Elesclomol-copper therapy improves neurodevelopment in two children with Menkes disease

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To the Editor: Menkes disease [MIM #309400] is a fatal copper (Cu) metabolism disorder caused by pathogenic variants in the X-linked *ATP7A* gene that encodes a Cu transporter. Currently, no FDA-approved drug exists, and clinical studies with copper histidine (Cu-His) treatment (1) have shown limited efficacy, with outcomes dependent on residual ATP7A activity and the timing of administration (2). Recent preclinical studies demonstrated that a Cu ionophore, elesclomol-copper (ES-Cu), significantly improves the Cu-deficiency phenotypes of a mouse model of Menkes disease (3) without inducing toxicity at therapeutic doses (4).

Here, we present clinical and therapeutic responses to ES-Cu in two children, NP#1 and NP#2, with Menkes disease (Supplemental Material Table 1). Both patients were diagnosed within the first days of life because of family history. The sequence variants predicted a frameshift in *ATP7A* mRNA and loss of full-length ATP7A protein, which was confirmed by western blotting and immunofluorescent staining of ATP7A in patients' skin fibroblasts (Supplemental Figure 1).

To evaluate the feasibility of treatment with ES-Cu, the Menkes International Association (MIa, https://menkesinternational.com) created the Copper(less) Committee. After carefully evaluating the potential risks and benefits, the Committee agreed that both patients were suitable candidates for ES-Cu treatment under an exceptional use clinical protocol authorized by the Spanish Agency of Medicines and Medical Devices.

ES-Cu was first administered to NP#1 at 20 months of age as a weekly subcutaneous injection adjunct to daily doses of Cu-His, which was withheld on days of ES-Cu administration to ensure the daily Cu dose did not exceed the RDA. Stage I involved dose escalation of ES-Cu, starting at 4 µg (0.4 µg/kg) and increasing to a maximum of 250 µg once-a-week. This dose was later adjusted to 125 µg weekly based on tolerability (Supplemental

Figure 2A). NP#2 started ES-Cu treatment at 2 months of corrected age. The initial dose for NP#2 was 6 µg and then escalated to a maximum of 140 µg (Supplemental Figure 2B). Both patients exhibited mild to moderate skin inflammation around the injection site, which partially responded to topical corticosteroids and oral ibuprofen (Supplemental Figure 2C). Ultrasound imaging revealed fat necrosis at injection sites. Overall, the medication was well-tolerated except for these injection-site side effects.

As an endpoint, we selected neurodevelopmental evolution with the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III). For NP#1, the Bayley-III test was administered every two months during the first year of treatment. Before starting ES-Cu, his scores in all domains were below the normal range (<5th percentile) except for receptive language (Figure 1A). After two months of ES-Cu treatment, we observed improvements in all domains, with the most striking improvements in cognitive, expressive language, and fine motor domains, which reached normal percentile ranges by ten months of treatment, though improvements in the gross motor domain occurred later (Figure 1A). The patient is now 57 months old, walks freely without orthopedic support, is able to run, converses with several back-and-forth exchanges, knows several colors, and can count up to 12.

NP#2 started ES-Cu treatment at 2 months of corrected age when baseline Bayley-III scores of all domains were rated within the normal range (Figure 1B). The goal was to maintain normal ranges during treatment without experiencing delays or loss of developmental milestones associated with Menkes disease. At 29 months corrected age, NP#2 remained within normal ranges across all domains except gross motor. Lower percentiles in the language domain could be due to a discrepancy in the patient's primary language (Arabic) and the language used for administering the Bayley-III tests (Spanish).

A comparison of neurodevelopmental status at 20 months of age, at which NP#1 received his baseline evaluation before starting ES-Cu treatment, and NP#2, who had received treatment for 18 months, suggests that early initiation of ES-Cu may lead to additional clinical benefits (Figure 1C-E).

After three months of ES-Cu treatment, NP#1 showed pili torti, trichorrhexis nodosa, and a lack of melanin granules (Supplemental Figure 3A-C). Notably, after 19 months of treatment, pili torti were reduced, and melanin granules were observed in the hair structure (Supplemental Figure 3D-F). Similarly, at baseline and 16 months of corrected age, NP#2's hair did not contain melanin granules, but they appeared at 22 months of corrected age (Supplemental Figure 3G-I). 3D structural analysis and autofluorescence imaging by confocal microscopy in NP#1 demonstrated improvements in hair structure (Supplemental Figure 3J-M).

