

## Wilson's disease: Early Diagnostic Value of Serum Ceruloplasmin Level to Prevent Chronic Psychosis - Case Report

Iqra Anis<sup>1</sup>, Maha Masood<sup>2</sup>, Shaista Ahmed<sup>3</sup>, Farasat Waqar<sup>4</sup>, Tahir Hussain<sup>5</sup>

### Abstract

Wilson disease is a rare autosomal recessive hereditary disorder of copper metabolism. It is characterized by excessive deposition of copper in the liver, brain, and other tissues due to mutation in the Wilson disease protein (ATP7B) gene which leads to impaired copper metabolism. We report a case of eighteen-year-old male patient, who presented at the Out-Patient Department of Medicine Unit 1, Abbasi Shaheed Hospital. He presented with history of ataxia for 2 years along with abnormal spastic hand movements and difficulty in speech for the same time period. These symptoms remained static till 12 months but later progressed with multiple episodes of fall after which he was bedridden. On further investigation, eye examination on slit lamp showed Kayser-Fleischer ring, low total leukocyte count and ceruloplasmin level of 0.03 g/L. Ultrasound results showed hyperechoic hepatic parenchyma with no mass or abscess. This case is notable to emphasize the diagnostic value of ceruloplasmin for early diagnosis and to prevent chronic psychosis along with neurological symptoms. We aim to review the clinical presentation, diagnostic modalities and current treatment and also to highlight the treatment trials underway for Wilson's disease in adult patients.

**Keywords:** Wilson's, Kayser-Fleischer ring, ceruloplasmin, extrapyramidal symptoms

(ASH & KMDC 21(1):68;2016).

### Introduction

Wilson's disease (WD) or Hepatolenticular degeneration is an autosomal recessive disorder of copper metabolism due to absence or dysfunction of a copper-transporting, P type ATPase which is necessary for the transport of copper into bile. Patients diagnosed with Wilson's disease present with excessive copper which promotes free radical formation that results in oxidation of lipids and proteins. It leads to hepatocellular injury, involving the endoplasmic reticulum, mitochondria, peroxisome and nuclei within the liver as well as the brain and other tissues leading to secondary damage<sup>1</sup>. Wilson's disease is caused by mutations in the ATP7B gene on chromosome 13, which encodes

ATPase 7B involved in copper transport. Wilson's disease has been found worldwide, with an estimated prevalence of one case per 30,000 live births in most populations<sup>2</sup>. It is mainly a disease of children and adolescents which is characterized by neurologic, hepatobiliary, psychiatric and ophthalmologic (Kayser-Fleischer rings) manifestations. Early diagnosis and proper management can make Wilson's disease one of the easily treated inherited errors of metabolism<sup>3,4</sup>. The most rapid and cost effective biomarker for early diagnosis is the measurement of ceruloplasmin concentration level which is <20mg/dl for diagnosis of Wilson's disease<sup>5</sup>.

### Case Report

After the consent of the patient and permission from the institution. We report the case of an eighteen-year-old male patient who presented at the Out-Patient Department of Medicine Unit 1, Abbasi Shaheed Hospital on 19th October, 2015. The patient arrived complaining of difficulty in walking and

<sup>1-5</sup> Karachi Medical and Dental College

<sup>3-5</sup> Abbasi Shaheed Hospital

**Correspondence:** Dr. Iqra Anis  
Karachi Medical and Dental College and  
Email: vapiiqra@gmail.com  
Date of Submission: 12th January 2016  
Date of Acceptance: 20<sup>th</sup> February 2016

recurrent episodes of fall. According to patient's attendant, he was in the usual state of health 2 years ago. He developed difficulty in walking and speech along with recurrent episodes of abnormal spastic movement of hands, which disappeared on their own. The patient had no history of fall, uprolling of eyes or convulsions. There was no history of urinary or faecal incontinence, headache, vertigo or weakness associated with limbs. The symptoms remained static for 12 months and later progressed manifesting into recurrent episodes of fall after which the patient was bedridden. The patient had no history of blood transfusion. His father passed away 5 years ago due to Hepatitis and younger brother is mentally retarded.

