Case report

Wilson's disease

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Abstract *Wilson's disease is a rare autosomal recessive disorder characterized by accumulation of copper in liver, brain, corneas and kidneys. The disease is known to have various hepatic manifestations like acute hepatitis, chronic hepatitis, cirrhosis of liver and acute fulminant hepatic failure, which can occur in early childhood. We experienced a case of an 18 year old girl who presented with anemia, jaundice and ascites. A diagnosis of Wilson's disease with hepatic failure was made on the basis of history, physical findings, lowserum ceruloplasmin level, elevated urinary copper and the presence of Kayser Fleischerringin both eyes on slit lamp examination. She was prescribed copper chelator, D-penicillamine. Clinical improvement was observed at follow up visits after treatment. Wilson's disease is an inherited metabolic disorder. Early diagnosis and proper management help to prevent complications. Siblings are needed to be screened to prevent manifestations.*

Keywords: *Wilson's disease, Copper accumulation, Hepatolenticular degeneration, Kayser Fleischer ring*

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Introduction:

Wilson disease (WD), also known as hepatolenticular degeneration, was first described in 1912 by Samuel Alexander Kinnear Wilson as a familial lethal disease accompanied by chronic liver disease leading to cirrhosis.[1,2] Over the next several decades, the role of copper in the pathogenesis of WD was established, and the pattern of inheritance was determined to be autosomal recessive. In 1993, the responsible genetic defect, mutation in a P-type copper dependent AT Pase, ATP7B localized to chromosome 13, was identified.[1] Most of the patients are compound heterozygotes.[2,3] More than 500 mutations in the WD have been found. The ATP7B protein transports copper out of the hepatocytes into bile for its incorporation into ceruloplasmin, the plasma copper carrying protein.[3,4] The estimated prevalence of the condition is 1 in 30,000 individuals.[2] Normally, dietary copper, after absorption from stomach and small intestine, is rapidly taken into the liver where it is stored and incorporated into ceruloplasmin and then secreted into the blood. The main physiological abnormality in WD is excessive absorption of copper from the small intestine and also its decreased excretion into bile owing to absence or reduced function of ATP7B protein.[2] This results in accumulation of copper in liver, brain, cornea and kidneys with subsequent oxidative injury to these organs.[3,4] Patientswith WD may present with hepatic dysfunction (40%),

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neurological symptoms (40%), psychiatric and behavioral disorder (20%).[1,4] Various hepatic forms like acute hepatitis, chronic hepatitis, cirrhosis of liver and acute fulminant hepatic failure can occur in early childhood characterized by ascites, spider nevi, palmar erythema and digital clubbing. Neurological damage causes tremor, choreo-athetosis, ataxia, dystonia, behavioral changes and dementia.[5,6,7] Deposition in the kidneys may manifest as renal tubular acidosis, nephrolithiasis, aminoaciduria and hypouricemia.[2] Kayser Fleischer (KF) ring, apathognomonic feature, though found less often among children, is characterized by demonstration of fine greenish-brown pigmented granular deposits of copper in the Descemet membrane of corneal margin on slit lamp examination. The KF ring is more common in patients with neuropsychiatric WD. It gradually disappears with treatment. Deposition of copper in the eye can also result in sunflower cataract visible on slit-lamp examination.[7,8,9]

Case report:

An 18 year old school girl presented with abdominal distension for 2 months which had increased over the last few days. It was associated with mild upper abdominal pain, anorexia and nausea, but was not related to any food intake. She noticed yellow coloration of her eyes and urine for the previous couple of weeks. There was no history of hematemesis, melena, itching, any behavioral changes or loss of consciousness. She did not take any hepatotoxic drug in recent years. She neither received any blood transfusion nor was she an intravenous drug abuser. She did not give a past history of jaundice or liver disease. She was an offspring of non-consanguineous parents and none of her siblings or other family members had any history of hepatic or neurological manifestation suggesting WD. On clinical examinations she was found to be icteric (Fig 1) and anemic. Moderate ascites was present. But there was no other stigmata suggestive of chronic liver disease and also no feature of hepatic encephalopathy. The patient was meticulously examined for presence of any neurological or psychiatric abnormality but none was found.

