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Genetics Corner: Menkes Disease in an Infant who Presented with Recurrent Infections

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Case History:

A 3 ½-month-old male was admitted for emesis, hypotonia, worsening baseline congestion, decreased urine output, and respiratory distress. He was diagnosed with *Moraxella* pneumonia and treated with Rocephin for seven days. He had a positive blood culture for *Staphylococcus epidermidis* and *Streptococcus mitis*, for which he was treated with vancomycin. He had been previously admitted at approximately two months of age for COVID pneumonia. A genetics consultation was requested for thrombocytopenia, low T cells, and recurrent infections.

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He had normocytic anemia (Hgb trending down, 8.2-7.7, with normal MCV, possibly of iatrogenic origin), thrombocytopenia (43-128K), low T cells (CD4 39%, normal range 50-57%; CD4 count 831, normal range 2,800-3900, CD3 count 1,448, normal range 3,500-5,000). IgA and IgM were elevated, but IgE and IgG were normal. A brain MRI revealed stable widening of the bifrontal extra-axial fluid spaces without intracranial hemorrhage, likely representing benign enlargement of subarachnoid space in infancy. There was a left middle cranial fossa arachnoid cyst and brachycephaly. Other problems included chronic eczema, gross motor delay, poor head control, right inguinal hernia, pectus excavatum, GERD, and fair, friable hair. His parents were of Hispanic (Mexican) ancestry. The mother also had fair hair. The family history was negative for consanguinity and was non-contributory.

He was born at 35 weeks gestation and was described by his mother as being a "floppy" baby.

The physical exam revealed an alert, smiling, pale infant with generalized hypotonia and a paucity of spontaneous movement. He had brachycephaly with fair, sparse scalp hair. There was no hair on the occiput. The facial features were nonspecific and dysmorphic: shallow orbits, short nose, anteverted nares, and a small mouth. He had a mild pectus excavatum. There was an eczematous rash in the skin folds around the neck, the antecubital fossae, and the right groin. He made good eye contact. His muscle mass was diminished throughout, and he had poor to no head control.

A chromosome microarray was normal. A gene panel for primary immunodeficiency disorders was negative. Still, reflex testing for whole exome sequencing (WES) resulted after his discharge: a *de novo* pathogenic variant in the X-linked gene responsible for Menkes disease, ***ATP7A*: c.2770C>T.** At 7 ½ months, copper and ceruloplasmin levels were both low: copper 16 mcg/dL (normal range 24-152); ceruloplasmin 10 mg/dL (15 - 48).

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Discussion:

This infant with Menkes disease (MD) presented with recurrent infections, thrombocytopenia, and low T cells. The initial concern for an immune deficiency disorder may have prolonged the diagnostic process. In retrospect, other aspects, especially his sparse fair hair, were important clues to his diagnosis that were overlooked.

Menkes disease is a rare X-linked disorder of copper metabolism caused by a variant in *ATP7A*. (1) This gene encodes MNK, an essential copper transporting ATPase localized to the trans-Golgi network. Without MNK protein, copper cannot be absorbed from the gut. This leads to reduced activity of copper-dependent enzymes such as dopamine-beta-hydroxylase and lysyl oxidase. Most affected infants with MD are male, although some females with skewed X-inactivation or X-autosome chromosome translocations are rarely reported. About 1/3 of affected males do not have a positive family history of the disorder, as in this case.

Infants with MD appear healthy until 1 1/2 - 3 months, when they lose developmental milestones, fail to thrive, and classically present with hypotonia and seizures. Their hair is short, friable, sparse, kinky (pili torti) and lightly pigmented. Without treatment, there is an inexorable decline in neurologic function leading to early death, often by age 3.

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The early features of MD are nonspecific, which makes it difficult to diagnose in the newborn period. Although newborns with MD are more often preterm (34%), low birth weight (33%), or both (19%), more than half of patients with MD deliver normally without complications. (2) During the neonatal period (<1 month), 29% of the patients reported by Fujisawa had abnormal hair growth, 24% had prolonged jaundice, 17% had feeding difficulties, 15% had hypothermia, 13% had hypotonia, and 3% experienced seizures. These signs and symptoms became more prevalent with time. Only 3/64 of the affected Japanese patients without a family history of MD visited a physician in the first month of life. Although these three patients had symptoms (hair abnormalities, hypothermia, prolonged jaundice) during the neonatal period, the diagnosis of MD was not considered then. Among the cohort of 64 patients with MD, the mean age of diagnosis was 8.7 months, similar to our patient.

