Journal of Comprehensive Pediatrics
www.ComprPed.com

A Neglected Case of Wilson Disease

Aliasghar Halimiasl [1], Parviz Ghadamli [1], Solmaz Ehteshami Afshar [1], Farideh Moussavi [1], Amir Hossein Hosseini [1,*]

[1] Department of Pediatrics, Shohada Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran

*Corresponding author: Amir Hossein Hosseini, Department of Pediatrics, Shohada Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran. Tel: +98-2122718000, Fax: +98-2122718027, E-mail: amir1981hosseini@gmail.com.

ABSTRACT

Introduction: Wilson's disease is an autosomal recessive disorder, characterized by a disturbance in copper metabolism that leads to copper overload in different tissues of the body. Because of various manifestations of Wilson's disease, physicians should have high index suspicion when patients manifest any type of liver disease, neurologic and psychiatric signs and symptoms.

Case Presentation: A 7.5-year-old boy was referred, presenting with generalized pruritus and stammer since the age of 4. Initial evaluation showed abnormal liver enzymes. Abdominal sonography revealed multiple echogenic lesions without acoustic shadow in the gallbladder, which was suggestive for gallstone. After about two years, he suffered from weakness, drowsiness, fever, nausea, epistaxis and abnormal liver function tests. With through clinical and laboratory work up, Wilson's disease was finally diagnosed and appropriate treatment was started. Acceptable response to treatment was achieved.

Discussion: Wilson's disease has a wide range of manifestation so physicians should have high index suspicion when patients present any type of liver disease, neurologic and psychiatric signs and symptoms. Any delay in diagnosis or management can result in catastrophic outcomes.

Keywords: Hepatolenticular Degeneration; Pruritus; Gallstone

1. Introduction

Wilson's disease (WD), as a progressive hepatolenticular degeneration, is a rare autosomal recessive disease, which affects approximately 1 in 30,000 live births (1, 2). Although this disease has been known for almost a century, an exact pathogenesis of the disorder remains unclear (2). A mutation in ATP7B gene that encodes an essential protein for transportation of the cooper is suggested to play a role in WD (1). It is characterized by a disturbance in copper metabolism that leads to copper overload in different tissues of the body (1, 3). The overall clinical picture varies from asymptomatic to acute liver failure (1). Systemic accumulation of copper causes typical phenotypes that include progressive liver damage, neurological deficits, psychiatric illnesses, presence of Kayser-Fleischer (KF) rings, renal tubular disorders, arthropathy, cardiomyopathy, and hypoparathyroidism (2). Other manifestations of WD like hemolysis may occur with the formation of gallstones from the bilirubi-

Article type: Case Report; **Received:** 13 Sep 2012; **Revised:** 03 Feb 2013; **Accepted:** 10 Feb 2013; **Epub:** 01 Jun 2013; **Ppub:** August 2013

Implication for health policy/practice/research/medical education:
We would like to inform that this case report will be useful for pediatric gastroenterologists and pediatricians.

Please cite this paper as:
Halimiasl A, Ghadamli P, Ehteshami Afshar S, Moussavi F, Hosseini AH. A Neglected Case of Wilson Disease. J Compr Ped. 2013; 4(3): 143-6. DOI: 10.17795/compreped-8164

nate calculations (1). Any unexplained acute or chronic liver disease in children and teenagers should raise the suspicion about Wilson's disease. The clinical suspicion is confirmed by studying indices of copper metabolism. Serum ceruloplasmin level is one of these indices that usually decreases in Wilson's disease (< 20 mg/dL). A 24-hour urinary excretion of copper should be investigated in all patients whom the diagnosis of WD is being considered. In symptomatic patients, this is typically > 100 micg/day, but finding > 40 micg/day is abnormal and needs further work up. The serum copper level may be elevated in early Wilson's disease. Demonstration of KF rings by an experienced ophthalmologist is a variable finding in liver diseases. They might be found in patients with chronic cholestatic diseases and in children with neonatal cholestasis. Therefore, it is not specific for Wilson's disease and its absence does not exclude the diagnosis (4, 5). Here we report on a neglected case of Wilson's disease initially presenting with pruritus and asymptomatic gallstones.