Our patient had no relevant surgical and medical history. Before developing his symptoms he used to follow commands and reply without any difficulty. On general examination, the patient was lying on bed, well oriented and aware about time and place. Cardiovascular and respiratory functions were normal and central nervous system was intact. He was detected with Kayser-Fleischer ring around his eyes (Fig.1) with low value of serum ceruloplasmin levels of 0.03g/l in diagnostic test. Magnetic resonance imaging (MRI), t2 weighted images revealed ill defined symmetrical high intensity signal in fronto-parietal region bilaterally, there was abnormal signal intensity also noted in bilateral basal ganglia, thalamus region, brain stem and midbrain region and low intensity signal in T1W1 image. There was no post contrast enhancement seen. The dilated ventricle and prominent cortical sulci finding most likely indicated changes secondary to demyelination or secondary to encephalitis. Marked bilateral maxillary, ethmoidal and frontal sinusitis was noted. Total leukocyte count was 5000/cu mL. Liver size on ultrasound was 12.4cm with hyperechoic parenchymal echogenicity with no mass, cyst or abscess with normal portal vein dilation and no dilation of intrahepatic ducts and veins. Cerebrospinal fluid investigations were normal along with normal levels of LFTs, bilirubin, gamma GT, SGPT, alkaline phosphatase, urea and creatinine. The hepatic profile of the patient was normal.

Patient was prescribed tablet Memantine 10mg once daily dose, tablet Trihexyphenidyl 0.5mg twice daily, Zinc and Penicillamine. He was then discharged and was asked to come for a follow up, regularly after every 4 weeks, to the Out Patient Department. Our patient fulfilled all the clinical and MRI requirements with signs of abnormal cerebellar motor functions at early age. However, due to ignorance at the initial phase of the disease, the patients outcome included it chronic psychosis along with increased motor and extrapyramidal disabilities.

### **Discussion**

Wilson disease is a rare autosomal recessive hereditary disorder of copper metabolism. It is characterized by excessive deposition of copper in the liver, brain, and other tissues due to mutation in the Wilson disease protein (ATP7B) gene which leads to impaired copper metabolism. Absorbed dietary copper is mainly bound to albumin in portal circulation which is then extracted by the hepatocytes. Hepatocellular copper can be used for cellular metabolic needs, can be incorporated into ceruloplasmin or can be excreted in bile. The transport of hepatocellular copper to bile is dependent upon a vesicular pathway, which includes ATP7B (copper transporting P-type ATPase) function<sup>6</sup>. Dysfunction or absence of ATP7B results in decreased biliary copper excretion which then leads to accumulation of copper in Wilson's disease. Excessive accumulation of copper to toxic levels can cause hepatocellular injury along with generation of free radicals, lipid peroxidation of membranes and DNA, altered levels of cellular antioxidants and inhibition of protein synthesis. Toxic levels of copper can also cause secondary damage to organs, brain being most important site for extrahepatic accumulation of copper.

Ceruloplasmin (a serum glycoprotein), which is a major carrier of copper in blood, is synthesized predominantly in the liver. Due to decrease rate of synthesis of ceruloplasmin, Wilson's disease patients are usually diagnosed with low ceruloplasmin

levels. Dietary copper is incorporated into ceruloplasmin in the Golgi apparatus. During synthesis of ceruloplasmin the newly transported copper must also pass through the Golgi apparatus membrane, the process is ATP7B dependent which is dysfunctional in Wilson's disease patients<sup>7</sup>. Reduction of the incorporation of copper in ceruloplasmin leads to diminished synthesis of ceruloplasmin thus decreased plasma level of ceruloplasmin. Other conditions associated with ceruloplasmin deficiency are hereditary deficiency of ceruloplasmin, Menkes' disease and conditions, which lead to a temporary deficiency of ceruloplasmin such as nephritic syndrome, protein losing enteropathy and hepatic failure<sup>8</sup>.

