Infantile Neurodegeneration and Hair Changes: A Rare Case of Menkes Disease

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Menkes disease - Copper storage disease

Abstract
A 4-month-old, previously healthy boy presented with acute onset of prolonged, recurrent seizure activity followed by neurodevelopmental deterioration and concurrent hair shaft hypopigmentation with fragility. Initial evaluation revealed significant low serum copper and ceruloplasmin, electrical status epilepticus on electroencephalography, and generalized subcortical white matter changes with diffuse tortuosity of intracranial vessels on MRI brain. In addition, a genetic study with whole-genome sequencing demonstrated a hemizygous pathogenic variant at c.2179G>A p(Gly727Arg) on ATP7A, thereby confirming the diagnosis of Menkes disease. Symptomatic treatment with antiepileptic medications was provided along with an urgent referral to an advanced center for multidisciplinary care and copper histidine replacement therapy.

Introduction
Menkes disease is a lethal neurodegenerative disorder due to defective ATP7A gene function. A perturbation in copper metabolism leads to failure of dependent cellular enzyme function and subsequent multisystem disease. The inheritance pattern is X-linked recessive; however, approximately one-third of affected males have a negative family history [1], and recent studies have demonstrated carrier female disease phenotype [2]. Onset is in early infancy with relentless deterioration and an early demise by 3 years of age. Response to copper histidine is guarded and heavily dependent on the timing of therapy. We report a prototypal case of severe Menkes disease with genetically proven ATP7A defect.
of white matter in the bilateral temporoparietal region suggestive of gliosis along with cortical atrophy and extradural hydrocephalus (Fig. 3, 4). With a clinical suspicion of a genetic metabolic defect, focused investigations were sought, and subsequent reports were highly suggestive of the underlying Menkes disease (Table 1).

The patient attained seizure freedom by 6 months of age; however, he relapsed once his mother tapered medications. In light of the above, the child traveled abroad for genetic investigations. Whole-genome sequencing revealed a hemizygous pathogenic variant at c.2179G>A p.(Gly727Arg) on ATP7A while the mother carried a novel pathogenic heterozygous variant c.2179G>A p(Gly727Arg) in the ATP7A gene, consistent with the diagnosis of Menkes disease.

The Pediatric Neurologist reviewed the child; rehabilitation and home-based physiotherapy were recommended. Urgent referral was made to a center with higher specialization for multidisciplinary care and copper histidine replacement therapy.

**Discussion**

Copper is an essential element involved in cellular health. It is the third most abundant element in the body after iron and zinc, and its delicate homeostasis is crucial for preserving normal bodily functions, particularly neurologic and connective tissues [3]. Among the 2 most well-recognized disorders of copper metabolism is Menkes disease, arising due to copper deficiency, and Wilson disease, a consequence of copper toxicity.

![Fig. 1. Short, coarse, hypopigmented, brittle, and twisted hair.](image1)

![Fig. 2. EEG features suggestive of electrical status epilepticus with bilateral centrotemporal epileptiform activities (more prominent on the right side).](image2)
Menkes disease holds an estimated prevalence of 1 in 8,664 live male births [4]. It is among a spectrum of disorders arising from defective ATP7A, the critical X-linked gene encoding copper transporting ATPase. The fundamental disease process is of a preserved cellular copper uptake but aberrancy in transportation and subsequent utilization by its dependent enzymes [1, 3, 5]. Key examples of the latter include cytochrome c oxidase required for electron transport, superoxide dismutase responsible for free radical detoxification, dopamine beta-hydroxylase needed for catecholamine production, lysyl oxidase required for cross-linking of elastin and collagen, and peptidyl-glycine alpha amidating monooxygenase needed for bioactivation of peptide hormones [3].

There has been a demonstrated parallel between the degree of residual ATP7A activity and disease phenotype, which would explain the spectrum of disease presentation from mild occipital motor horn syndrome to lethal classical Menkes disease [6, 7]. Recent reports have even demonstrated disease phenotype in carrier females (in addition to the rare occasions of sex chromosome aneuploidy or X-autosome translocation) [2]. Classic Menkes disease typically manifests at 6–8 weeks of age with progressive loss of developmental milestones, new onset of seizures, hypotonia, failure to thrive, and the concomitant onset of characteristic hair shaft anomalies (sparse, coarse, brittle, short, twisted hair with a microscopic picture of pili torti, monilethrix, and trichorrhexis nodosa) [8–16].

Diagnosis is hinged upon characteristic clinical features; lab findings of low serum copper and ceruloplasmin; EEG features of focal spikes with subsequent secondary generalization [17]; MRI brain evidence of vascular anomalies, myelination delays, and neurodegenerative changes [18–20]; as well as absolute confirmation via genetic analysis. Disease prognosis remains poor, with most children dying by 3 years of age after respiratory tract infections.

### Table 1. Laboratory investigations

| Test                        | Patient result |
|-----------------------------|----------------|
| FBC                         | Normal         |
| Urea electrolytes           | Normal         |
| Liver function test         | Normal         |
| Serum copper                | 24 g/dL (reference range: 72–166 g/dL) |
| Serum ceruloplasmin         | 0.03 g/L (reference range: 0.15–0.62 g/L) |
| Blood amino acid chromatography | Normal     |
| Amino acid acyl carnitine  | Normal         |

Fig. 3. Diffuse subcortical white matter signal changes in the bilateral temporoparietal regions suggestive of gliosis with hypointense signal in T1 and FLAIR images with hyperintense signal in T2 with no restricted diffusion or blooming artifacts.

Fig. 4. Cortical atrophy and extra-axial hydrocephalus.

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Therapeutic modalities are limited to parenteral administration of copper histidine, which can ameliorate neurologic disease but cannot reverse the connective tissue manifestations [1]. Major confounding factors include timing of replacement therapy (negligible response if treatment delayed beyond) and ease of access to copper histidine therapy (both financially and geographically). Prenatal diagnosis is of utmost importance once a proband is diagnosed, as that would aid in early identification in the following offspring [1, 13].

Conclusion

Menkes disease is a lethal neurodegenerative condition with onset in a previously well infant. Diagnosis hinges on astute clinical observation – the combination of pathognomonic hair shaft changes and neurodegeneration in a well-child, should spark confirmation via investigations as available. Treatment is with parenteral copper histidine administration at the earliest time possible, along with general supportive management.

Statement of Ethics

Ethical approval was not required for this study in accordance with the Dubai Health Authority Research Committee policies. Written informed consent was obtained from the patient’s parents for publishing the case report including any accompanying materials.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors have contributed to writing, researching, and finalizing the case report.

Data Availability Statement

All data generated or analyzed during this case are included in this article. Further enquiries can be directed to the corresponding author.

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