

CASE REPORT

WILSON'S DISEASE: A RARE AUTOSOMAL RECESSIVE DISORDER OF COPPER METABOLISM

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ABSTRACT

Wilson's disease is an autosomal recessive disorder caused by mutations in the ATP7B gene, a membrane-bound copper-transporting ATPase. Clinical manifestations are caused by copper toxicity and primarily involve the liver, the brain and the eye. Because effective treatment is available, it is important to make this diagnosis early.^{1,6} We report a patient who developed features of neurological and ocular manifestations: incoordination and tremor and blurring of vision with presence of Kayser-Fleischer ring circling the cornea but no signs of hepatic dysfunction.

Key Words: ATP7B gene, Ceruloplasmin, Kayser-Fleischer ring, Wilson's Disease.

INTRODUCTION

The frequency of Wilson's disease in most populations is about 1 in 40,000 and the frequency of carriers of ATP7B mutations is about 1%. Based on these gene frequencies, the risk of Wilson's disease in the children of an affected patient is about 1 in 200.¹ Wilson's classic description of "progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of liver appeared in 1912. Similar neurological disorder had been described previously by Gowers (1906) under the title of "Tetanoid Chorea" and by Westphal (1883) and Strumpell (1898) as Pseudosclerosis. None of these authors however recognized the association with cirrhosis. The clinical studies of Hall (1921) and histopathologic studies of Spielmeyer (1920), who reexamined section from liver and brain of Westphal and Strumpell cases clearly established that pseudosclerosis described by these authors was the same disease as that had been described by Wilson.²

The gene defect in Wilson's disease affect copper transport system that produces dual defect: decreased incorporation of copper into ceruloplasmin in liver and decreased excretion of copper in bile. Accumulation of copper in liver increases the formation of hydroxyl free radicals causing damage to hepatocytes. In a few years, unbound copper is released from liver into the circulation where it damages brain, cornea, kidneys and other tissues.³ Defective copper incorporation into apoceruloplasmin leads to excess catabolism and low blood levels of ceruloplasmin.¹ The onset of neurologic symptoms is usually in the second and less often in the third decade, rarely beyond that time. In all instances, the initial event is deposition of copper in the liver, leading to acute or chronic hepatopathy and eventually to multilobular cirrhosis and splenomegaly. The first neurologic manifestations are almost invariably

extrapyramidal and with proclivity to affect the oropharyngeal musculature. The typical presentations are tremor of limb or of head and generalized slowness of movement (i.e. Parkinsonian syndrome). Usually elements of cerebellar ataxia and intentional tremor are present in some stage of disease.² Sunflower cataracts and Kayser-Fleischer (golden brown) ring around cornea may be seen.^{1,2,4}

CASE PRESENTATION

26 year gentleman from Ramechhap was admitted to CMS-TH, Bharatpur on 25th Dec, 2013 with chief complaint of abnormal body movements in form of tremors for 3 years, Blurring of vision for 3 years and Headache on/off for 3 years. Abnormal movement first started in right hand mainly involving small joints, then it progressively involved head within six months duration. After another six months, tremor also occurred in left hand and finally both the lower limbs. Tremor was so severe that patient had difficulty in performing daily activities. Patient also complained of blurring of vision which is gradual in onset and progressive. His color vision was intact. There was history of migraine type headache and slurring of speech. Patient's past history revealed that he was treated for the same problem 2 year back and symptoms subsided after taking medication (not documented). After he discontinued the medication he is having the same problem. Patient doesn't give any history of jaundice, urinary or fecal incontinence, seizure, fever and head trauma. He doesn't consume alcohol neither he smoke.

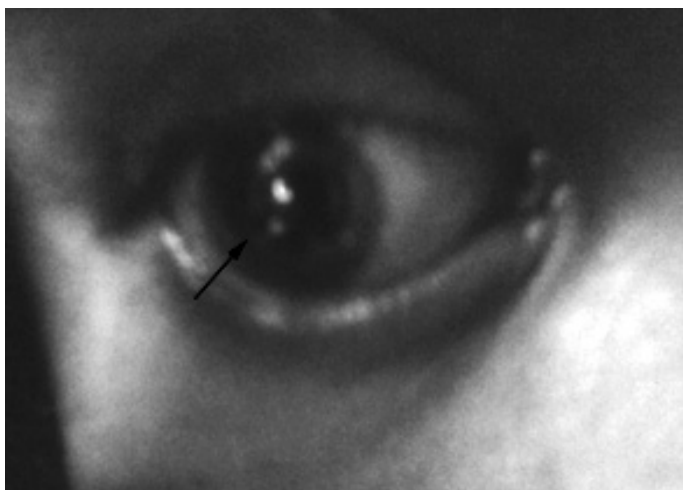


Fig: KAYSER-FLEISCHER RING



Fig: Intention tremor in both hands

The Pedigree Chart is as follows:

GENERAL EXAMINATION: Pallor, Icterus, Clubbing, Cyanosis, Lymphadenopathy, Edema and Dehydration-not present, B.P:-110/80 mmHg, P.R. - 80/min, R.R- 16/min, Temp:-98.60F.

