

Case report

A Case of Wilson's Disease Presenting as Chronic Liver Disease
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Abstract:

Wilson's disease is one of the most common inherited liver diseases with a worldwide incidence of 10-30 million cases. The increased frequency in certain countries is due to high rates of consanguinity and the fulminant presentation of the disease is more common in females than in males. It is an autosomal-recessive disorder caused by mutation in the ATP7B gene, with resultant impairment of biliary excretion of copper. Subsequent copper accumulation, first in the liver but later on in the brain and other tissues, produces clinical manifestations that may include hepatic, neurological, psychiatric, ophthalmological and other derangements. Genetic testing is impractical because of the multitude of mutations that have been identified, so accurate diagnosis relies on judicious use of laboratory and other diagnostic tests. Lifelong palliative treatment with a different combination of medications, or with liver transplantation if needed, can successfully ameliorate or prevent the progressive deterioration of the disease, otherwise death would inevitably ensue. Since effective treatment is available for this disease, early and correct diagnosis is very important. Here, we report a case of Wilson's disease in a 15-year-old girl presenting to us as chronic liver disease.

Key words: Wilson's disease; autosomal recessive; mutation; ATP7B gene; chronic liver disease

Bangladesh Journal of Medical Science Vol. 15 No. 03 July'16. Page : 495-498

Introduction:

Mild forms of the liver disease are non-progressive or show slow progression, whereas other more severe forms are associated with architectural disorganization, which can lead to cirrhosis¹. Chronic liver disease often leads to nonspecific symptoms such as malaise, fatigue, and weakness, or no symptoms at all. It is commonly identified by blood tests performed either for screening or for evaluating nonspecific symptoms. Hepatitis B and C are the most common causes of chronic liver disease^{2,3}. Drug-induced, alcoholic and autoimmune hepatitis are other common causes of chronic liver disease. In many cases, physicians can correctly diagnose the condition underlying by using clinical and laboratory findings. In some cases, physicians may misdiagnose, because they do not consider the hidden causes of chronic liver disease. However

less common aetiologies like Wilson's disease must be kept in mind and looked for, whenever there is strong suspicion.

While the prevalence of WD is very low, it is a treatable liver disease and therefore needs to be properly identified⁴. Here, we report a case of Wilson's disease in a 15-year-old girl presenting to us as chronic liver disease.

Case report:

A 15-year-old school girl, presented to us on 8th March, 2015 with three weeks history of abdominal pain and a one week history of fever with jaundice, nausea, vomiting and loss of appetite. She gave history of jaundice for two episodes in last one year. She had no history of intake of any drug with known hepato-toxicity in last six months and was non-smoker and non-alcoholic. Her parents were consanguineously married but neither she

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nor her two siblings had history of any hepatic or neurological manifestations suggesting Wilson's disease.

On physical examination, the patient was conscious and mildly icteric. Her pulse rate was 92 beats/min, blood pressure 90/60 mm hg, temperature was 100F and resp. rate was 16 breaths/min. Auscultation of heart and lungs were normal. Abdominal examination revealed soft and non-tender abdomen with splenomegaly and presence of umbilical and right sided inguinal hernia. Neurological examination yielded normal findings. Her laboratory investigation revealed Hb% - 10 gm/dL, ESR 5 mm, total WBC count 3500/cmm, platelet count 50000/cmm. PBF showed pancytopenia and bone marrow study revealed secondary reactive marrow. The levels of blood sugar, serum electrolytes and creatinine were normal. ICT for malaria was negative and CXR P/A view was normal. Liver enzyme assay revealed the levels of AST, ALT, ALP and total s. bilirubin to be 87 U/L, 75 U/L, 277 U/L and 2.6 mg/dL respectively. S. albumin was 1.57 gm/dL PT- control 11 sec, test 31 sec and INR 2.81. We, therefore, checked for Anti HAV IgM, HBsAg and anti-HCV antibodies, but the results were negative. USG of W/A suggested cirrhotic change in the liver with splenomegaly and Endoscopy of upper GIT revealed oesophageal varix.

Keeping the patient's clinical profile and investigations in mind, differential diagnosis of Wilson's disease and autoimmune hepatitis was kept. Patient's ANA was negative. Her serum ceruloplasmin level had reduced to 9 mg/dL (normal, 17.9 to 53.3 mg/dL), whereas 24 hours urinary copper excretion rate was 58 μ g/day which was near the upper limit of normal range (normal, 15-60 μ g/day). Slit lamp examination showed the presence of Kayser-Fleischer ring. Liver biopsy was not done due to abnormal coagulation profile. All these findings pointed to our diagnosis of CLD due to Wilson's disease.

The patient was started on copper chelation therapy with oral penicillamine and zinc along with supportive treatment and dietary restriction of copper. Penicillamine was started at 500 mg daily in two divided doses but unfortunately the patient was unable to tolerate penicillamine and developed severe hypersensitivity reaction in the form of fever, rash and joint pain. After a few days interval we restarted penicillamine but that time she experienced hypersensitivity reaction in more severe

form. Then her treatment was continued with oral zinc 20 mg twice daily. However patient's general condition was improved to some extent and she was discharged with advice for regular follow up.

