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A Case Report of Secondary Adrenal Insufficiency in Wilson Disease

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ABSTRACT

Wilson disease is an autosomal recessive disorder characterized by abnormal copper homeostasis resulting in the accumulation of copper in various organs in the body. Wilson is a multisystem disease with predominant liver damage and neuropsychiatric manifestations. The endocrine abnormalities encountered in association with Wilson disease are rare. We present a case of a 33-year-old male, a known case of Wilson disease who presented with extreme prostration and anorexia. He had refractory hypotension for which a comprehensive laboratory test and hormonal panel was done, which suggested secondary adrenal insufficiency. Magnetic resonance imaging of the Sella with contrast was done which showed no abnormality in the pituitary. The absence of structural pathology in the neuroimaging of the pituitary in the presence of hypopituitarism could be attributed to the copper mediated oxidative neuronal injury in the hypophysis. It is plausible that copper chelation and hormone replacement might improve pituitary function in Wilson disease. This paper aims to highlight the endocrine manifestations associated with Wilson disease.

Keywords: Wilson disease; Adrenal insufficiency; Hypopituitarism; KF ring; Metabolic bone disease; Central hypothyroidism; Fanconi syndrome

INTRODUCTION

Wilson disease is one the well understood inborn error of copper metabolism, characterized by ATP7B gene dysfunction which results in failure of incorporation of copper into ceruloplasmin, thereby leading to copper deposition across various organs in the body.[1,2,3] Wilson disease encompasses protean extrahepatic

manifestations. The endocrine abnormalities encountered in association with Wilson disease include hypopituitarism manifesting as central hypothyroidism,[1,2] secondary adrenal insufficiency,[1,2] short stature,[3] anovulation, infertility and amenorrhea.[3,6,7] Metabolic bone disease as part of hepatic and renal osteodystrophy can take shape in the form of osteopenia, osteomalacia, rickets and osteoporosis.[3,10] The plausible underlying mechanism of the metabolic bone disease include the renal loss of calcium and phosphorus, renal tubular acidosis as a part of Fanconi syndrome and impaired vitamin D metabolism at the liver and kidney.[3,5,10] It is also possible that copper and iron excess might cause oxidative damage to the pancreatic islets thereby precipitating endocrine pancreatic insufficiency in the form of diabetes.[3,5]

CASE REPORT

A 33-year-old male, a known case of Wilson disease under liver transplant workup, presented to our hospital with complaints of extreme prostration, easy fatiguability, giddiness and anorexia of three months duration.

Past history revealed that he had two episodes of psychosis and he had undergone endoscopic ligation of esophageal varices.

Family history revealed that the elder male sibling expired at the age of 14 due to liver failure of unknown etiology.

On clinical examination, the patient was conscious, oriented, afebrile and was not dyspneic. Pallor, icterus and bilateral pitting pedal edema was present. There was no evidence of cyanosis and clubbing. Heart rate was 76/minute, Respiratory rate-15/minute, Capillary refill time was delayed and blood pressure was 80/30mmHg. Capillary blood glucose was noted to be at 123mg/dl. Abdominal examination revealed splenomegaly and ascites. Evaluation of the other systems were normal. Slit lamp examination showed a Kayser-Fleischer ring, a yellowish green band of copper deposition in the Descemet membrane of the cornea.

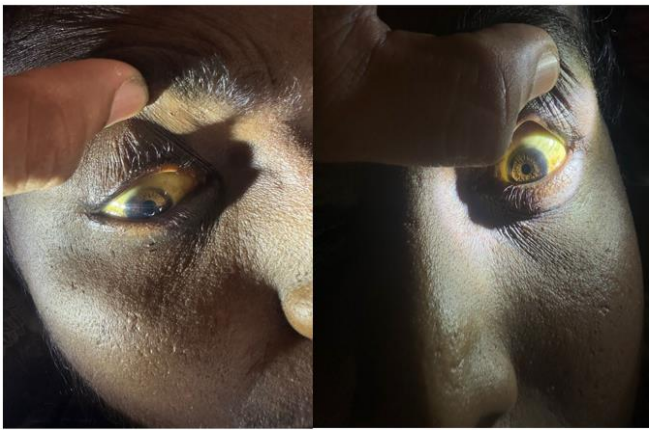

Image1: Kayser-Fleischer ring

A comprehensive laboratory test to look into the cause for hypotension revealed that Hemoglobin was 7.8 g/dl, MCV- 99, Total count-2900 cells/mm^3, platelet count 42,000 cells/mm^3, Total bilirubin-14.6 mg/dl, Direct bilirubin-7.2 mg/dl, Aspartate transaminase- 22 IU/L, Alanine transaminase- 40 IU/L, Alkaline phosphatase-122 IU/L, Total protein-4.6g/dl, Serum albumin 1.6g/dl , urea- 27 mg/dl ,Serum creatinine- 0.8 mg/dl, Serum sodium-128 mEq/L, Serum potassium-4.8 mEq/L. PT- 24.3 seconds, INR- 1.75. Viral panel for hepatitis and HIV was negative. Direct and indirect comb test was negative. Serum LDH of 399 U/L and reticulocytosis in

