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Case Report

Unraveling Menkes kinky hair disease: a rare but telltale disorder in infancy

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ABSTRACT

Menkes kinky hair disease also known as "trichopoliodystrophy" resulting from a mutation in the ATP7A gene, which disrupts copper distribution across various tissues. Herein this report presents a case of a 4-month-old boy who presented with unprovoked seizures in status and developmental delay. He was evaluated for refractory seizures and developmental delay, and his serum copper and serum ceruloplasmin levels were found to be low and was later genetically diagnosed as Menkes kinky hair disease. Despite copper histidine therapy and multiple antiepileptics, seizures persisted until initiation of adjunctive cannabinoid therapy, after which the child became seizure-free. This case underscores the diagnostic and therapeutic challenges of Menkes disease and highlights the potential role of cannabinoids in seizure management.

Keywords: Menkes kinky hair disease, Neurodegenerative disorder, Copper, ATP7A, Cannabinoids

INTRODUCTION

Menkes disease (MD) is a rare neurodegenerative disorder of copper transport, first described by John Menkes in 1962.[1] It results from mutations in the ATP7A gene, leading to defective absorption and distribution of copper.[2] This pathological mutation results in an abnormal cellular transport of copper which leads to dysregulated copper metabolism.[3,4] As a result of which there is an abnormally low levels of copper in brain and liver but higher levels in intestines and kidneys.[3] In affected cells, copper significantly accumulates as metallothionein-bound copper in the cytosol and copper transport to the organelles, as well as copper efflux, is disturbed. As a result, cuproenzymes cannot receive the copper necessary for their normal function.[5] This impaired function of copper-dependent enzymes, manifest as neuro-developmental delay, seizures, connective tissue abnormalities, and the characteristic "kinky" hair.[6] The condition is typically fatal in early childhood without intervention.[2] While parenteral copper supplementation can improve outcomes if initiated in the neonatal period, efficacy decreases once neurological manifestations are established.[2,6,7] Seizures in MD are often refractory to standard antiepileptic drugs, creating a need for novel therapeutic approaches.[8,9]

CASE REPORT

A 4-month-old male infant, born of a third-degree consanguineous marriage, presented with the first episode of unprovoked seizures in status. He was delivered preterm at 32 weeks by emergency lower segment cesarean section (LSCS) (indication: foetal bradycardia) with a birth weight of 1.82 kg. The antenatal period was notable for reduced perception of foetal movements in the third trimester. At birth, the neonate cried immediately but developed respiratory distress requiring continuous positive airway pressure (CPAP) for 10 hours followed by oxygen supplementation via hood for 2 days. He remained in the NICU for 12 days, during which he received phototherapy for neonatal hyperbilirubinemia. No neonatal seizures were reported, though poor sucking was noted (Figure 1).

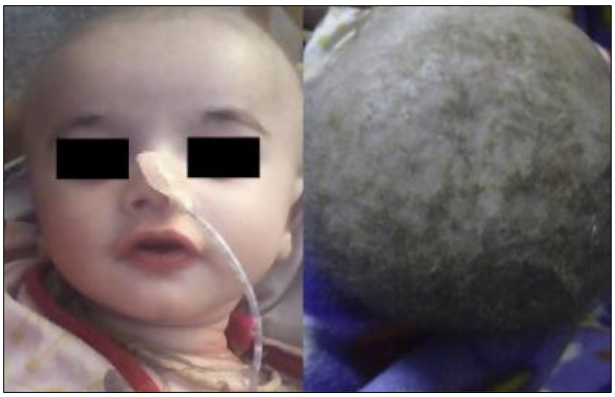

Figure 1: Image of the kid at 4 months.

Developmentally, he did not achieve age-appropriate milestones. At 4 months of age, he could only momentarily hold his head horizontally and alert to sounds. Parents reported abnormal silvery, brittle, sparse hair with patchy alopecia over the vertex. A proximal forearm fracture occurred at 2 months of age following trivial trauma, was managed conservatively.

On examination at admission, his weight (4.75 kg) and length (54 cm) were below the 3rd percentile, while head circumference was at –2 SD (39 cm). Dysmorphic features included plagiocephaly, depressed nasal bridge, micrognathia, retrognathia, high-arched palate, and pectus excavatum. Hair was hypopigmented, brittle, and woolly. Skin examination revealed dryness, cutis laxa, and a café-au-lait macule. Neurologically, he was hypotonic with frog-leg posture, weak spontaneous movements, power 2/5 in all limbs, and diminished reflexes except for elicitable knee jerks. Differential diagnoses for the condition include inborn errors of metabolism such as biotinidase deficiency and copper transport deficiency.

