Case Report

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Wilson's Disease: A Rare Case Report in Western Maharashtra

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Abstract

Copper is an essential trace element, utilized as a cofactor by numerous enzymes regulating vital cellular functions. The importance of copper for normal cell metabolism is best illustrated by the existence of genetic disorders, in which the normal distribution of copper is disrupted. Wilson's disease (WD) is a genetic disease of copper toxicity. It is also known as hepatolenticular degeneration and is an autosomal recessive inherited disorder of abnormal copper metabolism resulting from the absence or dysfunction of a copper-transporting. The disease is mainly seen in children, adolescents and young adults and is characterized by hepatobiliary, neurologic, psychiatric, and ophthalmologic Kayser-Fleischer (KF) rings manifestations. WD can be a lethal disease if left untreated. We present here a case report of WD in 12 year old child.

Key words: Copper metabolism, Kayser-Fleischer ring, Wilson's disease

INTRODUCTION

Copper is an essential trace element, utilized as a cofactor by numerous enzymes such as cytochrome-*c* oxidase, tyrosinase, superoxide dismutase, dopamine-hydroxylase, and ceruloplasmin regulating vital cellular functions, including oxidative phosphorylation, neurotransmitter biosynthesis, free radical detoxification, iron uptake, maturation of connective tissue, and many others.[1,2]

Wilson's disease is a rare but major metabolic disorder of copper toxicity. It is an autosomal recessive condition characterized by inability of the liver to transport, store and excrete normally absorbed dietary copper and causes an excessive deposition of the copper in many organs such as the liver, central nervous system (CNS) with an involvement of the lenticular nucleus, cornea, kidney, joints, and cardiac muscle where the physiological functions of the affected organs are impaired.[3,4] Deposited copper in the liver produces toxic effects via modulating several molecular pathways. The underlying molecular mechanisms for Wilson's disease (WD) in homozygous state is a mutation in P-type adenosine triphosphatase (ATP7B) gene on chromosome 13, encoding the copper transporting P-type ATPase. The gene plays a key role in removing excess copper from human body by transporting copper from the liver to the bile.[5]

The degeneration was first described in 1912 by Kinnear Wilson as progressive lenticular degeneration.[6] WD has worldwide frequency of 1 in 40,000 and a carrier frequency of 1 in 9.[7] 40% patients first show hepatic dysfunction, 40% neurological symptoms, and 20% with psychiatric or behavioral disorder. There are some diseases of copper transport such as Menkes disease, Occipital horn syndrome, Indian childhood cirrhosis, Neurodegenerative diseases which should be differentiated from WD.

If diagnosed early and properly managed, WD is one of the more easily treated inborn errors of metabolism. We report here a rare case of WD in Western Maharashtra, presented with hepatic involvement and CNS involvement without the neurological manifestations.

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Case Presentation

A 12-year-old boy, 2nd child of non-consanguineous parents presented with moderate fever and pain in left side of abdomen since 7 days. There was history of similar episodes over 3-4 months since 3 years. No h/o chills, rigor, vomiting, loose motions, rash, joint pains, chest pain, jaundice, hematemesis, melena, hemoptysis. No h/o blood transfusions in the past. The patient had taken the treatment for same complaints (diagnosed as hepatitis) details were not available. H/o full term normal delivery with up to date immunization. There is no significant family history. His developmental milestones were normal.

On examination, his vital signs were stable. The patient was conscious and well oriented. Per abdominal examination was soft, nontender, revealed spleen palpable 2 cm below left costal margin, hard in consistency with a smooth and regular surface. The liver was not palpable. Neurological examination and Psychological assessment were normal. Complete blood count revealed hemoglobin concentration of 10.1 gm%. The white blood cell count was 2,340 cells/cumm (neutrophil 61%, lymphocytes 39%, eosinophils 0%) and platelets count was 90,000/mm.[3] In peripheral smear, RBCs showed anisopoikilocytes, microcytes. Serum urea (18 mg/dl), Serum creatinine (1.1 mg/dl), Serum bilirubin (0.4 mg/dl) was normal. S.G.P.T. (86 Iu/lit), S.G.O.T. (58 Iu/lit), and alkaline phosphatase (165 Iu/lit) were slightly raised. Serum total protein (6.2 g/dl) and serum albumin (4.0 g/dl) was normal. S.Globulin (2.2 g/dl) was slightly low. Serum sodium and serum potassium were normal. A urine examination was normal. Bleeding time, clotting time, and prothrombin time were normal. Serum iron, serum total iron-binding capacity, and serum amylase were normal. Serum ceruloplasmin level was <0.08 g/L (normal range 0.25-0.46 g/L), i.e., low. 24 h urinary copper was 660 ug/24 h (normal range 20-50 ug/24 h), i.e., very high. Serum copper was 30.3 ug/dl (normal range 90-190 ug/dl), i.e., low.

