

## Case Reports

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# Generalized Hyperpigmentation of Skin as an Atypical Presenting Feature in Wilson Disease

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### Abstract

**Background:** Wilson disease is an autosomal recessive disorder of copper metabolism, where excessive copper accumulation occurs in various tissues. Although hepatic and neurological symptoms predominates, it may present with some other unusual features which sometimes confuses clinicians and makes a diagnostic dilemma. We present here an 11 years old boy presented with gradual darkening of whole body over last 2 months and jaundice for 5 month. His clinical features and laboratory parameters were suggestive of Wilson disease. Being one of the common causes of chronic liver disease (CLD) in childhood, Wilson disease may present with some atypical features like darkening of complexion.

**Key words:** Chronic Liver Disease, Hyperpigmentation, Wilson disease.

### Introduction

Wilson disease (WD) is an inherited disorder of copper metabolism, occurring due to defect in gene ATP7B, causing reduced biliary excretion of copper. Thus copper is accumulated excessively in the hepatocytes and manifesting typically as hepatic disease in children, ranging from acute hepatitis, acute liver failure, chronic hepatitis, chronic liver disease and its consequences. Subsequently, when hepatic storage capacity for copper becomes saturated, circulatory 'free copper' level is increased and deposited in various organs, notably the brain, kidneys, and cornea. Thus causes various neurologic, psychiatric, renal, hematological, musculoskeletal and ophthalmological manifestations. Besides, copper is essential for synthesis of various enzymes, like mitochondrial cytochrome c oxidase, superoxide dismutase,

tyrosinase. Therefore, excess copper increases the activity of the enzyme tyrosinase, a rate-limiting enzyme for controlling the production of melanin, which causes hyperpigmentation of skin in many cases.<sup>1</sup>

### Case Report

An 11 year old boy, immunized as per EPI schedule, 2<sup>nd</sup> issue of non-consanguineous parents, presented with the complaints of gradual darkening of whole body over last 2 months (Figure 1 and 2) and jaundice for 5 month. There was no associated feature of coagulopathy or encephalopathy. He had no history of previous jaundice, blood transfusion or any surgical procedure. There was no history of liver disease or such type of illness in his family. They used to have their food in steel plate, and use aluminium utensils for cooking purpose. They have never used brass vessels.

On examination he was alert, mildly icteric. His vitals were within normal limit and anthropometrically he was well thriving. There were some stigmata of chronic liver disease, like thener –hypothener wasting and leuconychia. His complexion was dark. He had hepatosplenomegaly, but had no feature of ascites or any neuropsychiatric manifestation. Examination of all other systems were within normal limits.

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Slit lamp examination of eyes revealed Kayser-Fleischer rings (KF rings) and sunflower cataract bilaterally.

On investigations, his complete blood count was within normal limit (hemoglobin 11g/dl, total leucocyte count  $11,000/\text{mm}^3$ , platelet count was  $300,000/\text{mm}^3$ ). His liver function test revealed mildly elevated ALT (76 U/L), low serum albumin (29g/L) with mildly elevated INR (1.64) and normal serum bilirubin level (1.1 mg/dl). Serum ceruloplasmin level was low (04mg/dl; normal 20-60 mg/dl). Twenty-four hour urinary copper level was raised (basal:  $294 \mu\text{g}/24$  hour and after penicillamine challenge:  $554 \mu\text{g}/24$  hours). Liver biopsy, to estimate hepatic copper content, couldn't be done due to lack of facility. His early morning serum cortisol level was  $13 \frac{1}{4} \mu\text{g}/\text{dl}$  (normal:  $7-28 \frac{1}{4} \mu\text{g}/\text{dl}$ ) and serum electrolyte was within normal limit (Na 137 meq/L, K 4.9 meq/L, Cl-104 meq/L,  $\text{HCO}_3$  23 meq/L). Infection with hepatitis B & C and autoimmune hepatitis were excluded through relevant investigations.



**Fig.-1:** Complexion of the boy.

Ultrasonography of hepatobiliary system revealed coarse hepatic parenchyma. Diagnosis was done on the basis of Leipzig score.<sup>2</sup> The patient had a score of 6 (a score of  $\geq 4$  is diagnostic). His treatment was then started with Penicillamine, Zinc and other supportive medications, like Pyridoxin, antioxidants (vitamin C, E). He was then counselled adequately along with his parents, specially regarding maintaining

a copper restricted diet, regular intake of medications and for regular follow up visits. The parents consented eagerly regarding the publication of their son's condition for academic purpose.



**Fig.-2:** Leuconychia and darker complexion of the boy in comparison to his mother.

### Discussion

Wilson disease is an autosomal-recessive disorder of chronic copper toxicosis. It is caused by mutation in the ATP7B gene, which is located within 13q14-q21 on chromosome 13. It results in the impairment of biliary excretion of copper and subsequent accumulation of it in various tissues, initially in the liver and ultimately in brain, kidneys and Descemet's membranes of the eyes. As a result, there occurs various hepatic, neurological, psychiatric & ophthalmological manifestations.<sup>3,4</sup>

Various other presentations may be there in Wilson Disease, including- neuropsychiatric disorder, Coombs negative hemolytic anemia, gall stone formation, cardiac involvement, ovarian dysfunction, hypoparathyroidism, renal tubular lesion and subsequent renal calculi. Some osseomuscular defect with bony deformity, spontaneous fracture and arthropathy are also seen. KF rings are found in 50-60% cases without neurological symptoms.<sup>5</sup> Occasionally these patients develop some atypical features, which produces diagnostic dilemmas.<sup>3,4</sup>

Darkening of skin or hyperpigmentation is one of such atypical features in a patient with Wilson disease with which he/she may present. Steiner et al.<sup>6</sup> reported a case of a 16-year-old adolescent, presented with signs of hypersplenism due to cirrhosis, neurological disturbances and with hyperpigmentation in lower legs, unlike our case who had generalized skin darkening.<sup>6</sup>

Gurubacharya et al.<sup>7</sup> reported a case of Wilson's disease in a 9-year-old child with generalized hyperpigmentation with liver disease.

Among the case series published on Wilson's disease, the authors have reported the incidence of skin hyperpigmentation in only two research articles.<sup>8,9</sup> In a case series from Brazil, the authors found skin hyperpigmentation in 4 out of 36 cases (11.1%).<sup>10</sup>

In another study done in Taiwan, the authors had reported hyperpigmentation of skin 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.<sup>11</sup> In our case, there was gradually progressive generalized darkening of skin. X-linked adrenoleucodystrophy was also one of the diagnostic possibilities because of hyperpigmentation but normal electrolyte level and cortisol level ruled out this diagnosis.

We could not measure the copper or melanin content of the skin lesions due to lack of facilities. Moreover, we did not have facilities for mutational analysis. It has been speculated that, the cause of this darkening of skin is due to increased activity of the enzyme tyrosinase resulting in increased melanin synthesis. Copper is essential for the activity of this enzyme.<sup>1</sup> The index case had gradual progressive generalized uniform skin hyperpigmentation. Remarkably, many of the cases, reported previously in literature, had hyperpigmentation on lower limbs unlike our case.

Our aim was to highlight the importance of hyperpigmentation or darkening of skin as a diagnostic indicator of Wilson's disease.

### Conclusion

Copper is an essential catalyst in many physiological processes and thus Wilson disease has variable clinical manifestations. As hepatitis are often anicteric in children, along with other clinical features, hyperpigmentation or darkening of skin can be considered as an indicator of such a, life threatening but treatable, metabolic disease like Wilson disease.

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