Generalized Hyperpigmentation - An Unusual Feature in Neurologic Wilson Disease: Report of Two Cases
RUMANA ISLAM1, GOPEN KUMAR KUNDU2, SHAHEEN AKHTER3, ANJIR ANWAR4

Abstract
Wilson disease also known as hepatolenticular degeneration is an autosomal recessive disorder of copper metabolism, usually presents either with hepatic or neurological features. But sometimes along with common features, some atypical presentations may also co-exist. We report here two cases of Wilson disease, a 15 years old girl and 14 years old boy presented with some neurological manifestations along with gradual darkening of whole body.

Key words: Wilson disease, Neurologic manifestation, Generalized hyperpigmentation

Introduction
Wilson disease- which is also known as Hepatolenticular degeneration is an autosomal recessive disorder. It was first described by the English neurologist, S. A. K. Wilson in 1912. It is a disorder of copper metabolism caused by mutations of ATP7B gene, encoding a copper-transporting, P-type ATPase which leads to progressive copper accumulation in the liver and subsequent deposition in other organs including brain, so most of the patients present with hepatic and neuro-psychiatric features. It can also involve other organs such as corneas, kidneys, bones, and joints and may present with other features like Kayser-Fleischer rings, renal tubular acidosis, nephrolithiasis, premature osteoporosis, arthritis, cardiomyopathy, pancreatitis, hypoparathyroidism, and infertility or repeated miscarriages. Despite these, there may be some other atypical presentation, one of which is dermatological presentation. It is diagnosed on the basis of clinical manifestations, decreased serum ceruloplasmin level, increased 24 hr urinary copper excretion and presence of K F (Kayser-Fleischer) ring on both eye. Unlike other neurodegenerative disease, Wilson disease is one of the treatable condition that can be managed successfully with currently available anticopper treatment, if diagnosed early.

Case-1
A 15 years old girl of consanguineous parents, initially presented with neurologic abnormality including instability during walking and frequent fall. Subsequently she developed involuntary movement in the form of dystonia. She also developed progressive darkening of skin over the whole body. She had history of jaundice at 10 years of age.

She was alert but emotionally labile. There was diffuse hyperpigmentation all over the body [Figures 1]. She was vitally stable, speech was slurred, dystonia present in all four limbs. All the deep tendon reflexes were normal and plantar were bilaterally flexor. She had parkinsonian gait. No stigmata of chronic liver disease was present.

Her Hb% was 12.2 g/L, WBC-7000/mm³, Platelet count was 1.6 lakh/mm³, peripheral blood film showed normal picture and reticulocyte count was 1.2. Liver enzymes were within normal limits. Serum Na+ was 137 meq/L and K+ level was 3.5 meq/L. Serum ceruloplasmin was reported as 3.03 mg/dl (normal 20-60 mg/dl). Twenty-four hour urinary copper level was 2764 ìg/24 hrs after challenge (normal 1600 ìg/day). Slit lamp examination of eyes revealed K F (Kayser-Fleischer) ring bilaterally. Ultrasonography of abdomen revealed coarse hepatic echotexture, endoscopy of upper GIT was normal. Magnetic Resonance Imaging (MRI) of brain revealed bilaterally symmetric hyperintensities involving the thalami, adjacent putamen, globus pallidus, & head of the caudate nucleus.[Figures 2]. We treated the patient with low dose penicillamine, zinc sulphate along with antidystonic drugs and her condition was gradually improving.
Case-2
This was a 14 years old boy, his initial presentation was gradual darkening of skin all over the body, speech difficulty, progressive tremor of both hand with writing difficulty, as well as unstable gait. He was cooperative but looked depressed. There was diffuse hyperpigmentation all over the body [Figures 3]. He was vitally stable, speech was slow and slurred. Rigidity was present in all four limbs along with tremor in both upper limbs. All the deep tendon reflexes were normal. Plantar were bilaterally flexor. No stigmata of chronic liver disease was present.

