



Case Report

Wilson Disease Presenting with Amenorrhea and Normal Urinary Copper Levels

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Abstract

Wilson's disease (WD) or hepatolenticular degeneration is an inherited autosomal recessive disease characterized by a defect in the biliary copper excretion, leading to copper accumulation in many organs. The absence of family history and relative lack of previous hepatic involvement may lead to the delay in diagnosis. Atypical presentation of Amenorrhea has been reported in untreated women with Wilson's disease (WD). Clinical phenotypes include hepatic, haemolytic, neurologic and psychiatric diseases. We present an adolescent patient with Secondary Amenorrhea, hemolytic anemia and psychiatric manifestations as the initial presentation.

Keywords: Secondary amenorrhea, psychiatric manifestations, haemolytic anemia, kayser fleischer ring, Wilson disease.

Introduction

In 1912, Samuel Alexander Kinnier Wilson, an American-born neurologist working in Great Britain, first described progressive lenticular degeneration.^[1] In 1948, Cummings showed the presence of excess copper in the tissues of affected individuals, and soon thereafter Scheinberg and Gitlin showed a deficiency of ceruloplasmin in the serum of patients with Wilson disease.^[2] The worldwide prevalence is about 1 in 30,000, which may vary by population.^[3] Wilson's disease is caused by mutations in the ATP7B gene. ATP7B encodes a hepatic copper-transporting protein, which is important for copper excretion into bile.

ATP7B gene present on the long arm of chromosome 13 (13q14-q21) has 21 exons and encodes a 1465 amino acid-long transmembrane ATPase (ATP7B).^[4] The dysfunction of the ATP7B that is expressed in hepatocytes causes copper deposits in the liver and subsequently Wilson's disease. The most common ATP7B mutation seen in European patients is the histidine to glutamate substitution at position 1069 (H1069Q).^[4] Although, the accumulation of copper begins at birth, symptoms of this disorder appears later, generally between second and fourth decade of life.^[5] Growth and puberty may be significantly affected in patients with Wilson's disease,

secondary to the presence of a long standing chronic illness.^[5] There are few case reports which might suggest that infertility, anovulation, amenorrhea, and short stature do occur in patients with Wilson's disease.^[5]

Case Report

24 year old female presented with a 5 month history of Amenorrhea despite having regular menses since menarche, pain in abdomen and fever (intermittent and low grade) since 2 months. Since the patient refused the gynecologic examination, only an abdominal ultrasound scan was performed which revealed normal findings. No further examination was performed. After 2 months, the patient was admitted to the hospital with pruritus of 2 weeks duration and jaundice for a week. There was no history of consanguinity in the family. Physical examination result revealed anemia. Dry skin with excoriation marks were remarkable. Hesitation cut marks were present on left hand. On Per-abdominal examination, abdomen was non-tender with no hepatomegaly nor splenomegaly. Breast and pubic hair development was concomitant with Tanner stage 4. Ophthalmologic examination with slit-lamp microscopy was performed and revealed Kayser-Fleischer rings in both eyes with normal visual acuity and normal findings in fundoscopy. The dimensions of the uterus were normal and no major follicle in the ovaries was observed. No endometrial echogenicity was recorded. Laboratory findings included - Hemoglobin: 5.7 g/dL, Hematocrit: 17.1%, WBC: 9000/mm³ and the platelet function test were normal. Peripheral smear suggestive of microcytic, hypochromic with moderate anisopoikilocytosis, Schistocytes, tear drop and target cells seen, Reticulocyte percentage: 1.8% (N: 0.5-1.5%), Lactate dehydrogenase: 800 U/L (N: 185-640U/L), Serum iron: 24.9 g/dL (N: 60-180g/dL), Iron Index: 5.58, Erythrocyte sedimentation rate: 55 mm/h and Coombs test was negative Serum total bilirubin: 0.6mg/dl, direct bilirubin: 0.3 mg/dL, total proteins: 6.5g/dL, Albumin: 3.3 g/dL, SGOT

SGPT and Alkaline phosphatase were normal. Prothrombin time and International normalised ratio were 12.1/1.31. Serology for human immunodeficiency virus, hepatitis B and hepatitis C viruses were negative. Total serum copper value was normal, Serum ceruloplasmin level was below the normal values 9mg/dl (N: 20–55 mg/dL) using an immunoturbidimetric method. 24hour urinary copper level was found within normal limits 24 g/dL (N <100 g/dL) and the urine examination showed dibasic aminoaciduria. Serum urea and creatinine values were normal. Using the scoring system proposed by the 8th International Meeting of Wilson Disease and Menkes Disease, our patient achieved a score of 5 (compatible neuropsychiatric features = 1; K-F rings = 2 and Ceruloplasmin level of 9mg/dL =2) and a diagnosis of Wilson's disease was made. Treatment was initiated with Zinc acetate 150 mg twice daily, later on tablet Penicillamine 500 mg twice daily, tablet Amitriptyline 10mg/day along with Iron supplementations and Vitamin B6 (pyridoxine)10 mg per day were added. Also, the avoidance of copper containing food (liver, shellfish, nuts and chocolates) and utensils was advocated. No clinical or biochemical manifestations of toxicity were observed. Medications were continued and she is maintaining well with regular follow- up and compliance with medications.

