An Unusual Presentation of Menkes Disease Masquerading as a Leukodystrophy with Macrocephaly

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Background: Menkes disease is an X-linked neurodegenerative disease caused by mutation in ATP7A gene, which codes for copper-transporting ATPase. It usually presents in early infancy with neuro-regression, hypotonia, seizures, and kinky hair. Magnetic resonance imaging (MRI) of the brain shows cerebral atrophy, subdural effusions, and tortuous cerebral blood vessels. Case Characteristics: We report the case of a 7-month-old boy who presented with global developmental delay, seizures, and increasing head size since 2 months of age and history of sibling death. He had macrocephaly, sparse, hypopigmented hair, seborrheic dermatitis of scalp, hypotonia, and brisk reflexes. Brain MRI was suggestive of megalencephalic leukodystrophy. Careful reexamination of films revealed tortuous blood vessels. Serum copper and ceruloplasmin levels were significantly reduced, leading to diagnosis of Menkes disease. Conclusion: This case exemplifies a rare presentation of Menkes disease, simulating a leukodystrophy with macrocephaly. Tortuosity of cerebral blood vessels is an important finding, which can help in differentiating Menkes disease from white matter disorders.

Keywords: Copper; hair abnormalities; neurometabolic disorder

INTRODUCTION

Menkes disease is an X-linked recessive neurodegenerative disease due to mutation in ATP7A gene, which codes for a copper-transporting P-type ATPase. The mutation leads to defective intestinal copper absorption and transport causing copper deficiency in brain, skin, bones, and joints. Reduced activity of various copper-containing enzymes is responsible for the neurological deterioration.

CASE DETAILS

A 7-month-old boy, resident of Agra, Uttar Pradesh, was presented with complaints of delayed attainment of milestones since birth and progressively increasing head size since 2 months of age following a febrile illness. The child was delivered vaginally at a hospital at term, with a birth weight of 1.25 kg. The birth and perinatal period was uneventful. He never attained neck holding, social smile, or cooing. At 2 months of age, child developed a febrile illness for which he was admitted for 25 days. He also developed multiple seizures in the form of tightening of the whole body with vacant staring look. He received multiple antibiotics and antiepileptic drugs during the hospital stay and was discharged on antiepileptic medications. There were no further episodes of seizures since discharge. There was history of flaky lesions on the scalp, which have been persisting since then despite treatment. Since this episode, his mother noticed gradual increase in head size of the baby. She also complained that the child was excessively irritable. There was history of apparent visual and auditory impairment.

The child was born out of a non-consanguineous marriage and was fourth in birth order. The first child had died at the age of one and a half years of a similar illness. The second child was 5 years old and is alive.
and healthy. The third pregnancy terminated in a spontaneous abortion at 3 months of amenorrhea.

On examination, child looked small for age, with a large head. He weighed 4.6 kg and had a length of 62 cm. His weight for length was less than –3 standard deviation (SD). He had a head circumference of 48 cm, which was greater than +3 SD. He had short sparse coarse lightly pigmented hair with seborrhoeic dermatitis of the scalp [Figure 1A and B]. He had a depressed nasal bridge. On neurological examination, child was irritable and not interacting with the surroundings or parents. Visual fixation and response to auditory stimulus were absent. The tone was low in all four limbs. He was moving all four limbs symmetrically. Deep tendon reflexes were brisk and plantars were upgoing. Fundus examination was within normal limits. There was no nystagmus. Hepatosplenomegaly was absent. Rest of the systemic examination revealed no abnormality.

Hematological parameters were normal except for mild anemia with a hemoglobin of 10.5 g/dL. Serum lactate levels were elevated. Magnetic resonance imaging (MRI) of the brain carried out at the time of febrile illness showed hyperintense signals involving subcortical and deep white matter in bilateral temporal regions with changes suggestive of megalencephalic leukodystrophy. A careful reexamination of the films revealed tortuous blood vessels [Figure 2]. Microscopic examination of the hair revealed pili torti and monilethrix. Serum copper levels (15.74 µg/dL, reference range 90–190 µg/dL) and serum ceruloplasmin levels (7.75 mg/dL, reference range 20–60 mg/dL) were significantly reduced. The diagnosis of Menkes disease was made on the basis of clinical presentation, hair microscopy findings, and reduced serum copper and ceruloplasmin levels. We could not start copper histidine therapy because of nonavailability. However, supportive care was started and prognosis was explained to the parents.

**Discussion**

Our patient presented with developmental delay, seizures, and macrocephaly, with a history of sibling death. This, along with diffuse white matter changes on MRI, suggested a possibility of Canavan’s disease. However, the peculiar appearance of hair with seborrhoeic dermatitis of scalp prompted a diagnosis of Menkes disease, which was confirmed on investigations.

Typical MRI findings in Menkes disease include progressive cerebral and cerebellar atrophy, subdural hematomas or effusions, and tortuous cerebral blood vessels. However, white matter changes have also been described in Menkes disease especially early in disease course, before the classical cerebral atrophy sets in.[1-4] White matter lesions may be restricted to deep periventricular white matter or may be present diffusely. Earliest changes are usually seen in temporal lobes.[5] MRI in our case showed changes in deep white matter of bilateral temporal lobes, but this was obtained at the age of 2 months when the clinical features first became apparent. Few tortuous blood vessels could be identified in these films. A subsequent neuroimaging may show the classical features of atrophy and effusions.

Two similar presentations with a large head and white matter changes have been described previously. Jayawant et al.[6] described a biochemically proven case of Menkes disease with atypical clinical and radiological

![Figure 1: (A) Child who was severely wasted and stunted and had macrocephaly. His hair was short and sparse with seborrhoeic dermatitis of the scalp. (B) The short, sparse, coarse, and hypopigmented hair of the child](image)
features. The case was of a 6-month-old infant who had large head, seizures, hypotonia, hypothermia, and coarse sparse hair. MRI showed diffuse cerebral white matter changes involving the basal ganglia, but no atrophy, subdural fluid collection, or tortuous blood vessels. Another case was described by Jain et al.,[7] who was a 10-month-old child with developmental delay, seizures, macrocephaly, hypotonia, and sparse hypopigmented hair.

**CONCLUSION**

This case exemplifies a rare presentation of Menke disease, simulating a leukodystrophy with macrocephaly. Tortuosity of cerebral blood vessels is an important finding, which can help in differentiating Menke disease from other white matter disorders.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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