our patient suggested Coombs negative hemolytic anemia. Triple phase CT abdomen showed macronodular cirrhosis with splenomegaly and multiple dilated peri gastric, umbilical and splenorenal collaterals. The CT findings were in favor of Wilson disease. Alpha fetoprotein level was within normal limits. Immunological panel was negative for Serum antinuclear antibody, antimitochondrial antibody, anti-smooth muscle antibody, soluble liver pancreas antigen and LKM1 antibody. ESR was 5mm/hour; CRP-negative (3mg/dl), blood and urine culture did not reveal growth of any microbes. Cardiac evaluation with cardiac biomarkers was negative and an echocardiography revealed a normal ejection fraction with no regional wall motion abnormalities and a stable cardiac status. The hypotension did not significantly respond to fluid challenge and inotropes. At this point, cardiogenic shock and septic shock were less likely to be the cause for refractory hypotension. Further, to rule out the endocrine etiology of hypotension, 8am Serum cortisol was done and the levels were too low (2.58 mcg/dl against a reference interval of 6.7 to 22.6 mcg/dl). To ascertain the cause of adrenal insufficiency, 8am ACTH was done and the levels were too low. (4.87 pg/ml against a normal reference range of 7.2 to 63.3 pg/ml). Hence a diagnosis of secondary adrenal insufficiency was made.

To corroborate the diagnosis of secondary adrenal insufficiency, we measured the levels of FSH, LH, TSH, testosterone and prolactin, the lab values of which were within normal limits. The thyroid function test was normal. Magnetic resonance imaging of the Sella with contrast did not show any abnormality in the pituitary. Serum iron level was high (191.5 mcg/dl against a normal reference interval of 60-150mcg/dl).

The cause of refractory hypotension in our patient with Wilson disease is likely to be attributed to secondary adrenal insufficiency in view of low cortisol and ACTH levels. The patient was promptly put on steroid replacement therapy following which the patient improved dramatically with the resolution of the prostration and hypotension. The patient is symptomatically better now and on follow up.

ENDOCRINE LAB PARAMETERS [TABLE1]

Parameter	value	Reference values
Baseline cortisol, µg/dL	2.58	6.7–22.6
ACTH, pg/mL	4.87	7.2–63.3
TSH, mU/L	2.20	0.27–4.2
Free T3, pg/mL	2.33	2.21–4.43
Free T4, ng/dL	0.92	0.8–1.77
Insulin-like growth	178	106–256

factor 1, ng/mL		
LH, IU/L	1.82	1.2-7.8
FSH, IU/L	2.94	1.4– 15.4
Prolactin, ng/mL	15.20	4.79– 23.3
Estradiol, pg/mL	52	45 – 95
Testosterone, ng/dl	301	249-836
HbA1C	4.9%	Less than 5.6%
Parathyroid hormone, pg/ml	20.23	15.0-65.0
Vitamin D (25 OH), ng/dl	18.40	30-100
Corrected calcium, mg/dl	10.02	8.5 to 10.2
Serum phosphorus, mg/dl	2.9	2.8 to 4.5

DISCUSSION

Wilson disease is a disorder affecting copper homeostasis due to a genetic defect in the membrane protein called ATP7B, which helps incorporation of copper into ceruloplasmin. ATP7B dysfunction impairs biliary elimination of copper, thereby promoting brain copper and iron accumulation. Ceruloplasmin belongs to a class of enzymes called oxidoreductases, which help in metabolizing both copper and iron in the brain. Ceruloplasmin is otherwise called as serum ferroxidase, which promotes oxidation of ferrous ion to ferric form which is incorporated into transferrin, thereby playing a pivotal role in brain iron metabolism. Low ceruloplasmin levels in Wilson disease impairs its ferroxidase activity causing iron overload in the brain. Both iron and copper excess

might cause free radical mediated oxidative stress and neuronal injury in the pituitary causing hypopituitarism. [1,2]

Wilson disease manifested in our patient as decompensated liver disease, Coombs negative hemolytic anemia, Kayser-Fleischer ring, psychoses and secondary adrenal insufficiency. This discussion highlights various endocrine manifestations of Wilson disease.

Central hypothyroidism might occur in parallel due to thyrotropes' dysfunction and it is noted that thyroid function test normalises with thyroxine supplementation and copper chelation therapy as discussed by Hae Won Lee et al[1]and Nina Dauth et al[2], in their case reports.

