

Generalized hyperpigmentation in Wilson's disease: An unusual association

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ABSTRACT

Wilson's disease, an autosomal recessive disorder of copper metabolism, most commonly presents either with hepatic or neurological features. But, it may sometimes have certain atypical presentations posing diagnostic difficulties. We report here a case of Wilson's disease presenting with generalized hyperpigmentation of skin who also developed neurological manifestations subsequently. We aim to highlight the importance of keeping Wilson's disease as one of the differentials in patients who present with hyperpigmentation and neurological symptoms compatible with copper deposits in the central nervous system and proceed for investigations accordingly.

Key words: Copper toxicity, hyperpigmentation, Wilson's disease

Introduction

Wilson's disease is a rare autosomal recessive disorder of copper metabolism. Hepatic and neurological symptoms are the main clinical features of the disease.^[1] But, it often has certain unusual presenting features which may pose a diagnostic dilemma for the clinicians.^[2]

Case Report

A 9-year-old male child presented with progressive darkening of skin over the whole body for last 3 years [Figure 1]. He also had regression of motor milestones and slurred speech for last 1 year. The neurological abnormality started with frequent falls and instability during walking. He had no history of jaundice, hepatomegaly, splenomegaly or ascites.

He had bladder incontinence but his bowel habit was normal. He had two younger female siblings who were

apparently asymptomatic. His parents were first-degree cousins.

On examination, the child was alert but irritable and apprehensive. There was diffuse and uniform hyperpigmentation all over the body [Figures 1 and 2]. His pulse rate, blood pressure, temperature and respiratory rate were normal. There was no cranial nerve abnormality. There was generalized hypertonia. All the deep tendon reflexes were exaggerated. Plantar was bilaterally flexor. There were no meningeal or cerebellar signs. There was no focal deficit. Examination of all other systems were within normal limits.

On investigations, hemoglobin level was: 10.5 g%, total leucocyte count was 9000/mm³, platelet count was 1.6 lakh/mm³ and reticulocyte count was 1.2. Serum Na⁺ was 140.1 meq/l and K⁺ level was 3.36 meq/l. Serum bilirubin, liver enzymes, albumin and globulin were within normal limits. Serum ceruloplasmin was reported as 3.01 mg/dl (normal 20-60 mg/dl). Twenty-four hour urinary copper level was 153 µg/24 hour without penicillamine challenge and 442.75 µg/24 hrs after challenge (normal 20-50 µg/dl). Slit lamp examination of eyes revealed Kayser-Fleischer (KF rings) bilaterally.

Ultrasonography of abdomen and chest X-ray were within normal limits. Magnetic resonance imaging of brain revealed bilaterally symmetric hyper intensities involving the thalami, adjacent putamen and mid

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brain. Mild cerebral atrophic changes were also present [Figure 3]. The examination of cerebrospinal fluid did not reveal any abnormality. Serum cortisol level at 8 a.m. was 7.6 µg/dl (normal range 3.7-19.4 µg/dl). Serum very long chain fatty acid (VLCFA) could not be done due to nonavailability of facilities. On the basis of reduced serum ceruloplasmin, raised 24-hour urinary copper (both unchallenged and challenged) and presence of KF rings the diagnosis of Wilson's disease was established.



Figure 1: Photograph of the boy showing generalized hyperpigmentation



Figure 2: Photograph of the boy during the follow-up visit showing hyperpigmentation and deteriorating neurological impairment

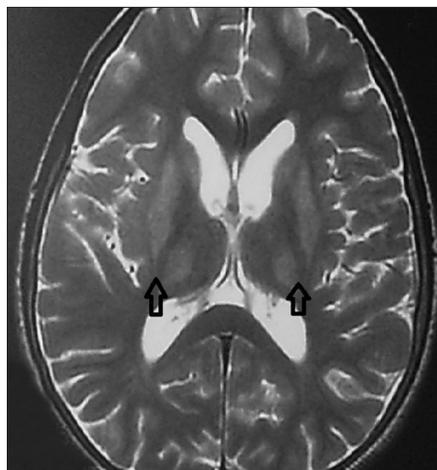


Figure 3: MRI image showing bilaterally symmetric hyperintensities involving the thalami and adjacent putamen

We did a family screening. He had two younger female siblings. Both were asymptomatic. One of them had hepatomegaly. Her liver function tests revealed raised liver enzymes but normal bilirubin level. Her serum ceruloplasmin was 11 mg/dl. The other sibling did not show any abnormality clinically or biochemically.

Discussion

Wilson's disease an inborn error of copper metabolism is inherited as an autosomal recessive condition. In this disease, the process of incorporating copper into ceruloplasmin and excreting excess copper into bile are impaired. The transport of copper by the copper-transporting P-type ATPase is defective secondary to one of several mutations in the *ATP7B* gene, which is localized in chromosome arm 13q. This results in the loss of the ability to export copper from the liver into the bile duct. As a consequence, copper accumulates in the liver, brain, kidneys and Descemet's membranes of the eye.^[1,3] Correct diagnosis is important because it is a treatable condition, but often presents with diagnostic dilemmas especially when it presents with atypical features.^[2]

The association of hyperpigmentation in Wilson's disease has rarely been reported in literature. Only a few case reports are available. Gurubacharya *et al.* reported a case of Wilson's disease in a 9-year-old child with generalized hyperpigmentation but with liver disease.^[4] Steiner *et al.* reported a case of a 16-year-old adolescent who presented with signs of hypersplenism due to cirrhosis and neurological disturbances but with hyperpigmentation of only lower legs, unlike our case who had generalized skin darkening.^[5] Out of many case series published on Wilson's Disease,^[6,7] we could find only two research articles in which the authors have reported the incidence of skin hyperpigmentation. In a case series from Brazil, the authors found skin hyperpigmentation in 4 out of 36 cases (11.1%).^[8] In the other study, from Taiwan, published in 1970, the authors reported skin hyperpigmentation in 12 out of 20 patients (60%). Histopathological analysis of skin samples revealed increased melanin deposits whereas copper and iron content was not different from that in controls.^[9] We could not measure the iron, copper or melanin content of the skin lesions due to lack of facilities.

Also we did not have facilities for mutational analysis. It has been speculated that the cause of these melanin

deposits is increased activity of the enzyme tyrosinase as body copper is high. Copper is essential for the activity of this enzyme.^[10]

The index case had gradually progressive generalized uniform skin hyperpigmentation. Remarkably, almost all the cases reported previously in literature had hyperpigmentations on lower limbs unlike our case. X-linked adrenoleucodystrophy was also one of the diagnostic possibilities because of hyperpigmentation and neurological abnormalities, but normal electrolyte level and cortisol level ruled out this diagnosis.

The wide spectrum of symptoms in patients with Wilson's disease have raised the question whether these features are determined by the type of the ATP7B mutation. As we could not do mutational analysis, we are not in a position to comment on the genotype–phenotype correlates of hyperpigmentation in Wilson's disease. Future long-term studies may throw light on this issue. The need to highlight the importance of hyperpigmentation as a pointer to the diagnosis of Wilson's disease prompted us to report this case.

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