On MRI brain, T2-weighted images revealed high signal hyperintensities in the bilateral ventrolateral thalami and putamen region, midbrain, pons and cerebellum on the left side, same region is hypointense on T1-weighted image not showing diffusion restriction and no post contrast enhancement. Ophthalmic examination by slit lamp showed a rusty brown Kayser-Fleischer (KF) ring in descemet's membrane of cornea near limbus in both eyes, on lens no deposits seen as shown in Figure 1 and dilated fundus examination was normal. Patients were diagnosed as WD and started on a penicillamine therapy (Figure 1).

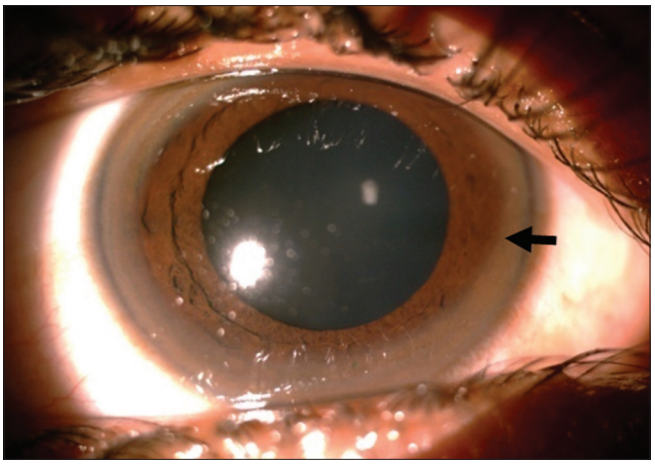

Figure 1: Slit lamp examination showing Kayser-Fleischer (KF) rings (Black arrow)

DISCUSSION

Absorbed dietary copper is bound to albumin in the portal circulation goes to liver. It is then used for cellular metabolic needs, incorporated into ceruloplasmin; only a tiny fraction enters urine and major excreted through the bile. The excretion of copper in bile depends on ATP7B function. Dysfunction of ATP7B results in a decrease in biliary copper excretion, which is responsible for the hepatic accumulation of copper in WD.[5]

Copper stored in the liver, when accumulates beyond the cellular capacity for its safe storage, hepatocellular injury may result. Toxic effects of excess copper include the generation of free radicals via Fenton's reaction, lipid peroxidation of membranes and DNA, inhibition of protein synthesis and altered level of cellular antioxidants. Then, unbound copper splits out of liver and goes to other organs and tissues where it also begins to accumulate. It accumulates mainly in brain, cornea, kidney, joints, and cardiac muscle.

Ceruloplasmin is synthesized predominantly in the liver and is major copper containing protein. The majority of patients with Wilson's disease have low ceruloplasmin levels due to decreased rate of synthesis of the ceruloplasmin molecules in the liver and a reduction of the incorporation of copper into ceruloplasmin.[8]

Wilson's disease is the most frequently recognized as a trait of liver disease, neurological symptoms, and K-F rings. Nevertheless, because multiple organ system can be affected, patients may present in a number of different ways. A clinical presentation of WD is between 5 and 50 years. Early childhood WD usually presents with chronic liver disease or hemolytic anemia but neurological manifestations become increasingly important later

on. Patients presenting after age 20 years usually have neurological symptoms.[9] The two types may overlap.

Various hepatic forms such as acute or chronic hepatitis, cirrhosis of liver are the most common hepatic presentations, but acute fulminant hepatic failure can occur in early childhood and signs and symptoms are enlargement of the liver or spleen, progressive jaundice, ascites, encephalopathy, hypoalbuminemia, and moderately elevated plasma levels of liver enzymes.[3]

Neurological signs include tremor, rigidity, drooling saliva, speech changes, incoordination, difficulty with fine motor tasks, dysarthria, dystonia, lack of motor coordination, spasticity, and deterioration in school work.[4] Psychiatric manifestations include compulsive behavior, aggression, depression, emotional lability, anxiety, frank psychosis, impulsive behavior, phobias, sudden, and changeable mood swings, anger explosiveness and memory loss. It may be confused with the adolescent crisis, primary psycosis, or schizophrenia.