Her blood count showed hemoglobin 7.8 gm/dl, ESR 65 mm in the 1st hour, total count of WBC 10000/cu mm, platelet 150000/cu mm, neutrophil 65%, lymphocyte 29%, eosinophil03% and monocyte 03% with a hemolytic picture. Coombs test was negative. Her serum bilirubin was4.8 mg/dl, serum creatinine was 1.1 mg/dl, albumin was2.4gm/dl, ALT (Alanine Transaminase) was 51 U/L, alkaline phosphatase was 144 IU/L, and prothrombin time was 22 second with INR 1.92. She was HBs Ag and anti HCV negative. Urine for routine and microscopic examination revealed normal findings. USG of whole abdomen showed mild splenomegaly and ascites. Paracentesis was done and ascitic fluid study showed transudate (protein 1.89 g/dl), normal ADA (2.08 IU/L), lymphocyte 05/cu-mm and absent malignant cell. Esophago-duodenoscopy revealed pangastritis but no varix. Her liver stiffness index was 45 K Pa on fibro scan. Her serum ceruloplasmin was 0.07 g/L, urinary copper excretion was 387microgram/24hour(an excretion above 100microgram/24hour confirms WD). On slit lamp examination of the eyes by an expert ophthalmologist revealed Kayser Fleischer rings in the corneas.

The patient was diagnosed as a case of WD (Leipzig criteria score 7)[10]and cirrhosis of liver (based on liver stiffness index >12 K Pa) with hepatic failure. Her anemia was corrected by two units of whole blood transfusion and she was prescribed with oral D-penicillamine, a copper chelator, at a dose of 500 mg three times a day, with a supplement of oral pyridoxine 60 per week.[2]She tolerated the drugs well except for mild gastro-intestinal upset symptoms in the initial few days. Diet devoid of shell fish, nuts, organ food, mushroom and chocolate[2] was advocated. Improvement of clinical features (general wellbeing, reduction of ascites, edema and anemia) were observed at follow up visit after 4 weeks.

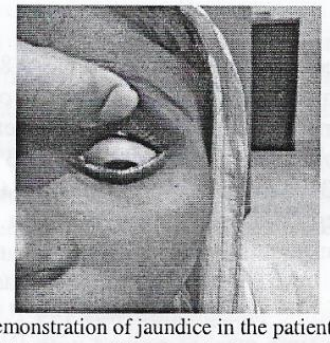

Fig. 1: demonstration of jaundice in the patient, though no KF ring was visible to naked eye examination

Discussion:

WD is an autosomal recessive condition characterized by inability of the liver to transport and store absorbed dietary copper resulting in abnormal deposition of copper in the basal ganglia, eyes, liver and other tissues, presenting with hepatic and or neuropsychiatric problems.[8] We present in this report, a case of WD presenting with hepatic failure but without any neuropsychiatric features, admitted and treated in the medicine inpatient of Sylhet Women's Medical College. Though no imaging (MRI/ CT scan) of brain[11] was done, the patient had no involuntary movement, ataxia, dystonia or behavioral abnormalities on careful physical examination. Previously, we experienced another case of WD several years back, in the same institute, a 19 year old boy presenting with extra pyramidal features (ataxia, rigidity and proximal 'wing-beating' type coarse tremor) and mood swings.[5]Children with hepatic WD may remain entirely asymptomatic, and hepatic enlargement or abnormal serum amino transferases are found only incidentally. Some patients have a brief clinical illness resembling an acute viral hepatitis, and some may present with features in distinguishable from autoimmune hepatitis.[8] Many patients present with features of chronic liver disease, either compensated or decompensated. Patients may present with isolated splenomegaly due to clinically inapparentcirrhosis with portal hypertension.[2,3,8] WD may also presentas acute liver failure with an associated Coombs-negative hemolytic anemia and acute renal failure. Some patients have transient episodes of jaundice due to hemolysis. Neurologic manifestations of WD typically reveal later than the liver disease, most often in the third decade of life.[2,5]When symptoms manifest between the second and third decades of life, approximately 50% of the patients show neurological symptoms.[12]

The diagnosis of WD is challenging, but is based on a combination of clinical suspicion and laboratory data.[2]In this case report Leipzig criteria for scoring WD were used.[10] According to this system, a score of 4 or more is diagnostic of WD. Our patient had a score of 7 (Table: 1).