Overall, blood Cu and ceruloplasmin levels remained relatively stable in the lower normal range for both patients (data shown for NP#1 in Supplemental Figure 3N). For NP#1, dopamine remained normal, and norepinephrine and epinephrine remained low (Supplemental Figure 3O). Additionally, Cu and biogenic amines related to catecholamine metabolism, such as HVA/MHPG, were measured in CSF of NP#1 at weeks 17 and 69 (Supplemental Table 1). Cu was detected at both time points (5 µg/L at week 17 and 2.1 µg/L at week 69; normal range: 4.2-19 µg/L), and HVA/MHPG ratios were 13 and 16.8 nmol/L, respectively (normal range: 5-30 nmol/L).

Our findings suggest that ES-Cu has therapeutic benefits on various tissues, particularly the brain, implying that ES-Cu can facilitate Cu delivery across the blood-brain barrier. However, we found that connective tissue defects persist, resulting in lung disease, brain vascular tortuosity, and bladder diverticula. These are likely related to insufficient metallation

of lysyl oxidases, which cross-link collagen and elastin. In summary, our results with ES-Cu, combined with Cu-His, provide preliminary evidence of the safety and efficacy of this promising treatment regimen for Menkes disease, however, a future clinical trial with additional patients is required to fully assess the therapeutic benefits.

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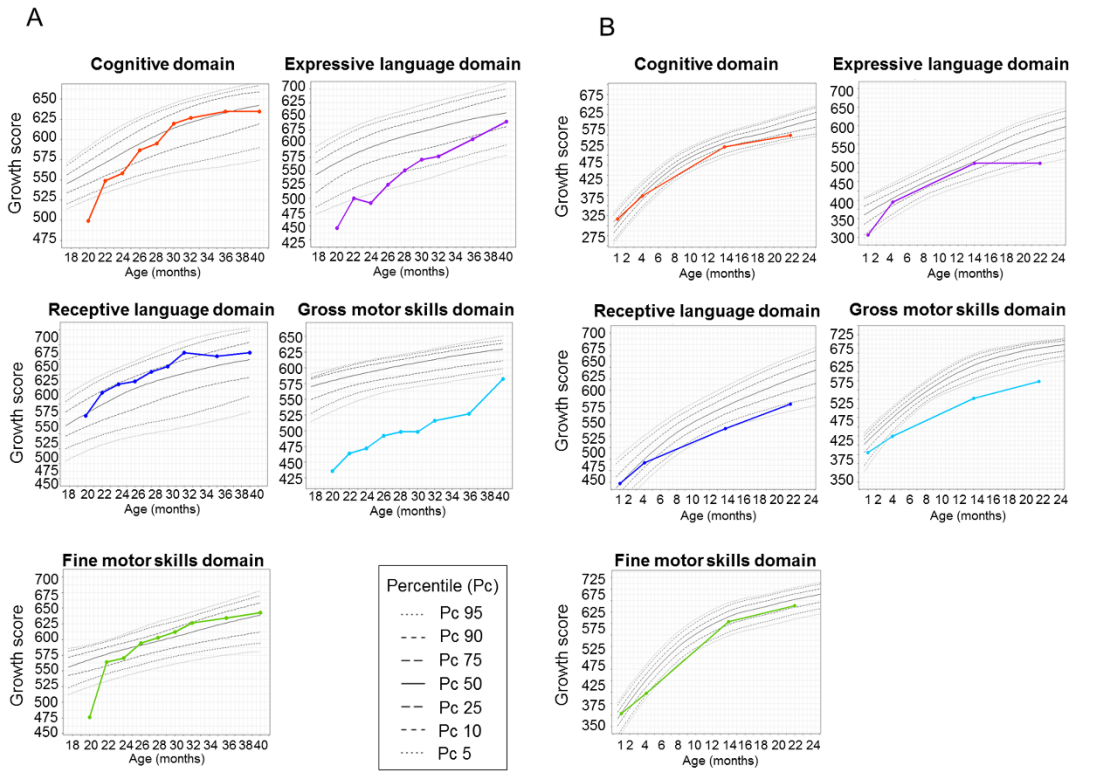
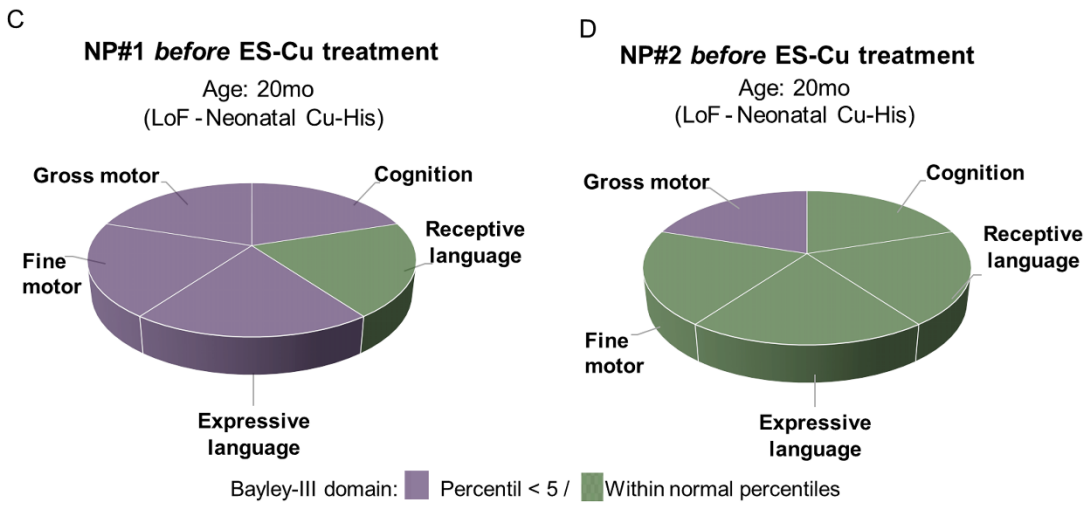