Due to secondary damage of multiple organ system, Wilson's disease patient may present with variable symptoms. Hepatic disorders are usually manifested amongst teenagers with neuropsychiatric features becoming prominent later<sup>9</sup>. Patients presenting after 20 years, show neurological symptoms. Wilson disease is a disease of motor function; extrapyramidal symptoms are the most common symptoms. Patients manifesting psychiatric symptoms of Wilson's disease are usually misdiagnosed as having primary psychosis or schizophrenia<sup>10</sup>.

Kayser-Fleischer (KF) rings represent copper deposition on Descemet's membrane at the limbus of cornea, mostly bilateral but unilateral KF rings have also been defined. KF rings are not pathognomonic of WD, they've also been found in non-Wilson's hepatic condition<sup>11</sup>. Sun-flower cataracts represent deposits of copper in the lens. Both Kayser-Fleischer rings and sun-flower cataracts gradually disappear with effective medical treatment.

The key factor in early diagnosis of WD is suspicion of the disease. WD should be considered and excluded in any individual between the age of 3 and 40 years with unexplained neurological (especially with extrapyramidal or cerebellar motor disorder), psychiatric, hepatic, with or without family disorder of neurological or hepatic disease.

The suspected patients should be recommended following examination and tests for early diagnosis (1) slit lamp examination by ophthalmologist for the detection of Kayser-Fleischer rings. Patients presenting with neurological symptoms are mostly detected with KF rings with 5% not showing any signs of it<sup>12</sup>. (2) 24 hour urinary copper test ; Urinary copper is basically derived from the circulating plasma free copper. The level taken as diagnostic of WD is greater than 100 µg/24 hours in symptomatic patients<sup>13</sup>. (3) Serum ceruloplasmin concentration; The most significant and early diagnostic test for Wilson's disease is serum ceruloplasmin concentration which is considered as diagnostic if ceruloplasmin levels are less than 20mg/dl and is associated with Kayser-Fleischer rings<sup>14</sup>. (4) Magnetic resonance imaging (MRI) is an indicator of brain involvement in WD. Basal ganglia are the mostly involved brain area, with the brain stem and thalamus also affected. Increased signal intensity on T2-weighted images is the characteristic abnormality<sup>15</sup>. Our patient fulfilled all the clinical and MRI requirements with signs of abnormal cerebellar motor functions at early age. Due to ignorance at initial phase it resulted in chronic psychosis along with increased motor and extrapyramidal disabilities.

Treatment of Wilson's disease is classified into four primary approaches: Reducing copper content in diet of the patient, to decrease intestinal absorption of copper (by zinc, and tetrathiomolybdate), therapy to increase copper chelation and eradication (by penicillamine, trientine, and BAL), and liver transplantation. Our patient was prescribed zinc along with penicillamine, as a chelating agent along with drugs to reduce extrapyramidal symptoms.

The prognosis of delayed diagnosis and untreated Wilson's disease is progressive and fatal. Patients presenting with acute neurological symptoms and fulminant cases are frequently fatal. Final prognosis also depends on the response of the patient to 6 months of continuous penicillamine therapy. Our patient has up till now shown no posi-

tive response to penicillamine therapy, hence his condition is progressively deteriorating.



**Fig 1.** Kayser-Fleischer (KF) rings, copper deposition on Descemet's membrane at the limbus of cornea in an 18 year old patients with Wilsons Disease.

The American Association for the Study of Liver Diseases (AASLD) has published practice guidelines for diagnosis of Wilson's disease<sup>14</sup>. Some important recommendations are: (1) WD should be considered in any individual between the ages of 3 and 45 years with liver abnormalities of unexplainable symptoms. (2) Kayser-Fleischer ring should be detected with slit-lamp examination by an experienced ophthalmologist. (3) Low serum ceruloplasmin level (<5 mg/dL) is strong evidence for the diagnosis of WD. (4) 24-hour urinary copper is typically greater than 100 µg in symptomatic patients. (5) MRI, should be considered before the treatment in patients with neurologic symptoms of WD. (6) First-degree relatives of patient newly diagnosed with WD must be screened for WD. (7) Initial treatment for symptomatic patients should include a chelating agent (penicillamine or trientine). (8) Patients with fulminant hepatic failure or severe liver disease, unresponsive to chelation treatment should be recommended liver transplantation.

