.5±1.5 with male : female is 2:1[3] and majority were from rural area. Positive family history in siblings was observed in 31 (41%) with a high rate of consanguineous parents and hence family screening is an integral part of management as recommended by position paper because the chance of being a homozygote and developing clinical disease is 25%.[4] Screening of family members include physical examination, estimation of serum ceruloplasmin, liver function tests and urinary copper if molecular testing for ATP7B mutations or haplotype studies are not available.[5]

Clinical profile is also heterogeneous and hepatic phenotype was common in children as in our study similar to studies.[6,7] Our study also showed liver involvement with Jaundice in 45 (60%), chronic liver disease was in 40 (65.3) out of which 21(52.5%) had ascites. 14 children died during the study period with mortality of 18.7%. Neuropsychiatric symptoms usually develop in the second or third decade of life, and rare before 10 years of age.[8] Our study showed neurological involvement in 15 (25%) with seizures in 5 of them.. KF ring was seen in 45.7% of the patients as against two studies.[3, 9] The diagnosis of WD is made by constellation of clinical, ophthalmologic evaluation, biochemical tests with or without liver histology. Wilson disease should be suspected in a children born to consanguineous parents with positive family history presenting with hepatic or neurological symptoms. Diagnosis of WD may be challenging in young asymptomatic children with mild liver disease as ceruloplasmin levels and urinary copper excretion may be normal and Kayser-Fleischer rings may be absent. Low serum ceruloplasmin less than 20 mg/dl is often observed in Wilson disease though low value can occur in hypoproteinemic states like nephrotic syndrome, Kwashiorkor, fulminant liver failure and protein losing enteropathy.

Lab parameters in our study showed mean Hb of 9.8 gm/dl mean SGOT 254 IU/L, SGPT 154 IU/L, albumin 2.2 gm/dl, Low serum ceruloplasmin was observed in 49 (65.3 %) with mean 24 hours urinary copper after D. Penicillamine challenge of 680.4 µgm /day . Normal values range from 20 to 40 mg/dl and very low levels below 5 mg/dl are highly suggestive of WD. 24 hour urinary copper level >100 mcg/dl is considered virtually diagnostic, but recent studies have shown that lowering the cutoff levels to 40 mcg/dl for asymptomatic patients increases the sensitivity.[10] In children with acute liver failure, typical findings will have high total bilirubin levels (>300 mmol/L, >17.5 mg/dL) along with low serum transaminases levels (100–500 IU/L), low serum alkaline phosphatase level and a low alkaline phosphatase to total bilirubin value less than 1.[4] Medical management consist of usage of copper chelating agents like D-penicillamine and still remains the standard treatment for WD. D-penicillamine exerts copper "detoxifying" effect by inducing the endogenous hepatic metallothionein, a cytosolic metal-binding protein causing sequestration of copper and limiting damage to the liver that is found to be useful in majority of asymptomatic children. Worsening of neurologic symptoms has however been reported and withdrawal of drug due to adverse effects has been reported in up to 30% of cases both in children and adults. Majority tolerated oral D.Penicillamine and zinc was replaced in only 3 three children in our study. The recommended dose is usually increased progressively to 20 mg/kg/day given in 2 or 3 doses, with close monitoring for adverse events along with restriction of copper containing diets. Trientine, triethylene tetramine hydrochloride are other second-line chelating agents for those who develop adverse events.[11]

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