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Insights into Menkes disease: A case report on rare X-linked copper metabolism disorder linked to ATP7A mutation

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Abstract

Menkes' Disease (MD) is a X-linked recessive degenerative disorder, involving mutations of ATP7A gene, characterized by impaired copper transport at the intracellular level contributes to nervous system dysfunction. Clinical manifestations include brittle kinky hair, growth retardation, seizures and typical cherubic facial appearance. Here, we present a case of 1-year-old male with complaints of fever, excessive irritability, seizures like activity in form of up rolling of eyes and associated with postictal drowsiness passage of urine or frothing. MRI revealed brain abnormalities and final diagnosis with Menkes disease via genetic testing. Routine biochemical investigations were normal but copper and ceruloplasmin levels were found to be abnormal. Due to unavailability of copper histidine in our hospital and referred for further management. Symptomatically treated with Levetiracetam and biotin tablets. Reporting of this case is important, because of its rarity and association with association with significant microcephaly.

Keywords: Menkes disease; Kinky Hair Disease; ATP7A gene; Copper histidine.

Introduction

Menkes disease is also called as Kinky Hair Disease, Tripchopoliodystrophy. This condition is caused by improper copper transport and low amounts of copper levels in the brain and serum, which is necessary for appropriate growth and development [1].

Copper insufficiency is caused by a major flaw in copper transport. This condition is recessive and X-linked. The X chromosome's long arm contains the Menke's disease gene, which is roughly 200 KB in size. According to current sequencing, the cDNA codes for a 1500 amino acid protein [2]. The estimated prevalence of the disease ranges from 1 in 100,000 to 1 in 250,000 [3].

Three research teams isolated the ATP7A gene in 1992. An X; 2 translocation was discovered in a heterogeneous female who was expressing. The kind of copper distribution was categorized by the trans-

membrane copper transport protein implying the deduced gene product, which signifies the outcomes of research conducted by Vulpe C, Levinson B, Whitney S et.al in nature genetics in 1993 [4].

The clinical features of Menke's disease typically appear during infancy, with affected infants generally succumbing to the condition by the age of 3 to 4 years [2]. Clinical characteristics include a lack of copper-dependent enzymes, increasing neurological problems such as refractory epilepsy and psychomotor decline, thin, brittle hair, and a face that resembles a cherubic angel. The sparse, thin, brittle, and hypopigmented scalp hair is the most distinctive feature [5]. Quantifying blood and urine copper levels, serum ceruloplasmin levels, genetic analysis, hair changes, and radiological findings can all be used to validate the clinical diagnosis [1].

Once diagnosed, Menkes disease can be treated with daily subcutaneous injections of copper supplements, though the outcomes depend on the specific copper compound used and the severity of the ATP7A mutation. For instance, children who retain some ability to transport copper respond best to copper histidine (CuHis), which can enhance growth, survival, neurological development, and reduce epilepsy occurrences. Due to its complexity and rarity, Menkes disease poses significant treatment challenges, particularly the need for early diagnosis and initiation of therapy within the first 28 days of life. Additionally, since copper is essential for a developing nervous system, any treatment must be capable of crossing the blood-brain barrier [7]. Since copper histidine is inaccessible, copper chloride will be used as an alternative, resulting in significant improvements in serum copper and ceruloplasmin levels, along with effective management of generalized tonic-clonic seizures [6].

Case Description

A 1-year-old male baby presented to Department of Paediatrics with fever, excessive irritability for one day and complaints of seizures like activity in form of up rolling of eyes and associated with postictal drowsiness passage of urine or frothing. Anthropometric information includes a weight of 6 kg, 72 cm height and head circumference 41 cm. The systemic examinations include abnormal tone of motor system like Hypertonia of upper limb and Hyperflexia. Coordination could not be assessed. Previously the baby had convulsions from third month of birth and developmental delay, microcephaly with peculiar hair pattern and hair loss and diagnosed with Menkes disease and referred to CMC Vellore hospital for further management including copper histidine treatment in view of non-availability. Treatment includes Syrup. Levetiracetam (100 mg/ml), Syrup. Clobazam (1 mg/ml), Syrup. Valporate (200 mg/5 ml), Syrup. Phenytoin (30 mg/5 ml).

Mother had noticed that child had not attained even partial neck holding or does not roll over at 5 months of age. Other signs like motor skills at fingers were fine but no Bi-dexterous reach, no social smile, does not produce cooing sounds and sudden onset of head deviation to right with tonic posturing and up rolling with frequent eye blinking for almost 2-3 minutes, cluster of 3 episodes was observed. History of similar kind symptomatology in elder sibling with seizures from 3 months of age and with similar kind of hair and alopecia. Child expired at age of 5 months during to respiratory distress after seizure episode.

The decreased levels of copper and Ceruloplasmin were 10 mg/dl and 4 mg/dl respectively and other routine lab investigations were normal. MRI OF Brain showed Diffuse cerebral and cerebellar Atrophy. Asymmetrical tumefactive white matter T2/FLAIR hyper intense signal changes was seen in bilateral temporal lobes. Overlying cortex shows ribbon like diffusion restriction with Symmetrical diffusion restriction seen in bilateral caudate head and Globus. Bilateral symmetrical putaminal atrophy with cystic change and Mild degree of hypomyelination was seen. The short term VEEG showed multiple events and interictally poorly formed background, sleep attenuation and continuous epileptic activity discharges in central and left hemispheric.