## Conclusion

Early diagnosis by detection of low ceruloplasmin level along with abnormal extrapyramidal motor functions and Kayser-Fleischer rings can lead to initiation of early treatment therapy, preventing chronic psychosis along with extrapyramidal symptoms. Negligence on part of patient to ignore initial symptoms and then to report with exaggerated symptoms is a common practice. This inattention resulted in delayed diagnosis leading to delayed administration of required treatment which leaves management as the only strategy of choice.

## Conflict of Interest

Authors have no conflict of interests and no grant/ funding from any organization.

## References

1. Litwin T, Czlonkowska A. [Wilson disease-factors affecting clinical presentation]. *NeurolNeurochir Pol* 2013;47:161-9.
2. Huster D. Wilson disease. *Best Pract Res ClinGastroenterol* 2010;24:531-9.
3. Ala A, Borjigin J, Rochwarger A, Schilsky M. Wilson disease in septuagenarian siblings: raising the bar for diagnosis. *Hepatology* 2005;41:668-70.
4. Beyersdorff A, Findeisen A. Morbus Wilson: case report of a two-year-old child as first manifestation. *Scand J Gastroenterol* 2006;41:496-7.
5. Kim JA, Kim HJ, Cho JM, Oh SH, Lee BH, Kim GH. Diagnostic Value of Ceruloplasmin in the Diagnosis of Pediatric Wilson's Disease. *Pediatr Gastroenterol Hepatol Nutr* 2015;18:187-92.
6. Hung IH, Suzuki M, Yamaguchi Y, Yuan DS, Klausner RD. Biochemical characterization of the Wilson's disease protein and functional expression in the yeast *Saccharomyces cerevisiae*. *J Biol Chem* 1997;272:21461-6.
7. Terada K, Kawarda Y, Muira N, Yasui O, Koyama K, Suqiyama T. Copper incorporation into ceruloplasmin in rat livers. *Biochem Biophys Acta* 1995;1270:58-62.
8. Weiner WJ, Lang AE. Movement disorders: In: Mt Kisco, eds. *A Comprehensive Survey*. New York: Futura Publishing Co. 1989; p. 257-91.

9. Bellary SV, Van Thiel DH. Wilson's disease: a diagnosis made in two individuals greater than 40 years of age. *J Okla Stat Med Assoc* 1993;86:441-4.
10. Akil M, Brewer GJ. Psychiatric and behavioral abnormalities in Wilson's disease. *Adv Neurol* 1995;65:171-8.
11. Tauber J, Steinert RF. Psuedo-Kayser-Fleisher ring of the cornea associated with non-Wilsonian liver disease. A case report and literature review. *Cornea* 1993;12:74-7.
12. Demirkiran M, Jankovic J, Lewis RA, Cox DW. Neurologic presentation of Wilson disease without Kayser-Fleischer rings. *Neurology* 1996;46:1040-3.
13. Gross JB Jr, Ludwig J, Wiesner RH, McCall JT, LaRusso NF. Abnormalities in tests of copper metabolism in primary sclerosing cholangitis. *Gastroenterology* 1985;89:272-8.
14. Roberts EA, Schilsky ML. A practice guidelines on wilson's disease. *Hepatology* 2003;37:1475-92. Available from: <http://onlinelibrary.wiley.com/doi/10.1053/jhep.2003.50252/pdf>. Accessed on Dec, 2015.
15. Ronald F. Wilson's Disease. In: Ray LW, William CK, eds. *Movement disorders, neurologic principles and practice*. New York: McGraw-Hill; 1996. p. 623-37.