Indian Journal of Genetics and Molecular Research
Volume 1 Number 2, July - December 2012

Wilson's Disease (Coomb Negative Hemolytic Anaemia in Acute Liver Failure)

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Abstract

Wilson's disease or hepatolenticular degeneration is an autosomal recessive genetic disorder in which copper accumulates in tissues; manifesting as neurological or psychiatric symptoms and liver disease. This has varied range of manifestations like asymptomatic hepatomegaly, subacute or chronic hepatitis, acute hepatic failure etc. Because of this there is delay in diagnosis and initiation of treatment are common, even in patients with positive family history. There is no consensus regarding therapeutic protocols since the use of penicillamine, once a 'gold standard' for treatment, has been debated by experts. Mortality and morbidity of this potentially treatable disease and nonavailability of medications to the poor patients remain a major area of concern.

Keywords: Wilson's disease; Acute hepatic failure; K.F. ring; Coomb negative hemolytic anaemia.

Introduction

Wilson's disease (hepatolenticular degeneration) is an autosomal recessesive disorder, associated with degenerative changes in brain, liver disease and Kayser-Fleischer ring the cornea. The incidence is 1/50,000 to 1/1,00.000 births. Girls are 3 times more likely than boys to present with acute hepatic failure. After the age of 20 yrs neurological symptoms are predominant. Wilson's disease is progressive and potentially fatal if untreated.[1]

Case Summary

A 6.5 yrs girl child, product of non consangously wedded, Para 2 couple, with normal past history was brought for complaints of yellowness of eyes without any associated complaints. On examination, vitals and general examination revealed normal except icterus and 2 cm hepatomegaly. Investigations were done at 12 o'clock which were HB-8.6 gm%, W.B.C.-17,200/cmm, N.-78%, L.-18%, S. Bilirubin-T-6.1 mg/dl,D.-4.8mg/dl. Child was admitted along with treatment of Iv fluids, inj. Ceftriaxone and antimalarials (PS-MP-negative) At 4.00 O'clock, USG abdomen done which revealed Acute liver parenchymal disease with minimal fluids in abdominal cavity. So again in the night blood investigations repeated, which was Hb-4.9gm%, TLC-31,600/cmm, L-7300/cmm, N-21800/cmm, HCT-13.9%, RBC Count-1.62mil/cmm, Platelet count-Normal, S.Bilirubin-T-26.49mg/dl, D-18.95mg/dl, SGPT-234U/ML, SGOT-162, HBSAG-Negative, Blood gr. O positive, PT-29.09 Sec, PBS-S/O-Haemolysis. Immediately child was given blood transfusion.

On second day morning child was stable without any new complaints but her blood parameters were HB-7.3gm%, TLC-18800/cmm, N-13000/cmm, L-4700/cmm, Platelets -1,73,00/cmm, PT-26.40 sec, G6PD Test-Negative, S.Bilirubin-T-32.5mg%,D-26.8mg%, SGPT-382U/ML, USG Abdomen was repeated-showed Acute on chronic liver disease. On same day evening blood parameters worsend, with development of

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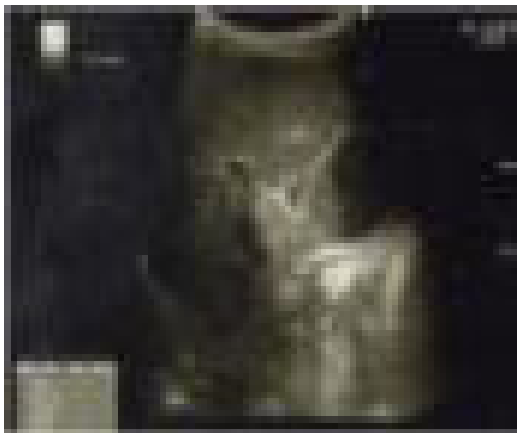
USG-Liver (2nd Day)



ascitis. Again blood transfusion and anti hepatic failure treatment started.