Although copper and ceruloplasmin levels are lower in newborns with MD, the values are not always diagnostic in the first few months of life because copper and ceruloplasmin are low in the newborn period, even among healthy newborns. As shown in Table 1, (2) the values for copper and ceruloplasmin in affected and healthy infants overlap in the first three months, with almost no overlap after three months of age:

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In MD, systemic copper deficiency suppresses the immune response. As our patient demonstrated, increased susceptibility to infection, especially pulmonary, urinary and systemic infections, is a feature of Menkes disease. Secondary neutropenia and humoral immunodeficiency are the most likely reason for increased susceptibility to infections in MD. Bhat *et al.* found low levels of natural killer T cells in a child with MD. (3) White et al. showed that silencing *ATP7A* expression attenuated bacterial killing, suggesting a role for *ATP7A*-dependent copper transport in the bactericidal activity of macrophages. (4)

Early treatment for MD with subcutaneous Copper Histidinate (CuHis) enhances survival and improves neurodevelopmental outcomes in MD. (1) CuHis received FDA FastTrack (2018) and Breakthrough (2020) designations from the US Food and Drug Administration. The European Medicines Agency Committee for Orphan Medicinal Products issued a positive opinion for an Orphan Drug Designation in 2020. CuHis treatment is currently available for individuals with Menkes disease in the United States through an expanded access clinical trial (NCT04074512). Our patient is enrolling in that trial. For updated preliminary results on subcutaneous CuHis treatment for Menkes disease, click here. The type and severity of the *ATP7A* pathogenic variant may partly

Table 1. Serum concentrations of copper and ceruloplasmin at diagnosis.

	0–3 months of age		**>3 months of age**	
	Menkes disease[a] (n = 8)	**Control**[b]	**Menkes disease (n** = 52)	**Control**
Copper (µg/dL)	16.4 ± 7.4 (8–30)	20–70	6.9 ± 3.4 (3–12)	75–150
Ceruloplasmin (mg/dL)	6.9 ± 3.4 (3–12)	5–20	7.4 ± 3.3 (2.8–20)	20–45

Caption: From Table 1 in Fujisawa et al. (2022)(2). [a]Data represent mean ± standard deviation; the range (minimum-maximum) is shown in parentheses. [b]Control values are based on the data from Kaler and DiStasio. (1)

influence response to early copper treatment. For maximum effectiveness, CuHis treatment should be started within four weeks of birth (corrected for prematurity/gestational age), which makes the early diagnosis of MD critically important.

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Newborn screening for Menkes disease is not included in the current Recommended Uniform Screening Panel(5), a list of disorders that the United States Secretary of the Department of Health and Human Services (HHS) recommends for states to screen as part of their state universal newborn screening (NBS) programs. Nevertheless, the feasibility of diagnosing MD through NBS has been demonstrated using a 544 gene panel designed for rapid genomic diagnostic evaluation of common phenotypes in newborns. Using this gene panel, Parad *et al*. applied next-generation sequencing in a blinded fashion to 22 dried blood spots from individuals known to have MD. They detected pathogenic variants in *ATP7A*, including copy number variants, in 95% of the affected patients (21/22).(6)

"Because the early signs of Menkes disease are underappreciated and nonspecific, newborn screening offers the best hope for its early diagnosis and treatment. Until then, the astute clinician should consider this diagnosis in males with fuzzy hair, frequent infections, failure to thrive, poor feeding or unexplained hypotonia."

Early diagnosis of MD in a sporadic (nonfamilial) case is rare. The combination of sparse, friable, and depigmented hair and hypotonia, common signs of MD in the newborn, do not demand urgent medical intervention. Because our patient presented at 3 ½ months of age, his diagnosis was not established within the optimal time period to initiate CuHis treatment. Eventually, it became clear that important clues to his diagnosis had been missed early in the course of his disease: his fair friable hair had not been appreciated as an important sign (pili torti). The family had downplayed it because his mother also had fair hair, and his hypotonia had been demoted to a secondary finding, a consequence rather than a cause of his multiple infections. When we framed his phenotype to conform to our expected diagnosis of primary immunodeficiency, it further delayed the diagnosis. A WES first approach was probably warranted in a delayed infant with multiple infections and failure to thrive.

Because the early signs of Menkes disease are underappreciated and nonspecific, newborn screening offers the best hope for its early diagnosis and treatment. Until then, the astute clinician should consider this diagnosis in males with fuzzy hair, frequent infections, failure to thrive, poor feeding or unexplained hypotonia.

Practical applications:

1. Remember that Menkes disease is not included in current Newborn screening protocols, so early diagnosis of this disorder relies on suspicion of an astute clinician. Consider Menkes disease in male newborns with nonspecific features of hypotonia, prolonged jaundice, hypothermia, or feeding problems, especially when scalp hair is kinky, sparse, fragile, or depigmented.
2. Recognize that serum copper and ceruloplasmin are lower in newborns with Menkes disease than in healthy newborns. Still, these values overlap because copper and ceruloplasmin are naturally lower in all infants in the first three months of life.
3. Understand that copper deficiency impairs the immune system, and infants with MD can present with recurrent infections.
4. Appreciate the importance of early diagnosis of Menkes disease and the benefits of starting treatment with copper-histidinate (CuHis) in the newborn period.

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