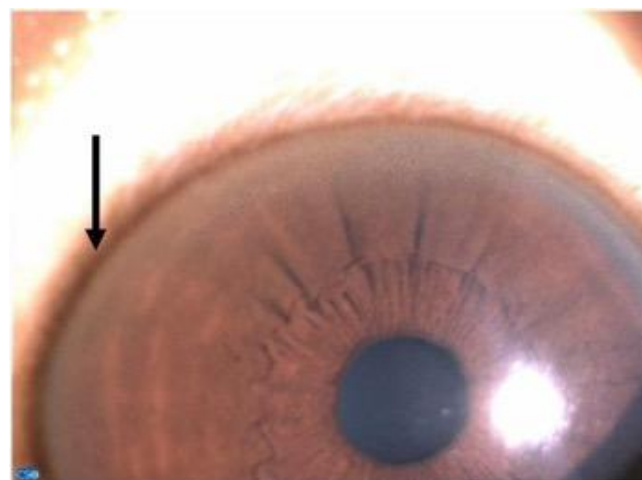


Figure 1: A slit-lamp examination showing Kayser-Fleischer ring (black arrow).

Discussion

Wilson's disease (WD) is an inherited autosomal recessive disorder of copper metabolism with a worldwide prevalence of 1 in 30,000.^[3] The two most fundamental disturbances of copper metabolism are a reduction in the rate of incorporation of copper into ceruloplasmin and a reduction in the biliary excretion of copper.^[1] The accumulation of copper begins at birth but the symptoms and signs do not appear until the end of the first decade of life. Later in life, the level of non ceruloplasmin copper in the plasma increases, leading to an increased copper excretion from the kidneys and deposition in various extra hepatic tissues like cornea (Kayser-Fleisher ring), brain (lenticular degeneration), kidneys (renal tubular acidosis and stones), bones and joints (osteoporosis and arthropathy).^[6] The long delay may be due to the illiteracy and ignorance of the patients along with absence of positive family history and the history of jaundice.^[7]

Firstly, Wilson's disease usually manifests as a chronic disease in its hepatic and/ or neurological form(s). Acute presentation of the disease is infrequent.^[7] Secondly, in chronic Wilson's disease, serum ceruloplasmin is raised as in our case, since ceruloplasmin is an acute phase protein.^[8] Thirdly, Kayser-Fleischer (KF) ring, accompanies chronic Wilson's disease as a diagnostic criteria it results from excessive deposition of copper in the cornea of Wilson's disease.^[8] Fourthly, acute Wilson's disease may be accompanied by 'Coomb's test negative' haemolytic anaemia, due to excessive lysis of red blood cells following sudden rise in copper in blood.^[9] And finally, it is expected that parents of Wilson's disease will be consanguineously married and one or more siblings will also be affected.^[10] Wilson's disease presenting with Amenorrhea probably originates from the hypothalamic and/or pituitary and/or ovarian levels.

The presence of low Ceruloplasmin levels, Kayser-Fleischer ring, hemolytic anemia with Amenorrhea strongly supports the diagnosis of

Wilson's disease in our patient.^[6] Kaushansky et al has demonstrated a disturbed ovarian function in a series of patients with Wilson's disease, as liver damage may also prevent the normal breakdown and metabolism of testosterone in the presence of a normal production rate with low estradiol, high total testosterone (T) levels along with a normal free T and elevated androstenedione by preventing normal function of the ovulatory mechanism by arresting follicular maturation and producing atretic follicles.^[10] An interference of ovarian follicular aromatase activity, possibly due to copper intoxication could also explain these findings as the cause of the ovulatory disturbances of Wilson's disease.^[10] Several other factors like excessive sex hormone binding globulin production, elevated prolactin levels, and direct suppression of Leydig cell function also contribute to gonadal dysfunction in these patients.^[10]

Psychiatric manifestations may precede neurological signs in the early stages of Wilson's disease.^[11] About 20% of them precede hepatic and neurological dysfunction. Suicidal behavior occurs in 4-16% of patients with Wilson's disease. Incongruous behavior, irritability, depression, and cognitive impairment were the most common psychiatric symptoms among patients with Wilson's disease.^[12] The lifetime prevalence of persistent personality change ranges between 46-71%, typically manifesting as irritability or aggression.^[12]

We used the scoring system proposed by the 8th International Meeting of Wilson Disease and Menkes Disease to make a definite diagnosis in our patient. A score of 4 or more makes the diagnosis of Wilson's disease.^[13] This scoring system has been validated with high sensitivity and specificity as well as high positive and negative predictive values. Dimercaprol a chelator was the earliest treatment for Wilson's disease (WD).^[14] The disease is treated with lifelong use of chelating agents such as D-penicillamine or trientine hydrochloride, drugs that help to remove copper from tissues. Potassium disulfide, ascorbic

acid, and vitamins B6 are of unproven value.^[15] Use of Zinc acetate for maintenance therapy as it inhibits the absorption of copper in the intestine.^[15] Dietary restrictions include ensuring that not more than 1 mg of copper is ingested a day.^[16] It is advised to avoid copper supplements and foods high in copper content.^[16] In addition, steps need to be taken to reduce copper consumption in drinking water.^[17] These include using only distilled water for drinking and cooking and installing copper removal systems in drinking water lines.^[18] Ceruloplasmin oxidase activity and serum free-copper concentration should be monitored in patients who are on long-term de-coppering therapy to prevent iatrogenic copper deficiency.^[19] Liver transplantation is life-saving for those with advanced disease.^[20]

Conclusion

Minor manifestations such as secondary Amenorrhea as a presenting feature of Wilson's disease is interesting and extremely unusual. Wilson's disease is encountered in the differential diagnosis of Amenorrhea, Hemolytic anaemia and Psychiatric disorder. Thus, we support the recommendation that adolescents with amenorrhea without any obvious cause, should be evaluated for Wilson's disease. Because treatment like D-Penicillamine is capable of reversing these changes and restoring a normal menstrual cycle. Early diagnosis is important because untreated patients of Wilson's disease die of the hepatic, neurologic, renal or hematologic complications.

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