On third day child was comfortable with stable vitals except ascitis and slight irritability. Keeping in mind, the possibility of Wilson's disease, she was put on D-penicillamine and investigations started, Ophthalmic examination K.F. Ring on slit lamp examination, Ceruloplasmin level-12 mg%(N-20-40 mg%), raised ammonia level, negative coombs test, Negative Haemoglobinuria, deranged RFT and LFT parameters, In the evening at 4 O'clock child had altered sensorium, distension of abdomen and neck stiffness with breathing difficulty. So she was put on ventilator but within 8 hrs she died of cardio-respiratory arrest. Because of time shortage 24 hrs urinary copper analysis was not possible but after death liver biopsy confirmed the diagnosis.

Final Diagnosis

Samuel Alexander Kinnier Wilson

Wilson's Disease: Comb's negative hemolytic anaemia in acute liver failure.

Discussion

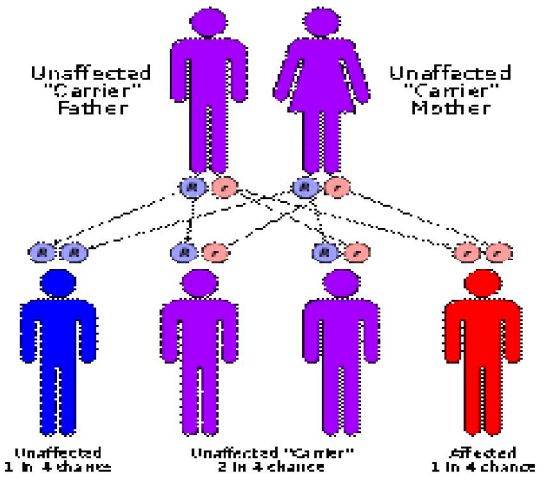
History

Wilson's disease is named after Samuel Alexander Kinnier Wilson (1878–1937), the British neurologist who first described the condition in 1912.[2]

Wilson's work had been predated by reports from German neurologist Carl Westphal (in 1883), who termed it "pseudo sclerosis"; by the British neurologist William Gower's (in 1888); and by Adolph (in 1898), who noted hepatic cirrhosis. Neuropathologist John Nathaniel Cumings made the link with copper accumulation in both the liver and the brain in 1948.[3] The first effective oral chelation agent, penicillamine, was discovered in 1956 by British neurologist John Walshe.[4]

Genetics

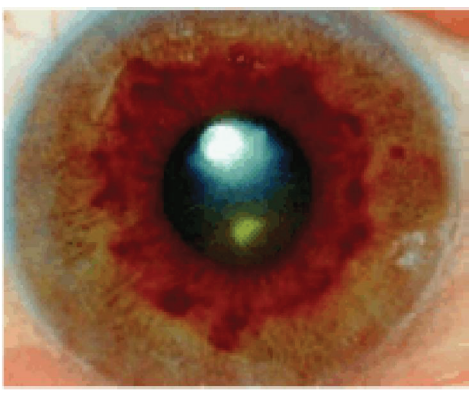
The Wilson's disease gene (*ATP7B*) has been mapped to chromosome 13 (13q14.3) and is expressed primarily in the liver, kidney, and placenta. The gene codes for a P-type.[5] The condition is inherited in an autosomal recessive pattern. In order to inherit it, both of the parents of an individual must carry an affected gene. Most have no family history of the condition. People with only one abnormal gene are called carriers (heterozygotes) and



may have mild, but medically insignificant, abnormalities of copper metabolism.[6]