2. Case Presentation

A seven and half-year-old boy referred presenting with generalized pruritus for 4 years. The itching had become progressively worse during the last couple of weeks before his attendance and had not responded to the treatments (topical calamine lotion and hydroxyzine syrup). He had no abdominal pain or any other gastrointestinal complaints and history of fever and icterus was negative. Parents revealed that in his past medical history his physical development had been delayed and he had had stammer. He had neither had history of drug ingestion, nor known allergies. Clinical examination had not revealed any rash or other abnormalities, although slight excoriation of the skin had been present. No abnormality had been observed in head and neck. Abdomen had been firm without tenderness or distention. Liver span had been 9 cm in physical examination. The Morphy sign had been negative. In liver function test SGOT of 148 U/L, SGPT of 243 U /L and alkaline phosphatase of 1157 U/L had been detected. However, total bilirubin had been 0.8 mg/dL and direct bilirubin had been 0.2 mg/dL. Hepatophilic viral markers had all been negative. His cholesterol and triglyceride had been 291 and 231 respectively. HDL of 68 and LDL of 178 had been detected. Lipid profiles of the parents had been totally normal. Abdominal sonography had revealed multiple echogenic lesions without acoustic shadow in the gallbladder which had been suggestive for gallstone. No specific evaluation for stone analysis had been done at this period. Hepatic and splenic spans had been reported 12 and 10 cm respectively in sonologist report. Thyroid function test had been normal. In ophthalmologic examination, allergic changes in both eyes had been seen. A pediatric gastroenterologist had visited him in course of hospital stay and due to abnormality in liver enzymes and pruritus, had prescribed ursodeoxycholic acid. At that time, no specific investigation for Wilson's disease had been recommended. The patient had been discharged with the diagnosis of allergic disease with topical calamine lotion and hydroxyzine syrup. No lipid-lowering medication had been prescribed to him. Two years later the patient referred, presenting with weakness, drowsiness, fever, nausea and epistaxis. This time, SGOT of 810 U/L, SGPT of 405 U/L, total bilirubin of 4.7 mg/dL and direct bilirubin of 2.3 mg/dL were detected. Prothrombin time (PT) was 18 seconds (INR = 1.9). Albumin level was about 2.2 gr/dl. In the abdominal sonography, liver was 14 cm and several stones were seen in the neck of the gallbladder. Thickness of gallbladder was 4 mm with the hypo-echoic rim around the inflammation, which was suggestive of acute cholecystitis. Initial measurements were done for stabilizing his condition. Due to concomitant neurologic and hepatic manifestations, we conducted through para-clinical investigations, which revealed low ceruloplasmin level (11 mg/dL). Twenty-four-hour urine collection for copper excretion was 483 micg/dL that is highly in favour of Wilson's disease. Presence of Kayser-Fleischer (KF) rings was approved via Slit-lamp examination by an ophthalmologist. His parents did not allow the clinician to carry out liver biopsy. Then after the appropriate medical and supportive treatment (d-Penicillamine and zinc appropriate to body weight) was started, finally, parents discharged him by informed consent to continue his treatment in a pediatric liver transplant center.

