



Wilson's Disease in Children –Experience from a Tertiary Care Centre

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Abstract

Objectives: To assess incidents clinical and investigational profile of Wilson's disease in children in a northern city of India, this study was done.

Methods: The children (age < 10 years) with Wilson's disease who were admitted in pediatric Gastroenterology ward of PGIMER – Chandigarh from July 1993 to June 2003 were enrolled for the study. Clinical examination, investigation (Ultrasonography, serum ceruloplasmin, 24 hour urinary copper, KF ring detection, LFT, liver biopsy, liver copper estimation etc.) were done.

Result: 50 cases of Wilson's disease were admitted in 10 years. Mean age was 7.5 years (range 5 – 10 years) Male was 30 out of 50 cases (70%) hepatosplenomegaly with transaminitis was presenting symptoms. cirrhosis was present in 15 cases (30%), fulminant Wilson's disease in 5 cases (10%), KF ring in 35 cases (70%), neuropsychiatric symptom in 2 cases (4%) renal tubular acidosis in 5 cases (10%). liver copper was increased in all cases.

Conclusion: Wilson's disease is an important cause of chronic liver disease in Northern India. Early detection is mandatory for better management of the cases.

Keywords: Wilson's disease in children, chronic liver disease.

Introduction

Wilson's disease (WD) is an important multi systemic disease due to defective copper metabolism which is genetically mediated. Wilson's disease in children may be obscure and requires extensive investigation to establish diagnosis. Genetic analysis is needed in equivocal cases. ⁽¹⁾

24 hour urinary copper excretion seems to be most sensitive test for diagnosis of Wilson's disease particularly when liver biopsy cannot be performed due to coagulation abnormality ⁽⁶⁾

It is currently recommended that screening for Wilson's disease should be limited to all siblings

and first degree relatives of affected patients. In case of asymptomatic individuals, prompt initiation of therapy will prevent otherwise inevitable hepatic and neurological injury. ⁽¹⁷⁾

Tissiere et al observed that alkaline phosphatase to total bilirubin ratio (less than 1) showed 86% sensitivity and 90% specificity for fulminant Wilson's disease diagnosis. It differentiates fulminant Wilson's disease from other causes of fulminant hepatic failure. ⁽²⁾

Mc cullough et al observed that fulminant hepatic failure due to Wilson's disease differs from idiopathic fulminant hepatic failure by (a) higher copper level in serum, urine, and liver (b) less

pronounced rise of transaminase (c) higher concentration of total bilirubin (d) lower hemoglobin level⁽³⁾

Ferenci P et al observed that neurological disease of Wilson's is diagnosed by KF ring, typical neurological symptoms and low serum ceruloplasmin level⁽⁴⁾

Tankanow RM et al observed that Wilson's disease, being autosomal recessive disorder, occurring between 6 to 60 years having defective copper metabolism resulting in accumulation of excess copper in liver, basal ganglia of brain (lenticular degeneration), cornea (KF ring) have multi systemic symptoms of hepatic failure, neuro psychiatric symptoms and have been screened by 24 hour urinary copper assay, radioactive up take of ⁶⁴ Cu and liver biopsy. Initial rapid decoppering with chelating agent with penicillamine and trientine followed by lifelong maintenance therapy with zinc is current method of treatment⁽⁵⁾

Mallikarjun et al observed that liver disease is more common in children in childhood Wilson's disease. The children may be asymptomatic and may present with hepatomegaly or raised transaminase. Some have Coombs' negative haemolytic anaemia, transient jaundice, low grade haemolysis.⁽¹⁴⁾ Some may present with acute liver failure as dramatic presentation in 30% cases⁽¹⁸⁾

Previously treated patients who stopped their medicine can have acute presentation.⁽⁶⁻⁷⁾

Liver disease manifestation are more common in younger age group usually in first and second decade of life. It may be asymptomatic to chronic liver disease in presentation⁽²⁰⁾

Both younger and older group may have liver manifestation. Neurological symptom is common in third decades onwards⁽¹⁹⁾

Splenomegaly may be an important clue to chronic liver disease or hypersplenism⁽²¹⁻²²⁾

El- Youssef M et al observed that Wilson's disease is a disease of children, adolescent and young adult.