Fig.-1: Generalized hyperpigmentation (Case-1)
Fig.-2: MRI of the brain showing bilateral basal ganglia & thalamic hyperintensities (Case-1)

Fig.-3: Generalized hyperpigmentation (Case-2)
Fig.-4: MRI of the brain showing bilateral Basal ganglia and thalamic hyperintensities (Case-2)
His HB% was: 13.1 gm/l, WBC count was 5000/mm³, Platelet - 1.2 lakh/mm³, peripheral blood film was normal. Liver enzymes were within normal limits. Serum ceruloplasmin was reported as 16mg/dl (normal 20-60 mg/dl). Twenty-four hour urinary copper level was 1225 ìg/24 hrs(normal-100 ìg/day). Slit lamp examination of eyes revealed K F (Kayser-Fleischer) rings bilaterally. Ultrasonography of abdomen revealed coarse hepatic echo-texture with spleenomegaly. Endoscopy of upper GIT revealed grade-II esophageal varices. MRI of brain revealed T2 and FLAIR hyperintensity in the basal ganglia (bilateral), thalamus, pons, mid brain and subcortical white matter of frontal lobe (Figures 4 & 5).

He was treated with low dose Penicillamine, Zinc sulfate and antidystonic drugs and beta blocker. His neurological status was improving. He had two younger brother, one of them was also diagnosed as Wilson disease on family screening and treated with zinc sulphate.

**Discussion**
Dermatological manifestation in Wilson disease is a rarely reported finding. A few case reports are available regarding this presentation. Out of many large series published on Wilson disease, we could find only two research article in which the authors have reported the incidence of dermatological signs in WD. One study, from Taiwan, published in 1970, the authors reported skin hyperpigmentation on anterior aspect of thigh in 12 out of 20 patients (60%). In a case series from Brazil, the authors found skin hyperpigmentation in 4 out of 36 cases (11.1%). In another study of 37 children with WD has shown that 70.3% had at least one dermatological finding. They also showed that 67.5%, 13.5% and 24.3% patient had at least one skin, mucosal and nail finding respectively and most common finding was xerosis of skin (45.7%). Many of the cases reported previously were associated with localized pigmentation specially involving the anterior aspect of thigh or associated with mainly hepatic manifestation. Both of our newly diagnosed patient of Wilson disease had generalized hyperpigmentation and neuropsychiatric manifestation.

Gurubacharya et al. reported a case of Wilson disease in a 9-year-old child with generalized hyperpigmen-
tation with liver disease. Madhumita et al. also reported another case, a 9 year old male child of Wilson disease with neurological manifestation preceded with generalized hyperpigmentation. Steiner et al. 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. Previously some cases were reported from Bangladesh where patients presented with features of chronic liver disease along with hyperpigmentation. The most striking finding in WD is the blue lunulae of the nails and it was found in 10% of patients. In addition, there may be gray-brown hyperpigmentation, which develops mostly on the lower extremities. A vague greenish discoloration of the skin on the face, neck and genitalia has also been described.

Both of our patients presented with gradual hyperpigmentation of the whole body & neuropsychiatric manifestation starting almost at the same time. Histologically, this was found to be caused by increased melanin deposition. Copper and iron content in skin biopsy specimens was not different from that in controls. Though we have not done skin biopsy for histopathology, due to lack of facility, It has been speculated that the cause of these melanin deposits was increased activity of the enzyme tyrosinase as body copper is high. Copper is essential for the activity of this enzyme.

X-linked adrenoleucodystrophy was also one of the diagnostic possibilities because of hyperpigmentation and neurological abnormalities but normal electrolyte level and presence of KF ring ruled out this diagnosis.

Conclusion
Wilson disease has a wide variety of presentation and diagnosis may be delayed because of wide spectrum of symptoms. Dermatological presentation, though uncommon can be an important indicator for early diagnosis of Wilson disease which is a treatable metabolic disorder.

References