Laboratory evaluation revealed mild anaemia (Hb 9.5 g/dl) with otherwise normal biochemical parameters including calcium, magnesium, liver function, and ammonia. Electroencephalography (EEG) demonstrated epileptiform discharges from the temporo-occipital and left parietal regions. Despite escalation of multiple antiseizure medications and addition of biotin, seizures remained refractory. Serum copper and ceruloplasmin levels were significantly low. Abdominal ultrasonography was normal.

Magnetic resonance imaging (MRI) brain revealed delayed myelination for age, prominence of subarachnoid spaces over bilateral frontal and temporal lobes, prominent cystic foci involving bilateral fronto-parieto-temporal white matter, and dilated third and fourth ventricles. Genetic testing (whole exome sequencing) confirmed a hemizygous nonsense variant in exon 15 of the ATP7A gene (c.2956C>T; p.Arg986Ter), consistent with Menkes disease (OMIM #309400). Based on these findings, a diagnosis of Menkes kinky hair disease was established (Figure 2).

Gene[4] (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification[5]
ATP7A (+) (ENST00000341514.11)	Exon 15	c.2956C>T (p.Arg986Ter)	Hemizygous	Menkes disease (OMIM#309400); Occipital horn syndrome (OMIM#304150)	X-linked	Pathogenic (PVS1, PM2, PP5)

Figure 2: Laboratory investigations.

At 6 months of age, the child was initiated on parenteral copper histidine therapy. However, seizures persisted despite multiple antiepileptics. Repeat EEG at 11 months revealed modified hypsarrhythmia, necessitating modification of therapy to levetiracetam. Cannabinoid therapy was added on a trial basis at 11 months, after which the child became seizure free.

At the most recent follow-up, at 1 year 4 months of age, the child's developmental age corresponded to approximately 1 month. He continues to receive physiotherapy, and occupational therapy, though adherence has been inconsistent due to intercurrent respiratory illnesses.

DISCUSSION

Menkes disease is a rare, X-linked recessive neurodegenerative disorder caused by mutations in the ATP7A gene, which encodes a copper-transporting ATPase.[2] This defect leads to impaired intestinal absorption and systemic distribution of copper, resulting in deficiencies of multiple copper-dependent enzymes such as cytochrome c oxidase, lysyl oxidase, and dopamine-β-hydroxylase.[10] Consequently, affected infants develop progressive neurodegeneration, connective tissue abnormalities, skeletal fragility, and the characteristic pili torti (kinky hair).

The clinical manifestations typically appear within the first few months of life, often presenting with feeding difficulties, hypotonia, seizures, and failure to thrive.[11] Seizures are a particularly challenging aspect of the disease and are frequently refractory to conventional antiseizure medications.[8] In the present case, our patient developed intractable seizures despite multiple antiepileptics, reflecting the severity of neuronal copper deficiency and secondary cortical dysfunction.

Diagnosis is based on a combination of clinical features, biochemical evidence of low serum copper and ceruloplasmin, and confirmatory genetic testing.[6] Our patient demonstrated a hemizygous nonsense variant in exon 15 of ATP7A (c.2956C>T; p.Arg986Ter), consistent with previously reported pathogenic mutations.[12]

Neuroimaging in Menkes disease often reveals cerebral and cerebellar atrophy, subdural effusions, and delayed myelination, all of which were evident in this child.[13]

The mainstay of therapy is early initiation of parenteral copper supplementation (preferably copper histidine), ideally within the neonatal period, which can improve neurodevelopmental outcomes in some cases.[7] However, delayed initiation, as in this case at 6 months, is associated with limited clinical benefit due to irreversible neurodegeneration already underway.

A novel aspect of our case was the introduction of cannabinoid therapy at 11 months of age, following which the chid became seizure free. Cannabinoids, particularly cannabidiol (CBD), have shown efficacy in refractory childhood epilepsies such as Dravet and Lennox-Gastaut syndromes.[9] Although not previously reported in Menkes disease, their use may represent a promising adjunct in managing intractable seizures in this population. This highlights the need for further clinical evaluation of cannabinoids as potential therapeutic agents in rare metabolic epilepsies.

Despite seizure control, the overall developmental outcome in our patient remains poor, with a developmental age equivalent to only 1 month at 16 months of chronological age. This underscores the irreversible nature of neurodegeneration in Menkes disease once clinical manifestations are established. Majority of these children do not live past the age of three years. A common cause of death is pneumonia, which leads to respiratory failure.

CONCLUSION

Menkes disease has no specific curative treatment, and it is a progressive multisystem disease. Also, currently, there are no newborn screening programs available. Early diagnosis of Menkes disease is clinically very challenging because of the subtle clinical features and nonspecific biochemical markers. Early genetic diagnosis, timely initiation of copper therapy, antiepileptics and comprehensive supportive care including physiotherapy, occupational therapy, and genetic counselling for families remain cornerstones of management.

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