Table: 1

Leipzig criterion	Finding in patient	Score	Total score
KF ring	present	2	=7
Serum ceruloplasmin	0.07 g/L	2	
Urinary copper excretion	more than 2 times normal	2	
Coombs negative	yes	1	

Serum ceruloplasmin is typically decreased by 50% of the lower normal value in WD, but as it is an acute phase reactant, it may be elevated in inflammatory conditions and thus false negative results may occur.[1] Its levels may be normal in 5-20% patients with WD.[2,4] The amount of copper excreted in the urine in a 24-hour period, which reflects the amount of non-ceruloplasmin bound copper in the circulation, is a useful tool for both diagnosing WD and monitoring prognosis after treatment.[2,10] KF ring in cornea is important finding for diagnosis of WD. It is present in half of the patients with hepatic WD and almost invariably present in patient with neurological feature. But sunflower cataract is a rather rare finding.[7,13]

A liver biopsy may be necessary in some patients to demonstrate histologic evidence of copper deposition in liver. Measurement of hepatic tissue content of copper (normal <55μg copper/g dry

liver) may show elevated levels (>250 μg copper/g dry liver) in WD. This is helpful in doubtful cases.[2,10]

Though acute, subcute and chronic liver failure are complications of hepatitis, it is not always possible to identify them as distinct entities, and thus consensus classification between different associations of study of liver diseases is lacking. ALF (Acute Liver Failure), caused by fulminant hepatitis, in persons with no previous history of cirrhosis, is characterized by a rapid onset and a dramatic clinical course and deterioration of liver function (e.g. coagulopathy - INR ≥ 1.5) and any degree of altered consciousness (encephalopathy).[14] SAHF (Sub Acute Liver Failure) is characterized by a gradual onset of symptoms and a slowly deteriorating clinical course. Ascites and jaundice are the main manifestations and the liver is either enlarged or normal. Encephalopathy is uncommon. The interval between jaundice and ascites, the two most important characteristics of the disease, is variable (15 days- 25 weeks, usually 10 to 12weeks). CLF (Chronic Liver Failure) is defined as hepatic decompensation developing six months after acute liver injury.[3]The interval between the onset of illness and development of advanced features of portal hypertension and liver failure easily differentiates CLF from SAHF.[2,3,15]

Though no histopathological evaluation of the liver was done in our patient, she most probably had cirrhotic liver as evidenced by the high hepatic stiffness index on fibro scan, with some features of liver failure (raised bilirubin, low albumin, raised INR and ascites). Her liver failure status was ALF (Acute Liver Failure) as per AASLD (American Association for the Study of Liver Disease 2006); ACLF (Acute on Chronic Liver Failure) Type C as per WGO (World Gastroenterology Organization 2014) working party , APASL (Asia-Pacific Association for the Study of the Liver 2009) and EASL-CLIF-Consortium (European Association for the Study of the Liver-Chronic Liver Failure 2013).[14] But, as the features (jaundice and ascites) of failure fulfilled the criteria of being present for 15 days-25 weeks, the patient's hepatic failure might also be categorized as SALF (Sub Acute Liver Failure) according to China and United Kingdom guidelines for liver failure issued in 2006 and AIIMS (All India Institute of Medical Science 1989 workshop).[14,15]Although widespread clinical utility of genetic testing is not practiced, the identification of a mutation in a family helps in screening the relatives of an index case.[2]

The pharmacological therapy for WD includes D-penicillamine, Trientine and Zinc. OralD-penicillamine, given ata dose of 0.75-2 g/day in divided doses, is the first agent of choice. It binds tissue copper and then leads to its excretion through the urinary tract. Gastrointestinal intolerance, hypersensitivity, autoimmune reactions, nephrotoxicity and bone marrow toxicity are the adverse effects of D-penicillamine warranting its discontinuation.[16] Oral pyridoxine, 50mg/week, is added since penicillamine is an antimetabolite to this vitamin.[2] Treatment should be continued indefinitely. But dose may be reduced when the plasma non-ceruloplasmin copper level becomes normal and/or when the patient becomes pregnant.[17] Survival and prognosis after a fulminant disease is dependent on the patient undergoing liver transplantation. Liver transplantation may also be considered in patients with decompensated cirrhosis and patients who are non-responsive to medical therapy.[1]

Conclusion:

WD should be suspected in any patient with unexplained liver disease with or without neurological or neuro-psychiatric disorders. In a suspected patient Kayser-Fleischer rings should be sought by slit-lamp examination by a skilled examiner. However, its absence does not exclude the diagnosis. So, other biomarkers should also be tested to either exclude or confirm diagnosis. Adherence to treatment after diagnosis reduces morbidity and mortality significantly. Biological siblings need to be screened and treatment is to be given to all affected individuals, even if they are asymptomatic.

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