Neuroimaging Highlight

Editors: William Hu, Mark Hudon, Richard Farb

"From Sheep to Babe" – Menkes Disease

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A four-month-old boy presented with a new onset focal seizure lasting 18 minutes. During the seizure, his head and eyes were deviated to the left, and he assumed a fencing posture to the left with pursing of his lips. He had been unwell for one week, with episodes of poor feeding, during which he would become unresponsive, limp and stare for a few seconds. Developmentally he was delayed. He was not yet rolling, and he had only just begun to lift his head in prone position. He could grasp but was not reaching or bringing his hands together at the midline. He was cooing but not laughing. His past medical history was significant for term delivery with fetal distress and meconium staining. He was flat and blue at birth, with birth weight of 3.5 kg, and Apgar scores of 1 at one minute, 4 at 5 minutes, and 8 at 10 minutes. He required resuscitation with positive pressure ventilation for two minutes, and then had no further postnatal complications. Family history was remarkable for a paternal cousin with cortical malformation, epilepsy, and developmental delay. His mother and maternal grandmother had migraine headaches and fibromyalgia.

On examination, his length (66 cm) and head circumference (43 cm) were at the 50th percentile, and his weight (6.6 kg) was at the 75th percentile. He had short bristly pale hair, and a cherubic appearance with full cheeks. His skin was velvety and lax. He was hypotonic with significant head lag and slip-through on vertical suspension. His cranial nerves were intact. He moved all limbs equally well with normal strength. His deep tendon reflexes were 3+ at patellar and brachioradialis, and 2+ elsewhere. Plantar responses were upgoing.

Laboratory investigations showed increased lactate (7.7 mmol/L) and alkaline phosphatase (505 U/L), with normal CBC, electrolytes, calcium, magnesium, phosphate, ammonia, and liver enzymes. A brain CT scan demonstrated diffuse atrophy of the cerebral hemispheres, initially attributed to perinatal hypoxic-ischemic insult. Subsequent brain MRI showed atrophy and impaired myelination, with abnormal hypointense T1 signal and hyperintense T2 signal in the white matter of both frontal and temporal lobes. Tortuous blood vessels could also be seen (Figure 1). His EEG was abnormal, with poorly organized

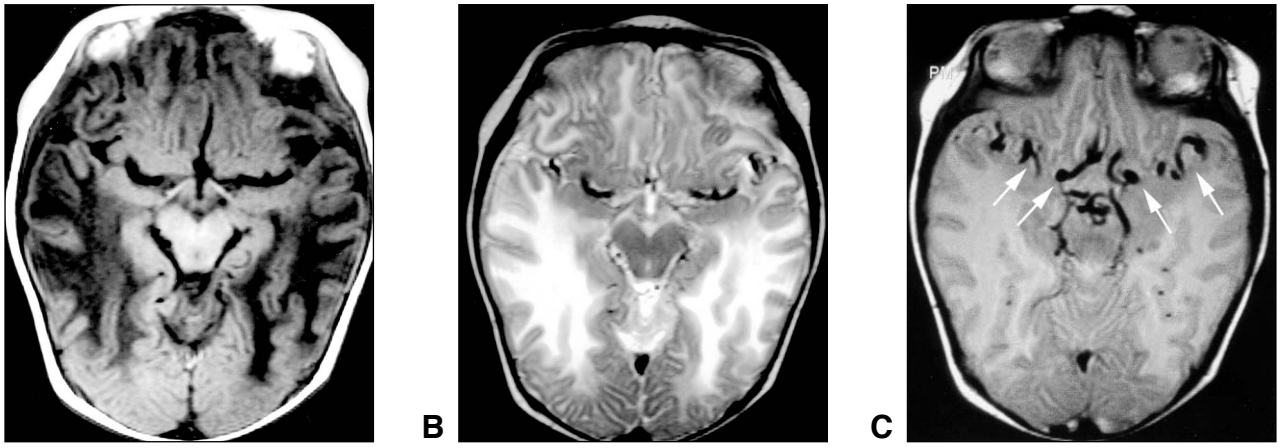

Figure 1: *a) T1-weighted and b) T2-weighted brain MRI of four-month-old infant with Menkes Disease, showing atrophy and impaired myelination, with abnormal hypointense T1 and hyperintense T2 signal in the white matter of both frontal and temporal lobes. c) Axial Proton Density weighted brain MRI, with arrows showing tortuous blood vessels.*