This rare disorder occurs due to defective copper metabolism resulting in accumulation copper in

liver and subsequently other organs like central nervous system and kidney⁽¹³⁾

Weiss KH et al described that genetic basis of Wilson's disease were ATP 7B gene as a copper transporting ATP ase (intra cellular transmembrane copper transporter). This ATP 7B gene is mutated in Wilson disease.

There are mutation of 800 variants of ATP 7B gene⁽²³⁾

DK Subhramayneum et al reported a case of distal renal tubular acidosis in Wilson's disease with coarse hepatic architecture, osteoporosis⁽¹⁶⁾. We also got five case of renal tubular acidosis out of 50 cases (10%).

Francisco Silva et al reported a case of attention deficit and hyper activity disorder who was initially treated with methyl phenidate but worsened after 3 years. He developed phobia, transminitis, disidiadochokinesia, low ceruloplasmin, high urinary copper, positive penicillamine test, high liver copper (853 micro gram per gram in liver biopsy) but normal brain MRI. ATP 7 B gene mutation was confirmed (25). We also got two (4%) cases of Wilson's disease with neurological symptoms in form of delayed learning, disidiadochokinesia. It is confirmed by low ceruloplasmin, 24 hour urinary copper, post penicillamine 24 hour urinary copper estimation.

Shiono Y et al observed iron over load related to low ceruloplasmin in Wilson's disease male patients. Post penicillamine treatment increases liver iron content, serum ferritin, serum transaminase level. This suggests for phlebotomy to prevent iron induced liver damage⁽¹¹⁾

Farinati F et al observed that Wilson disease patients have depressed level of reduced glutathione cysteine and high level of oxidized glutamine. This is prevented by zinc which increases glutathione molecules.⁽¹²⁾

Materials and Method

The children (age less than 10 years) with Wilson's disease who were admitted in pediatric gastroenterology ward of PGIMER – Chandigarh

from July 1993 to June 2003 were enrolled for the study. Detailed clinical examinations were done and noted. Investigation (Ultrasonography of whole abdomen, serum ceruloplasmin, 24 hour urinary copper, KF ring detection by slit lamp examination, LFT, liver biopsy liver copper estimation post penicillamine urinary 24 hour copper estimation were done. Treatment started after confirmation of diagnosis and regularly followed up in OPD.

Results

Fifty cases of Wilson's disease were admitted in 10 years. Mean age was 7.5 years (range 5 to 10 years.) Male was 30 and female was 20 in numbers. In 35 out of 50 cases (70%) hepatosplenomegaly with transaminitis was presenting symptoms. Cirrhosis was present in 15 cases (30%), fulminant Wilsons disease in 5 cases (10%), KF ring in 35 cases (70%), neuropsychiatric symptoms in two cases (4%) renal tubular acidosis in 5 cases (10%).liver copper was increased in all cases. In two cases (4%) who had neuropsychiatric symptoms had delayed learning, impaired cognitive function. Five cases of Wilson's disease who had fulminant hepatic failure died. Rest were regularly followed up in OPD.

Discussion

Wilson's disease is an important cause of pediatric Liver disease.

Brewer it all observed that Wilson's disease has defect in urinary excretion of copper caused by defect in an enzyme. It occurs mostly in older children and young adults with hepatic, neurological or psychiatric manifestation or some combinations⁽⁷⁾

We got neuropsychiatric manifestation only in 4% cases because our children were less than 10 years of age.

We got hepatosplenomegaly with transaminitis in 70% cases, cirrhosis in 30% cases and fulminant Wilson's in 10% cases. Obviously there was overlap in various subgroup in hepatic cases.