3. Discussion

Wilson's disease is an autosomal recessive disorder with the prevalence of approximately 1/30,000 newborns worldwide (6). This disorder is caused by over 480 different kinds of mutations in the ATP7B gene which encodes a membrane-bound copper transporting ATPase (7). Disorder of hepatic copper metabolism causes the accumulation of copper in many organs and tissues, initially liver and then other tissues (7, 8) .The hallmarks of the WD include hepatic, neurological and psychiatric symptoms. Kayser-Fleischer rings which show copper accumulation in brain, are common in neurological WD (9) and are present in 95% of patients with neurological symptoms, 50–60% of patients without neurological symptoms and only 10% of asymptomatic siblings. (8) Although Kayser–Fleischer rings and neurological abnormalities may not be present in most patients, it is believed that all patients have some degrees of hepatic dysfunction, which varies from acute and chronic hepatitis to cirrhosis and fulminant hepatic failure (6, 8, 10). Acute Wilsonian hepatitis is identical to other acute liver diseases caused by toxins or viruses. (8) Episodes of hepatitis with spontaneous regression can happen and liver cirrhosis would occur without adequate therapy. (7) Severe hemolytic anemia, which happens when stored copper is released from the liver, can complicate acute liver disease, although it is not pathognomonic (8, 9). Increased intravascular hemo-

lysis puts the patients with WD on the edge of gallstone formation. However, no association between WD and cholecystitis has been found (11). Our patient manifested abnormal liver enzymes, gallstones, and pruritus. Gallstones rarely happen in children. As recommended by many experts, any abnormalities in hepatic enzymes in individuals between 3 to 55 years of age, without definite cause, should be thoroughly investigated for Wilson's disease (12). However, a high index of suspicion for WD was needed for more work ups. In this patient, clean history of WD in the family, as well as normal eye examination and lack of neurologic signs and symptoms drew attention from WD. However, as said earlier, it was logical and evidence-based to perform 24-hour urine collection for copper assessment and ceruloplasmin evaluation at the initial presentation.

Hepatic dysfunction usually precedes neurological abnormalities in WD (2, 8). Initial neurological symptoms, which usually develop in the mid teenage years or twenties, may be very slight, such as mild tremor and speech and writing problems. The feature of neurological WD is a progressive movement disorder known as 'juvenile Parkinsonism'. About one-third of patients demonstrate abnormalities (8). This case had a history of delay in physical development and stammer in his past, which could be the initiation of the disease. According to current guidelines, a wide spectrum of different neuropsychiatric manifestations in Wilson's disease has been reported (12). Of neurologic complaints migraine headaches, insomnia, drooling, dysarthria, dystonia, changes in behavior, deterioration in schoolwork, have been reported in literatures. Depression, anxiety, and even frank psychosis are examples of psychiatric disorders in this disease (12). Again it should be emphasized to exclude Wilson's disease in any patient with neuropsychiatric disease with or without hepatic involvement. The diagnosis of Wilson's disease is often delayed, due to various reasons, such as different manifestations of the disease, low index of suspicion in various patients and laboratory errors (5). Untreated Wilson's disease is mostly fatal due to the permanent damages to the brain and liver (9, 13). However, proper treatment in the early stages of the disease would provide healthy lives for the patients (7) Therefore, it is essential that the first physician diagnoses WD properly to avoid unwanted injuries to the liver (11). As in our case, diagnosis was delayed for 2 years. The liver has an essential role in lipid transportation and metabolism; thereby the liver diseases are associated with alterations in lipoprotein composition and metabolism. Only limited data are currently available about the detailed lipoprotein alterations in Wilson's disease and large cohorts for investigating the lipid metabolism in WD has not been done. In a recent study, the most apparent change was a lower serum cholesterol level in the patient with hepatic manifestations (4, 10). However, in our case the alteration in lipid profile was consisted of high cholesterol and triglyceride.