KF rings represent a rusty brown ring of copper deposition in descemet's membrane of cornea near limbus in both eyes, sometimes unilateral.[10]

Other signs and symptoms of Wilson's disease include anemia, low platelet or white blood cell count, high levels of amino acids, protein, and carbohydrates in urine, nephrolithiasis, skeletal abnormalities such as premature osteoporosis and arthritis, cardiomyopathy, pancreatitis, and hyperparathyroidism.[11] The most important single 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, hepatic, or psychiatric dysfunction. The diagnosis is based on the clinical evaluation along with biochemical and neuroimaging confirmation.

Various diagnostic criteria as advocated by Sternlieb[12] are shown in Table 1. In the presence of chronic liver disease or a typical neurological manifestation, a combination of low ceruloplasmin and increased basal 24 h urinary copper is highly suggestive of WD.[13] The liver biopsy is not essential for diagnosis.[13]

Table 1: Diagnostic criteria for Wilson's disease as advocated by Sternlieb

Low serum ceruloplasmin levels (<20 mg%)
Kayser – Fleischer rings in eyes
High liver copper levels (>250 ug/g dry wt)
High 24 h urinary copper levels (>100 ug/d or >1.6 umol/d)
Radioisotope copper studies using 64 Cu, 67 Cu or 65 Cu, which assesses ability to incorporate copper into ceruloplasmin

Neuroimaging studies and gross pathology can show diffuse or focal atrophy. Typical sites of cerebral involvement are deep gray matter and central white matter. Gray matter nuclei involvement is the more common, usually bilateral symmetric in the putamen, caudate, thalamus, globus pallidus, pons, and mesencephalon. Cerebral atrophy with ventricular dilatation and cerebellar atrophy is also frequently observed in WD.[14]

The treatment of WD can be stratified into four primary approaches: Dietary therapy (by reducing copper content in diet) foods with very high concentrations of copper (nuts, chocolate and organ meats) should be avoided; therapy to reduce intestinal copper absorption (by zinc, and tetrathiomolybdate); therapy to increase copper chelation and elimination (by penicillamine, trientene) and liver transplantation. The disease is treated with a lifelong use of chelating agents. Liver transplantation is a life-saving and curative treatment for WD and is indicated for all WD patients with fulminant liver disease unresponsive to medical therapy.

Untreated WD is progressive and fatal. The prognosis for patients who comply with pharmacotherapy is excellent. Prognosis is poor in the acute neurological form and dystonia.

In our case, the presenting feature was hepatic involvement detected clinically and by liver function studies with a marginal elevation of hepatic enzymes. The patient had K-F ring on slit lamp examination. KF rings are almost invariably present in patients with a neurological presentation, but even in these patients they may not be found in 5%.[15] However, in this case, patient had K-F ring, CNS involvement on MRI, but neurological symptoms were not seen. Hence, this is an unusual presentation. Patient's serum ceruloplasmin level and serum copper level was low and 24 h urinary copper level was a very high. From all clinical, biochemical and neuroimaging studies patient was diagnosed as WD even before initiation of CNS symptoms. The treatment was started and parents were advised for screening for WD of all family members.

CONCLUSION

Recently the American Association for the Study of Liver Diseases has published practice guidelines.[8] We should follow these recommendations. Some important recommendations are: (1) WD should be considered in any individual between the ages of 3 and 45 years with liver abnormalities of uncertain cause. (2) The absence of KF rings does not exclude the diagnosis of WD. (3) An extremely low serum ceruloplasmin level (<5 mg/dl) and 24-h urinary copper greater than 100 μg is strong evidence

for the diagnosis of WD. (4) Neurologic evaluation and radiologic imaging of the brain, by MRI, should be done in all patient. (5) First-degree relatives of newly diagnosed patient of WD must be screened thoroughly for WD. (6) Initial treatment is chelating agent. (7) Treatment is lifelong and should not be discontinued unless a liver transplantation has been performed.

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