Short stature could be attributed to decreased ability of the liver to synthesise Insulin like growth factor and because of Renal tubular acidosis in the background of Fanconi syndrome which retards growth in paediatric population and adolescents with Wilson disease.[3]

Metabolic bone disease in Wilson might occur due to hepatic osteodystrophy because of decreased synthesis of hepatic insulin like growth factor-1 (IGF-1), which acts an osteoblast stimulator and due to impaired 25 hydroxylation of vitamin D at liver. It can be also be due to tubular dysfunction as a part of Fanconi syndrome leading to urinary loss of calcium and phosphorus.[3] Hypogonadism is another key factor affecting bone health as high levels of oestrogen and low levels of testosterone in patients with chronic liver disease increases the life span of osteoclast and decreases the life span of osteoblast, resulting in bone resorption, which in the background of absence of bone formation, causes a net reduction in bone mineral density.[10] Metabolic bone disease can manifest as osteopenia, osteomalacia, rickets and osteoporosis. It is important to know that Wilson disease stands as a differential diagnosis in children and adolescents with refractory rickets, short stature and proximal renal tubular acidosis who might have associated Fanconi syndrome as a part of the disease spectrum. [3,10]

Nina Dauth et al,[2] in their case report suggest hypoglycaemia and transient hyperglycaemia as the one of the initial presentations of secondary adrenal insufficiency in their case. Robert Krysiak et al,[7] on their work to assess the cause of recurrent hypoglycaemia in a patient with documented Whipple triad in the presence of normal pancreatic imaging study, normal levels of serum insulin and C peptide, found features of portal hypertension on doppler imaging and went ahead to perform a diagnostic liver biopsy which revealed copper deposits in the liver. Hypoglycaemia could be attributed to impaired carbohydrate metabolism in the cirrhotic liver and due to low cortisol levels. Hyperglycaemia could be due to copper deposits in the beta cells of islets of pancreas, as like iron deposits in hemochromatosis, leading to beta cell dysfunction and causing copper mediated endocrine pancreatic insufficiency. Hyperglycaemia can also occur because of augmented hepatic insulin resistance presenting as prediabetes. However, the patients achieved a euglycemic status with de-coppering therapy.[2,7]

Arieh Kaushansky et al,[6] proposed in their case report that levels of oestradiol were low in the presence of normal FSH and high testosterone levels. Ovarian follicular aromatase is the rate limiting enzyme in the biosynthesis of oestrogen from testosterone. It converts testosterone into oestradiol. Subnormal ovarian follicular aromatase activity due to copper intoxication of this enzyme lead to high circulating testosterone levels and low oestradiol levels in the follicular microenvironment, thereby causing arrest of ovarian follicular maturation. It is also possible that menstrual irregularities stem from low LH and FSH levels because of gonadotroph dysfunction in the pituitary.[5,6]

Robert Krysiak et al,[7] on evaluation for the cause of galactorrhoea and menstrual abnormalities in a patient with Wilson disease found that there was an hypointense lesion in the pituitary in the presence of normal pituitary hormonal assay. On initiation of Zinc acetate therapy, there was resolution of galactorrhoea and the menstruation returned. A check MRI of the Sella didn't reveal any abnormalities after de-coppering therapy.[7]

Magnetic resonance imaging of the brain in general shows T2 hyperintensities in putamen and globus pallidus which constitute the lentiform nuclei, due to copper deposition. Involvement of the tegmentum of the midbrain produces "face of the giant panda sign" and involvement of the dorsal pons produces "face of a miniature panda sign". Thus, it is possible to encounter "double panda sign" due to the simultaneous involvement of midbrain and pons which is characteristic of Wilson disease but its incidence is rare.[8,9]. It is important to understand that neuroimaging of the pituitary might be normal even in the presence of clinical features suggestive of hypopituitarism.[1,2]

In general, patient with secondary adrenal insufficiency tend to perform well with the improvement in pituitary function when prompt hormone replacement and copper chelation therapy is initiated.

CONCLUSION

It is prudent to understand the various endocrine manifestations in Wilson disease like central hypothyroidism, secondary adrenal insufficiency, short stature, menstrual irregularities, infertility, endocrine pancreatic insufficiency and metabolic bone disease. Hypopituitarism manifesting as secondary adrenal insufficiency in Wilson disease could occur secondary to impairment in brain iron and copper metabolism. It is possible that neuroimaging of the Sella might be normal, even in the presence of clinical features and hormonal assays suggestive of hypopituitarism. It is important to recognize the endocrine abnormalities associated with Wilson disease as it has a grave impact on the quality of life and because it is potentially treatable with the prompt initiation of copper chelation and hormone replacement therapy which might help tide over the secondary adrenal insufficiency.

CONFLICT OF INTEREST

The Authors declare that there is no conflict of interest.

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CONSENT

Written Informed consent for publication of the case and images has been obtained from the patient.

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