There is no single diagnostic test for WD and diagnosis is usually made by lab tests following clinical suspicions (1). Diagnosis is based on low serum copper and ceruloplasmin levels (< 20 mg/dL; immunoassay), high copper concentrations in the liver (> 250 mcg/g dry weight), high copper excretion in the 24-hour urine (> 100 mcg/day), and conducting a penicillamine challenge test (urinary copper excretion > 1,600 or 1,057 mcg/day) (6) if doubt remains, tests should be repeated at a later stage (2). In most of the cases, diagnosis can be made with the tests described above, however a group of patients cannot be diagnosed by them (6). Serum ceruloplasmin may be in the low to normal range in up to 45% of patients with hepatic Wilson's disease. Also in severely malnourished patients or in heterozygous carriers of the Wilson's disease gene or patient with autoimmune hepatitis, ceruloplasmin can be low. Mutation analysis for diagnosis is not valued, as there are many mutations, which are all rare, and most of the patients carry two different mutations (8). Finally, it should be mentioned again that because of various manifestations of WD, physicians should have high index suspicion when patients present any type of liver disease, neurologic and psychiatric signs and symptoms. WD has different faces and not even in two patients, is ever quite alike. Screening tests including slit lamp examination for KF ring by an experienced ophthalmologist, abdominal ultrasound for studying changes in liver, serum copper and ceruloplasmin, and 24-hour urinary copper should be done for all suspected patients (5, 12).

Acknowledgements

There are not any acknowledgments.

Authors' Contribution

All authors have the same contribution in writing this article.

Financial Disclosure

There is no financial disclosure.

Funding/Support

There is no funding or support.

References

1. Kleine RT, Mendes R, Pugliese R, Miura I, Danesi V, Porta G. Wilson's disease: an analysis of 28 Brazilian children. *Clinics (Sao Paulo)*. 2012;**67**(3):231-5.
2. Mak CM, Tam S, Fan ST, Liu CL, Lam CW. Wilson's disease: a patient undiagnosed for 18 years. *Hong Kong Med J*. 2006;**12**(2):154-8.
3. Thompson W, Hyslop PS, Barr R, Sass-Kortsak A. Wilson's disease: a common liver disorder? *Canadian Medical Association Journal*. 1977;**117**(1):45.
4. Seessle J, Gohdes A, Gotthardt DN, Pfeiffenberger J, Eckert N, Stremmel W, et al. Alterations of lipid metabolism in Wilson disease. *Lipids Health Dis*. 2011;**10**:83.

5. Schilsky ML. Wilson disease: new insights into pathogenesis, diagnosis, and future therapy. *Curr Gastroenterol Rep*. 2005;**7**:26-31.
6. Kodama H, Fujisawa C, Bhadhprasit W. Inherited copper transport disorders: biochemical mechanisms, diagnosis, and treatment. *Curr Drug Metab*. 2012;**13**(3):237-50.
7. Cho YH, Jeong DW, Lee SY, Park SK, Yoon KT, Kim YJ, et al. A Case of Wilson's Disease in Patient with Mildly Elevated Liver Enzymes. *Korean J Fam Med*. 2011;**32**(3):205-8.
8. Ferenci P. Review article: diagnosis and current therapy of Wilson's disease. *Aliment Pharmacol Ther*. 2004;**19**(2):157-65.
9. Eisenbach C, Sieg O, Stremmel W, Encke J, Merle U. Diagnostic criteria for acute liver failure due to Wilson disease. *World J Gastroenterol*. 2007;**13**(11):1711-4.
10. Bem RS, Muzzillo DA, Deguti MM, Barbosa ER, Werneck LC, Teive HA. Wilson's disease in southern Brazil: a 40-year follow-up study. *Clinics (Sao Paulo)*. 2011;**66**(3):411-6.
11. Chang SK, Chan CL, Yu RQ , Wai CT. Mimicry of acute cholecystitis from Wilson's disease. *Singapore Med J*. 2009;**50**(3):e102-4.
12. Roberts EA, Schilsky ML. Diagnosis and treatment of Wilson disease: an update. *Hepatology*. 2008;**47**(6):2089-111.
13. Asadi Pooya AA, Saeedi Eslami N, Haghighat M. Wilson disease in southern Iran. *Turk J Gastroenterol*. 2005;**16**(2):71-74.