After nine months, the patient was brought to the emergency department of our hospital with the history of convulsion for three to four times within 24 hours with fever for 3 days. Each episodes of convulsion was lasted for 5-6 minutes and it was generalized tonic-clonic in nature and associated with loss of consciousness without any bowel/bladder incontinence or tongue bite. On examination, patient was disoriented, GCS 6/15, mildly anaemic, neck stiffness was absent, coarse crepitation was present on all over the both lung fields, jerks were exaggerated with dystonic posture. Her temperature was 99F, pulse 120beats/min and blood pressure was 90/60 mm Hg. All the available resuscitation was given but her condition deteriorated due to aspiration following convulsion and she died after an hour of hospital admission.

Discussion:

Wilson's disease is a well recognized but less frequently encountered disease entity having the frequency of approximately 1 case in 94,000 individuals in most populations, and approximately 1 case in 156,000 individuals in populations older than 15 years of age⁴. Most patients present in their mid to late teenage years, although the age of presentation is quite broad and extends into the fifth decade of life.

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 (cation transport enzyme) ATPase that transports copper into bile and incorporates it into ceruloplasmin⁵.

Copper is an essential element for cellular function, yet free copper is highly reactive and damaging to cells of target organs and can produce irreversible cellular damage. To handle elemental copper in our body, elegant systems have evolved that bind the copper molecule to ensure safe transport of necessary copper to intended sites and safe elimination of excess copper through the biliary system. Both the ATP7B protein and ceruloplasmin are involved with copper transport. The ATP7B protein normally resides in the trans-Golgi network in hepatocytes, where it mediates the incorporation of six copper molecules into apoceruloplasmin, forming ceruloplasmin⁶. Under conditions of high copper levels, ATP7B is also redistributed

to cytoplasmic vesicles where it transports excess copper across the hepatocyte apical membrane into the bile canaliculus for subsequent biliary excretion^{7,8}. In individuals with Wilson's disease, mutation in the ATP7B gene results in defective ATP7B protein that cannot perform these functions. Consequently, copper progressively accumulates within the hepatocytes. Not only does this progressive copper accumulation ultimately compromise hepatic function, the hepatic storage capacity is also eventually exceeded and unbound copper spills out of the liver and is deposited in other organs and tissues, where it also provokes damage and dysfunction. As the excess copper escapes from the liver, urinary copper excretion rises dramatically, but is unable to compensate fully for the defect in biliary excretion. It has been assumed that the cellular damage characteristic of Wilson's disease is due to a direct toxic effect of excess copper. Recent evidence, however, suggests that a reduction in the protein, X-linked inhibitor of apoptosis (XIAP), induced by copper elevation, results in acceleration of caspase 3-initiated apoptosis with resultant cell death⁹.

There is no single specific test for the diagnosis of Wilson's disease. In a nation-wide survey of Wilson's disease, low serum ceruloplasmin (<20 mg/dL), high 24-h urine copper level (>100 g), high hepatic copper content (>250 µg/g of dry liver), and Kayser-Fleischer rings were found in 96%, 86%, 88%, and 73% cases, respectively⁴. A combination of any 2 of the above 4 laboratory findings forms a strong support for the diagnosis of Wilson's disease¹⁰⁻¹⁴. Genetic testing to confirm the diagnosis is a reasonable option, although a specific mutation cannot be identified in all patients.

Episodes of hepatitis can occur with elevated liver enzymes, and then, show spontaneous regression. Wilson's disease leads to liver cirrhosis without adequate therapy. Hepatitis often reoccurs, and most of these patients eventually develop cirrhosis¹⁵. In a study of 439 patients in Korea, 75% of the adult Wilson's disease patients with hepatitis were diagnosed with liver cirrhosis because of delayed diagnosis.

Dietary restriction of copper is insufficient as sole therapy. It is advisable to reduce consumption of foods high in copper content, like shellfish, nuts, chocolate, mushrooms and organ meats.

Aim of treatment in Wilson's disease is to achieve normal copper levels in the body in the shortest possible time and to maintain this. Of the drugs

used to treat Wilson's disease, penicillamine and trientine mainly act by increasing cupriuresis, while oral zinc mainly acts by inhibiting copper absorption from the intestine¹⁶. The commonly recommended regime is initial treatment with copper chelators like penicillamine or trientine to normalise copper levels in the body, followed by maintenance treatment with lower dose of copper chelators or zinc.

Transition from the initial high dose chelator therapy to maintenance therapy is made once patient is clinically well, has normal liver function tests, normal non-ceruloplasmin bound copper level and 24 hour urine copper of 200-500 µgm per day on treatment. Treatment needs to be continued lifelong. Measuring 24 hour urine copper excretion while on treatment is useful to monitor compliance. Antioxidants such as vitamin E may be useful adjuncts to treatment¹⁷.

Liver transplantation is treatment of choice in fulminant Wilson's disease and may be considered in patients with decompensated cirrhosis, non-responsive to medical therapy. Following liver transplantation hepatic insufficiency is corrected and neurological manifestations improve in upto 80% cases¹⁸.