Hoogenroad TU et al brings a new idea on paradigm shift of Wilson's diseases treatment and stresses importance on zinc rather than penicillamine.

He thinks that free copper (which is not bound to ceruloplasmin) is more toxic than bound copper. Zinc helps in storage of metallothionein bound copper in mucosa of gut and excretion of copper via stool. New regime recommends against decoppering by penicillamine which aggravates free copper toxicity.⁽⁸⁾

However it is still controversial whether we will choose only zinc and avoid penicillamine.

Sturniolo GC et al think that zinc administration increases intestinal metallothionein in duodenal mucosa of Wilson's disease patients.

Metallothionein blocks copper absorption, desquamates intestinal mucosa, excretes copper in stool. Metallothionein is increased by 1500% in Wilson's disease duodenal mucosa in zinc therapy but only 150% with penicillamine therapy. Even mucosal iron content is increased in penicillamine group.⁽⁹⁾

Medici V et al observed that penicillamine treated Wilson's diseases have higher liver iron or higher urinary prohepcidin compared to zinc treated patients⁽¹⁰⁾

Bruha R et al observed that long term follow up of Wilson's diseases showed satisfactory response and survival comparable with general population.⁽³²⁾

In our study 45 out of 50 wilson's diseases children showed satisfactory response to panicillamine and zinc therapy and 5 (10%) patients died of fulminant Wilson's diseases. Ferenci P et al stresses importance on mutation analysis for family screening with a index case with known causative mutation. Alternatively haplotype analysis is useful to differentiate heterozygous carrier gene in asymptomatic affected siblings

European population have H1069Q and Far East have R778L known mutation of Wilson's disease. There are more than 200 mutations available⁽¹⁵⁾.

Schisky M et al suggested Orthotopic liver transplantation in Wilson's disease if there is hepatic insufficiency, Wilsonian Fulminant hepatitis, intractable neurological Wilson's, and GI haemorrhage.⁽²⁶⁾

Charlotte et al described a case of asymptomatic Wilson's disease having dense KF ring, very high level of liver copper having normal neurological examination and normal liver function test.⁽²⁴⁾

We also got KF ring in 35(70%) cases out of 50 cases of Wilson's disease but all had hepatosplenomegaly with raised transaminase.

Palakar AV et al reported a case of metabolic bone disease caused by renal tubular acidosis due to Wilson's disease. The patient had lower limb deformity with walking difficulty, short stature, normal neuro development and secondary sexual character having splenomegaly, KF ring, low serum ceruloplasmin, copper, hyper calciuria, urinary acidification defect pointing towards distal RTA. The patient received copper chelation therapy and osteopenia was improved.⁽²⁷⁾

We also got 5 (10%) cases of renal tubular acidosis out of 50 case of Wilson's disease.

Cuthbert JA et al observed Wilson's disease gene (WND) controlling copper metabolism. WND expresses copper transporting protein which has a structure of P- type ATP ase. It has striking homology of another gene product for another copper related genetic disease called Menkes disease (ATP 7 A)

In Wilson's disease copper is deposited in liver, lens, CNS, but in Menkes disease copper cannot be absorbed so treatment of Menkes disease is to supplement copper⁽²⁸⁾

Okada et al noticed that ceruloplasmin and copper levels were absolutely low with heterozygotes. There is lot of diversity between genetic mutation and phenotype⁽²⁹⁾

Terada K et al observed that introduction of ATP 7B protein by recombinant adenovirus mediated gene delivery will be a potential approach for correcting Wilson's disease⁽³⁰⁾

Tomic A et al showed that genetic diagnosis of Wilson's disease can be done in 80% cases by

analysis of five most common mutation in their population. There is no correlation between different genotype and specific phenotype of Wilson's disease, presence of psychiatric disorder and cognitive deterioration⁽³¹⁾

Conclusion

Wilson's disease is an important cause of chronic liver disease in northern India. Early suspicion and detection is very important for better outcome. The parents are advised to continue lifelong treatment and regular follow up.

Conflict of interest – Nil

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