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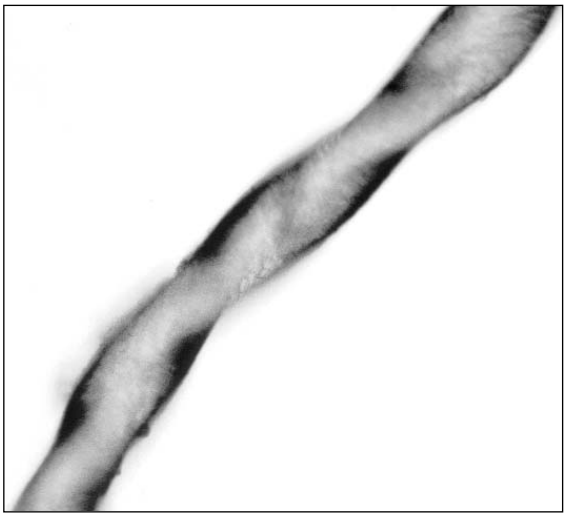

Figure 2: *Pili torti seen in hair of same patient with Menkes disease.*

background and multifocal epileptiform discharges. Further investigation revealed elevated CSF lactate, with an increased lactate/pyruvate ratio, normal CSF and plasma amino acids, and normal urine organic acids. Hair examination under light microscopy showed pili torti (Figure 2). Plasma ceruloplasmin (0.06g/L) and copper levels (0.7 μmol/L) were low, with excessive retention of copper by cultured skin fibroblasts, all compatible with a diagnosis of Menkes Disease. He was treated with phenobarbital, carbamazepine, and subcutaneous copper histidinate.

Copper was first recognized in 1937 as an important element for neurodevelopment, when ataxic lambs were born to sheep that had grazed in copper-deficient pastures in Australia.[1] In 1962, Menkes described a new syndrome in a family of five male infants who had neurological degeneration, peculiar hair, and failure to thrive.[2] It was not until 10 years later that Danks noticed the similarity between the unusual hair in infants with Menkes disease and the brittle wool in the copper-deficient lambs.[3]

Menkes disease is a rare X-linked recessive condition due to mutations in the copper transporting ATPase gene on Xq13.3, with an incidence of approximately one per 250,000 live births.[4] The mutations cause defects in intracellular copper transport into vesicles and decreased secretion of copper from cells. This results in low levels of copper in plasma, liver and brain, and subsequent reduction of several copper dependent enzymes.[5] Deficiency of lysyl oxidase, which cross-links collagen, leads to the brittle hair with pili torti (twisted hair shaft), trichoclasis (transverse hair shaft fracture), and trichoptilosis (longitudinal splitting of hair shaft). It also results in elastic skin, hernias, bladder diverticulae, and impaired blood vessel integrity, which is evident as vascular tortuosity on brain imaging and fundoscopy exam. Tyrosinase is required in the conversion of tyrosine to melanin. Deficiency of tyrosinase causes pale hair, skin, and irises, producing the cherubic appearance. Ascorbate oxidase deficiency leads to skeletal demineralization and elevated alkaline phosphatase. Decreased cytochrome C oxidase activity results in energy failure, lactic acidosis, and neurological deterioration. Dopamine-beta-hydroxylase is required in the synthesis of norepinephrine, the lack of which contributes to further neurological damage. Neuropathological studies revealed diffuse neuronal degeneration, with gliosis, white matter demyelination, and multifocal areas of infarction.[6,7]

Characteristic neuroimaging features of Menkes disease include abnormal myelination, diffuse atrophy, extra-axial fluid collections, and tortuosity of cerebral blood vessels.[8-10] Extensive white matter changes as seen in our patient are likely due to progressive ischemia and demyelination, and should be distinguished from other leukodystrophies such as Leigh syndrome, adrenoleukodystrophy, metachromatic leukodystrophy, Krabbe, Alexander, or Canavan disease.[11,12] Vasculopathy with "corkscrew" appearance of cerebral vessels can be best appreciated with magnetic resonance (MR) angiography.[13] Diffusion-weighted imaging and MR spectroscopy are useful for the detection of acute infarction.[14] The presence of subdural hematoma, cystic changes, and multiple long bone fractures in Menkes disease can resemble nonaccidental trauma.[15,16] Serial MRI studies may help to confirm the diagnosis of Menkes disease, and to monitor the response to copper replacement therapy.[17,18]

Most infants with Menkes disease have refractory epilepsy, with multifocal epileptic discharges and electrographic seizures. Subcutaneous injection of copper histidinate may correct the enzyme deficiencies but is not effective in all children. Once neurological damage has occurred, it is not reversible. Prenatal diagnosis and early treatment during the first 10 days of life may result in normal neurodevelopment.[19]

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