# Cu(e) the balancing act: Copper homeostasis explored in 5 siblings with variable clinical course

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Poster 595

## Objective

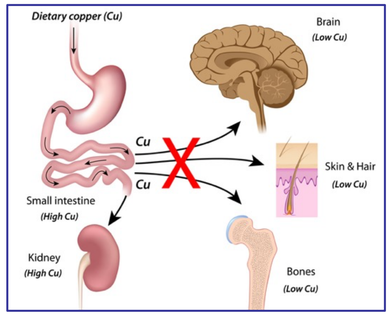
- Present a unique variation of phenotype and course in siblings with Menkes Disease (MD)

## Methods

- Review literature describing copper transport disorders
- Apply findings to our case of five affected siblings

## Background

- Mutations in ATP7A: copper deficiency (Menkes disease)
- Mutations in ATP7B: copper overload (Wilson disease)
- The amount of residual functioning copper transport influences disease severity as well as treatment response
- Phenotypes are influenced by the resulting deficient activity of cuproenzymes
- Early Cu(His) supplementation appears to lower risk of severe neuro-degeneration in some patients
- Treatment efficacy varies however, and depends on amount of functioning Cu transporters[1]




| Condition | Age of onset (years) | Neurological and other clinical signs | Biochemical findings | Molecular defects |
|---|---|---|---|---|
| Menkes disease | 0–1 | Hypotonia; seizures; developmental delay; coarse hair; jowly facies; lax skin and joints; decreased bone density; bladder diverticula; gastric polyps; vascular tortuousity and distension | Low serum copper and ceruloplasmin; abnormal plasma and CSF neurochemical levels; increased urine β2-microglobulin | Diverse mutations in *ATP7A*; 0–15% residual ATP7A function |
| Occipital horn syndrome | 3–10 | Dysautonomia;* slight reduction in muscle strength; coarse hair; occipital exostoses; hammer-shaped clavicular heads; lax skin and joints; bladder diverticula; vascular tortuousity and distension | Low to normal serum copper and ceruloplasmin; abnormal plasma and CSF neurochemical levels | Leaky splice junction or hypofunctional *ATP7A* missense mutations; 20–30% residual ATP7A function |
| ATP7A-related distal motor neuropathy | 5–50 | Atrophy and weakness of distal muscles; foot drop; decreased or absent deep tendon reflexes; abnormal nerve conduction studies;‡ pes cavus foot deformity; no other specific clinical abnormalities | No specific abnormalities | Missense mutations causing substitutions in or near transmembrane segments in carboxyl half of ATP7A; 60–70% residual ATP7A function |

*Syncope, dizziness, orthostatic hypotension, abnormal sinoatrial conduction, nocturnal bradycardia, and bowel or bladder dysfunction.
‡Decreased peroneal and median muscle amplitudes with normal conduction velocities.

## Case Presentation

- The graph below depicts the phenotypic spectrum seen in the 5 brothers
- Mom is a known carrier of ATP7A mutation
- There is limited information on the siblings who were not seen at UNC
- The 6th sibling is the youngest and is a healthy female infant (not included here)

| Sibling: birth order | Presentation | Exam | Diagnostic testing | Treatment Copper Histidine | Outcomes |
|---|---|---|---|---|---|
| 1 | O/AD: Infancy/12mos FTT, Seizures, DD | N/A | N/A | No | D: 16mos Brain hemorrhage |
| 2 | O/AD: Infancy/NA FTT | N/A | N/A | No | D: 13mos FTT, Meningitis |
| 3 | O/AD: 6yo/Birth FTT, DD, Ataxia and motor regression, Urogenital complications, Syncopal events, Food aversion 2/2 choking fear, Pyloric stenosis | - Macrocephaly<br>- Frontal bossing<br>- Mild dysmorphic features<br>- Pectus carinatum<br>- Ataxia (Speech, gait, hands)<br>- Low muscle tone<br>- Normal reflexes | Ceruloplasmin 7.1mg/dL (L)<br>Copper 0.20mcg/mL (L)<br>Vit C <0.1mg/dL (L)<br>CT head (2015): Unusually prominent CSF space ventral to brainstem and cerebellar hemispheres | Yes<br>- infancy to 3y<br>- 1 repeat course (not responsive) | L: motor regression<br>- Unable to ambulate unassisted |
| 4 | O/AD: 4yo/not tested FTT, Ataxia and motor regression, Urogenital complications, Syncopal events, Chronic b/l radial dislocations, Behavioral concerns | - Dysmorphic features: angular face, wide set eyes<br>- Muscle wasting<br>- Ataxia (Speech, gait, hands)<br>- Low muscle tone<br>- Normal reflexes | MRI brain (2017): Non-enhancing lesion within the left neck, possibly a lymphatic malformation<br>CT head (2017): Torturous intracranial vessels<br>Normal EKG, ECHO, EEG | Yes: infancy-3yo, 1 repeat course (responsive) | L: motor regression<br>- Unable to ambulate unassisted |
| 5 | O/AD: Infancy/Birth FTT, Seizures (Infantile spasms), Developmental regression | - Occipital flattening<br>- Hypotonia<br>- No contractures<br>- Malnourished | MRI brain: Foci of T2 hyperintensity in b/l frontal, parietal, temporal lobes<br>EEG: infantile spasms<br>Microarrary: Hemizygous deletion of the entire exon 1 within ATP7A gene | Yes: Neonatal period onward<br>- NIH Menkes study | D: 19 mos Severe malnutrition. |

O = Symptom Onset, AD = Age of Diagnosis, FTT: Failure to thrive
DD = Developmental delay, D =Deceased, L =living
Urogenital complications: Bladder diverticula, recurrent UTIs, VUR

## Discussion

- ATP7A mutations produce a clinical spectrum
- Siblings 1, 2, and 5 follow a more classic Menke's course, while siblings 3 and 4 exhibit a phenotypic variation
- This variation is suggestive of a milder form of Menkes such as occipital horn syndrome with residual copper transport function
- Siblings 3 and 4 had improvement with copper supplementation, however declined when off supplementation -suggesting residual ATP7A copper transport function
- In comparison, sibling 5 received Cu(His) twice daily since birth and had limited benefit -suggesting that he had minimal to no functioning transporters

## Conclusions

- Recognizing the unique clinical course in our patients is important in guiding management and providing appropriate genetic counseling.
- Importance of cuproenzymes should not be overlooked when treating Menkes
- Future research is indicated to clarify the affected common pathways and resulting phenotypic similarities.
- Sufficient copper delivery to the brain is essential for proper neurodevelopment. Therefore, early copper supplementation should be considered if concerned for Menkes

## References

1. Stephen G. Kaler. Nat Rev Neurol. 2011 January ; 7(1): 15–29. ATP7A-related copper transport diseases—emerging concepts and future trends
2. Kaler SG. Metabolic and Molecular Bases of Menkes Disease and Occipital Horn Syndrome. Pediatric and Developmental Pathology. 1998;1(1):85-98.
3. Borm B, Møller LB, Hausser I, Emeis M, Baerlocher K, Horn N, Rossi R. Variable clinical expression of an identical mutation in the ATP7A gene for Menkes disease/occipital horn syndrome in three affected males in a single family. J Pediatr. 2004 Jul;145(1):119-21..