Pathophysiology

Copper is needed by the body as a cofactor for a number of enzymes such as ceruloplasmin, cytochrom c oxidase, dopamine â-hydroxylase, superoxide dismutase and tyrosinase. Copper enters the body through the digestive tract. A transporter protein on the cells of the small bowel, copper membrane transporter 1 (CMT1), carries copper inside the cells, where some is bound to metallothionein and part is carried by ATOX1 to an organelle known as the trans-Golgi network. Here, in response to rising concentrations of copper, an enzyme called ATP7A releases copper into the portal vein to the liver. Copper accumulates in the liver tissue; ceruloplasmin is still secreted, but in a form that lacks copper (termed apoceruloplasmin) and rapidly degraded in the bloodstream. When the amount of copper in the liver overwhelms the proteins that normally bind it, it causes oxidative damage through a process known as Fenton chemistry; this damage eventually leads to chronic active hepatitis, fibrosis (deposition of connective tissue) and cirrhosis. The liver also releases copper into the bloodstream that is not bound to ceruloplasmin. This free copper precipitates throughout the body but particularly in the kidneys, eyes and brain. In the brain, most copper is deposited in the basal ganglia, particularly in the putamen and globus pallidus.[7]



Clinical Features

Tiredness, portal hypertension, enlargement of the spleen, ascites, behavioral changes, depression, anxiety and psychosis.[2] About 5% of all people are diagnosed only when they develop fulminant acute liver failure, often in the context of a hemolytic anaemia. This leads to abnormalities in protein production and metabolism by the liver. The deranged protein metabolism leads to the accumulation of waste products such as ammonia in the bloodstream. When these irritate the brain, the person develops hepatic encephalopathy.[2]

Other Organs Involvement

1. Eyes: *Kayser–Fleischer Rings* (KF rings) around the iris due to copper deposition in Descemet's membrane of the cornea, visible by slit lamp examination.[2]
2. Kidneys: renal tubular acidosis leads to nephrocalcinosis.[2]
3. Heart: cardiomyopathy is a rare.[2]

Diagnosis

Liver function tests: Raised aspartate transaminase, alanine transaminase and bilirubin level, the prothrombin time may be prolonged, Alkaline phosphatase levels are relatively low in those with Wilson's-related acute liver failure.[2]

Ceruloplasmin: Levels of ceruloplasmin are abnormally low (<0.2 g/L) in 80–95% of cases.[6] The combination of neurological symptoms, Kayser–Fleisher rings and a low ceruloplasmin level is considered sufficient for the diagnosis of Wilson's disease.[6]

Serum and Urine Copper: Serum copper is paradoxically low but urine copper is elevated in Wilson's disease. Urine is collected for 24 hours in a bottle with a copper-free liner. Levels above 100 ìg/24 h (1.6 ìmol/24 h) confirm Wilson's disease, and levels above 40 ìg/24 h (0.6 ìmol/24 h) are strongly indicative).[6]

Liver Biopsy: The gold standard or most

ideal test is a liver biopsy.[2]

Magnetic Resonance Imaging (MRI) of the brain

If there are neurological symptoms is usually performed; this show shy perintensities in the part of the brain called the basal ganglia in the T2 setting. MRI may also demonstrate the characteristic "face of the giant panda" pattern.[6]

Treatment

Dietary

A diet low in copper-containing foods is recommended with the avoidance of mushrooms, nuts, chocolate, dried fruit, liver, and shellfish.[2]

Medication

Generally, penicillamine is the first treatment used. This binds copper (chelation) and leads to excretion of copper in the urine.[2] Intolerant to penicillamine may instead be commenced on trientine hydrochloride or tetrathiomolybdate. Once all results have returned to normal, zinc may be used instead of chelators to maintain stable copper levels in the body. Zinc stimulates metallothionein, a protein in gut cells that binds copper and prevents their absorption and transport to the liver.[6]

Physiotherapy can assist in coping with ataxia, dystonia and tremors, as well as preventing the development of contractures that can result from dystonia.

Liver transplantation is an effective cure for Wilson's disease, but is used only in particular scenarios because of the numerous risks and complications associated with the procedure.[6]

Conclusion

Family members of patient with proven cases requires screening for presymptomatic Wilson's disease. Such screening should include determination of the serum Ceruloplasmin level and urinary Copper excretion. In asymptomatic siblings of affected patient early institution of chelation or zinc therapy can prevent expression of disease.

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