In this particular case, it was not possible for us to make an early diagnosis, because by the time patient presented to us, she already had developed CLD (e.g, splenomegaly, oesophageal varix, jaundice, high level of liver enzymes and prothrombin time). Although her main presenting complaints were fever with abdominal pain, her enzyme levels were elevated and we diagnosed Wilson's disease by using the results of additional tests. We started treating her with penicillamine but unfortunately she couldn't be able to tolerate this copper chelator and developed severe hypersensitivity reaction in the form of fever, rash and joint pain. After a few days interval we restarted penicillamine but that time she experienced hypersensitivity reaction in more severe form. Then we had to stop penicillamine, but we were unable to manage trientine for the patient. So, we started treating her with oral zinc only. Probably in advanced Wilson's disease, inhibiting copper absorption from intestine by using zinc is not sufficient enough to halt the progression of the disease. Eventually the patient presented with neurological symptoms of the disease (e.g, tremor, convulsion) later on after 8-9 months of treatment. In many cases, if the findings of viral hepatitis tests are normal, we prescribe conservative treatment

for patients with increased liver enzyme levels. However, if the blood level of liver enzymes is consistently higher than the upper normal limit, further tests are necessary. Wilson's disease can occur at various ages; therefore, early diagnosis and treatment are very important. Wilson's disease

patients lead healthy lives if they undergo proper treatment in the early stages of the disease. Therefore, it is imperative that the first physician does not fail to diagnose Wilson's disease.

Conflict of interest: None

References:

1. Hoofnagle JH, Di Bisceglie AM. Serologic diagnosis of acute and chronic viral hepatitis. *Semin Liver Dis* 1991;11:73-83.
2. Liaw YF, Chu CM. Hepatitis B virus infection. *Lancet* 2009;373: 582-92.
3. Smith AD, Rockey DC. Viral hepatitis C. *Lancet* 2004;363:661.
4. Seo JK, Kim YS, Hahn CJ, Baik SK. A nationwide survey for prevalence and clinical characteristics of Wilson disease in Korea. *Korean J Hepatol* 2004;10(Suppl):S5-15.
5. Ala A, Walker AP, Ashkan K, Dooley JS, Schilsky ML (2007). "Wilson's disease". *Lancet* 369 (9559): 397-408.
6. Hung IH, Suzuki M, Yamaguchi Y, Yuan DS, Klausner RD, Gitlin JD. Biochemical characterization of the Wilson disease protein and functional expression in the yeast *Saccharomyces cerevisiae*. *J Biol Chem* 1997;272:21461-21466
7. La Fontaine S, Theophilos MB, Firth SD, Gould R, Parton RG, Mercer JF. Effect of the toxic milk mutation (tx) on the function and intracellular localization of Wnd, the murine homologue of the Wilson copper ATPase. *Hum Mol Genet* 2001;10:361-370
8. Forbes JR, Cox DW. Copper-dependent trafficking of Wilson disease mutant ATP7B proteins. *Hum Mol Genet* 2000;9:1927-1935
9. Mufti AR, Burstein E, Csomos RA, et al. XIAP is a copper binding protein deregulated in Wilson's disease and other copper toxicosis disorders. *Mol Cell* 2006;21:775-785
10. Ferenci P, Caca K, Loudianos G, Mieli-Vergani G, Tanner S, Sternlieb I, et al. Diagnosis and phenotypic classification of wilson disease. *Liver Int* 2003;23:139-42.
11. Gaffney D, Fell GS, O'Reilly DS. ACP best practice no 163. Wilson's disease: acute and presymptomatic laboratory diagnosis and monitoring. *J Clin Pathol* 2000;53:807-12.
12. Nuttall KL, Palaty J, Lockitch G. Reference limits for copper and iron in liver biopsies. *Ann Clin Lab Sci* 2003;33:443-50.
13. Harada M. Wilson disease. *Med Electron Microsc* 2002;35:61-6.
14. Pfeil SA, Lynn DJ. Wilson's disease: copper unfettered. *J Clin Gastroenterol* 1999;29:22-31.
15. Walshe JM. Wilson's disease presenting with features of hepatic dysfunction: a clinical analysis of eighty-seven patients. *Q J Med* 1989;70:253-63.
16. Ferenci P, Steindl-Munda P, Vogel W, Jessner W, Gschwantler M, Stauber R, et al. Diagnostic value of quantitative hepatic copper determination in patients with Wilson's Disease. *Clin Gastroenterol Hepatol* 2005; 3(8): 811-8.
17. Sinha S, Christopher R, Arunodaya GR, Prashanth LK, Gopinath G, Swamy HS, et al. Is low serum tocopherol in Wilson's disease a significant symptom? *J Neurol Sci* 2005; 228(2): 121-3.
18. Sevmis S, Karakayali H, Aliosmanoglu I, Yilmaz U, Ozcay F, Torgay A, et al. Liver transplantation for Wilson's disease. *Transplant Proc* 2008; 40(1): 228-30.