Clinical Exome sequencing test was done and result showed that likely pathogenic variant causative of the reported phenotype was detected.

Table 1: Demonstrates result of single variant of gene at Exon 7

Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification$
ATP7A(+)	Exon 7	c.1809del	Hemizygous	Menkes disease	X-linked recessive	Likely Pathogenic
(ENST00000341514.11)		(p.Ala604HisfsTer22)		(OMIM#309400)		(PVS1, PM2)

Variant interpretation and clinical correlation

A hemizygous 1 base pair deletion in exon 7 of the ATP7A gene (chrX: g.78009203del; Depth: 83x) that results in a frameshift and premature truncation of the protein 22 amino acids downstream to codon 604 (p. Ala604HisfsTer22; ENST00000341514.11) was detected.

Inspite of a partial clinical match, the variant has been classified as likely pathogenic based on current literature evidence. The results have to be carefully correlated with the clinical findings of the patient. Based on the above evidence, this ATP7A variation is classified as a likely pathogenic variant and has to be carefully correlated with the clinical symptoms.

The child was treated with Inj. Levetiracetam (120 mg), Inj. Lorazepam (0.6 mg) to reduce seizures and Biotin tablets of dose 10 mg was supplemented for kinky hairs.

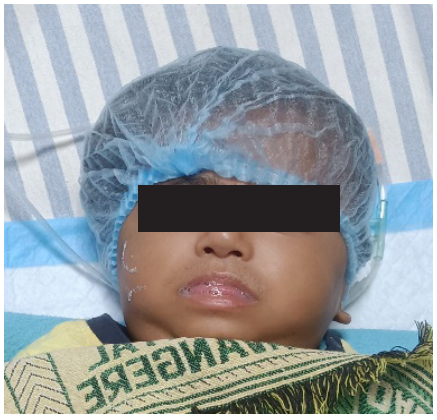

Figure 1: Chubby cheeks and microcephaly head of baby.

Discussion

Copper is an element that has vital role in cellular health. After iron and zinc, it is the third most prevalent element in the body. Maintaining its delicate balance is essential for maintaining proper physiological functions, especially in the connective and neurologic tissues. Menkes disease, which results from copper deficiency, and Wilson disease, which results from copper toxicity, are two of the most well-known illnesses of copper metabolism [7].

This condition is recessive and X-linked. The X chromosome's long arm contains the Menke's disease gene, which is roughly 200 KB in size. According to current sequencing, the cDNA codes for a 1500 amino acid protein [2]. The basic mechanism of the disease involves cellular copper absorption that is maintained but exhibits abnormalities in transportation and subsequent usage by its dependent enzymes. The enzymes like Cytochrome c oxidase, which is necessary for electron transport, superoxide dismutase, which detoxifies free radicals, Dopamine beta-hydroxylase, which is necessary for catecholamine synthesis, Lysyl oxidase, which is necessary for elastin and collagen cross-linking, and Peptidyl-glycine alpha amidating monooxygenase, which is necessary for the bioactivation of peptide hormones [8].

The diagnosis our patient is based on distinctive clinical characteristics; The decreased levels of copper and Ceruloplasmin were the lab findings where other routine lab investigations turns out to be normal. MRI Brain shows evidence of diffuse cerebral and cerebellar Atrophy, Asymmetrical tumefactive white matter T2/FLAIR hyper intense signal changes in bilateral temporal lobes, ribbon like diffusion restriction in cortex with symmetrical diffusion restriction seen in bilateral caudate head, Globus and bilateral symmetrical putaminal atrophy with cystic changes. The short-term video electroencephalogram (stVEEG) showed multiple events like interictally poorly formed background, sleep attenuation and continuous epileptic activity discharges in central and left hemispheric. a genetic confirmation was made by Clinical Exome sequencing test where ATP7A variation is classified as a likely pathogenic variant and was matched with patient's clinical symptoms. The only available treatment options are parenteral copper histidine injection, which can improve neurologic symptoms but not reverse connective tissue signs. The replacement therapy of copper has negligible response if treatment is postponed beyond and the accessibility of copper histidine therapy is both monetarily and geographically are important confounding factors which lies as an important factor for not treating our patient with copper histidine therapy [8]. There is no proof that parenteral copper administration linked to vitamin E5 or D-penicillamine is beneficial. When necessary, anticonvulsive medications must be used in the treatment of patients with Menkes illness [6].

Conclusion

Copper-histidine is the recommended treatment for MD; however, due to the improvement in copper levels and reduction in seizure burden seen in this case, readily available forms of copper supplementation, such as copper chloride, are viable alternatives in less resource-bound situations. The preferred treatment should be copper-histidine; however, if this is not possible, do not start treatment if copper-chloride supplementation may be started and can treated symptomatically with anti-epileptics.

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