CNS EXAMINATION: GCS -15/15

HMF (MMSE- 14/30): Impaired

Cranial nerves – intact; Meningeal sign - negative; Motor examination-tremors in all limbs, Power in upper and lower limbs -5/5, Tone– normal, Deep & superficial reflex- normal. Sensory examination – Intact; Cerebellar sign – Finger nose test impaired, Heel shin test impaired, Dysidiadochokinesia- positive, Intentional tremor- positive; Gait –swinging to right side.

EYE EXAMINATION: Snellen's chart- visual acuity Rt(6/24) Lt(6/24) , Kayser-Fleischer ring in limbus of cornea

LAB REPORTS:

Serum Ceruloplasmin: 0.09gm/L (N:0.2-0.6 gm/L) ;

Urinary 24 hrs copper concentration: 443.1ug/24hr (N:20-50 ug/24hr)

LIVER FUNCTION TESTS: Bilirubin(0.9mg/dl), ALT/SGPT-17U/L, AST/SGOT-26.4U/L, ALP-142.7 U/L, Protein-6.5gm/dl ,Albumin -3.4gm/dl, Globulin-3.1gm/dl, A:G ratio-1.1 ,Gamma GT- 18.7 U/L,PT-14S sec ,INR-1.1

COMPLETE BLOOD COUNT: Hb- 12.4gm/dl, TLC -7140 /mm³, DLC-(N-64 L-29 E-3 M-4 B-0) , Platelets-182000/mm³,ESR-13mm/hr.

Treatment:

Tab Zinc 50 mg po TDS

Cap. D-penicillamine 250 mg BD

The patient was kept under observation for 22 days in neurology ward and on regular medication with chelating agent i.e. D –Penicillamine. There was significant recovery from the symptoms so he was sent home with the medications as per prescription and called for regular follow up for observation.

DISCUSSION

Wilson's disease is a rare autosomal recessive disorder of copper metabolism that is characterized by excessive deposition of copper in the liver, brain and other tissues like descemet layer of cornea. ² In this patient, the presence of Kayser-Fleischer ring and serum Ceruloplasmin level less than 0.2gm/L (i.e.

0.09 gm/L) and urinary 24 hr copper excretion greater than 100ug (i.e. 443.1 ug) suggest strongly a diagnosis of Wilson's disease. Heterozygotes never have values >1.6umol (>100 ug) per 24 h.The "gold standard" for diagnosis remains liver biopsy with quantitative copper assays. However , this patient does not show any signs of hepatic degeneration ,neither hepatitis nor abnormal bilirubin level ,other signs such as neurologic manifestation: tremor all over the limbs , cerebellar signs - +ve support the diagnosis of Wilson's disease. Fine motor activities, incoordination, gait disturbances, drooling ,slurring of speech suggests deposition of copper extensively in basal ganglia, deep cerebellar nuclei ,white matter. Kayser-Fleischer ring are formed by the deposition of copper in the descemet membrane in the limbus of cornea. The colour may range from greenish gold to brown, as brown evidenced in this patient & is readily visible by the naked eye. This ring is observed in up to 90% of individuals with symptomatic Wilson's disease and are almost invariably present with neurological manifestations. Late manifestation (now rare because of early diagnosis and treatment) include dystonia, spasticity, grand mal seizures, rigidity and flexion contractures. These late complications are not seen in this patient. This explains the patient is in early stage of manifestations. Psychiatric features include emotional lability, impulsiveness, disinhibition, and self injurious behavior. The natural history of Wilson's disease may be considered in 4 stages, as follows: Stage I- The initial period of accumulation of copper within hepatic binding sites; Stage II- The acute distribution of copper within the liver and its release into the circulation; Stage III- The chronic accumulation of copper in the brain and other extra hepatic tissues,with progressively and eventually fatal disease; Stage IV- Restoration of copper balance by the long term chelation agents.The major complications in patients with untreated Wilson's disease are those associated with acute liver failure, chronic hepatic dysfunction with either portal hypertension or hepatocellular carcinoma, and sometimes relentless course to cirrhosis, bleeding from varices ,hepatorenal syndrome and as well as neuropsychiatric abnormalities. Patient should generally avoid copper containing foods such as liver ,chocolate, nuts ,mushrooms ,legumes and shellfish.The mainstay of therapy for Wilson's disease is pharmacological treatment with chelating agents. ⁵

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