A
Cognitive domain
Expressive language domain
Receptive language domain
Gross motor skills domain
Fine motor skills domain
Growth score
Age (months)
Percentile (Pc)
Pc 95
Pc 90
Pc 75
Pc 50
Pc 25
Pc 10
Pc 5
B
Cognitive domain
Expressive language domain
Receptive language domain
Gross motor skills domain
Fine motor skills domain
Growth score
Age (months)


C
NP#1 before ES-Cu treatment
Age: 20mo
(LoF - Neonatal Cu-His)
Gross motor
Cognition
Receptive language
Fine motor
Expressive language
D
NP#2 before ES-Cu treatment
Age: 20mo
(LoF - Neonatal Cu-His)
Gross motor
Cognition
Receptive language
Fine motor
Expressive language
Bayley-III domain:
Percentil < 5 /
Within normal percentiles

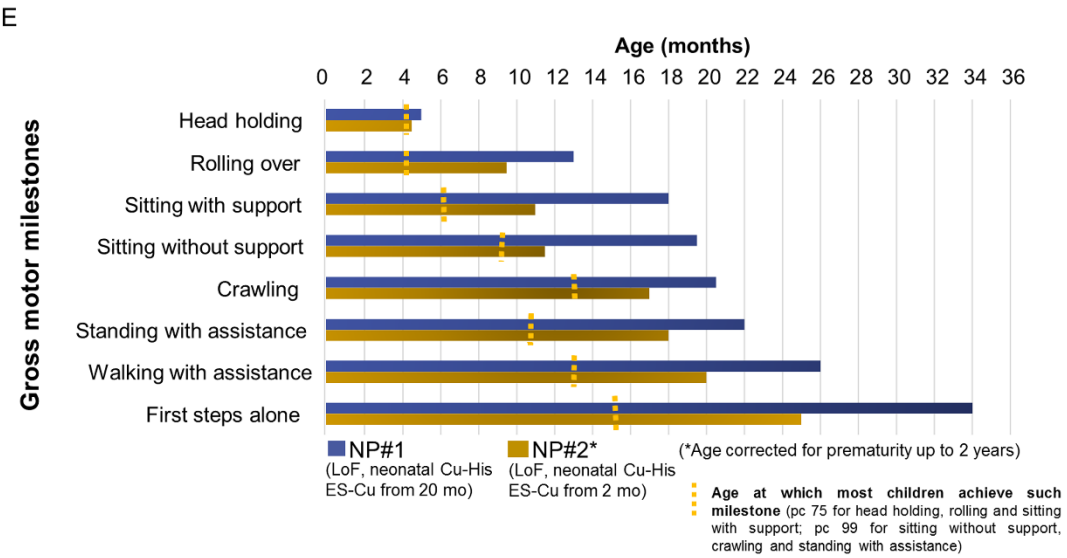

E
Age (months)
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36
Gross motor milestones
Head holding
Rolling over
Sitting with support
Sitting without support
Crawling
Standing with assistance
Walking with assistance
First steps alone
NP#1
(LoF, neonatal Cu-His ES-Cu from 20 mo)
NP#2*
(LoF, neonatal Cu-His ES-Cu from 2 mo)
(*Age corrected for prematurity up to 2 years)
Age at which most children achieve such milestone (pc 75 for head holding, rolling and sitting with support; pc 99 for sitting without support, crawling and standing with assistance)

Figure 1. Evolution of neurodevelopmental milestones in NP#1 and NP#2 following the treatment with ES-Cu. (**A** and **B**, respectively) Measurements for each neurological domain were taken using the Bayley-III scale. (**A**) For NP#1, evaluations occurred every two months during the first 20 months (from 20 to 40 months of age), while (**B**) NP#2 was assessed at four intervals. (**C and D**) Comparison of Bayley-III domain scores at age 20 months between NP#1 and NP#2. NP#1's scores. **(E)** Comparison of gross motor milestones acquisition between NP#1 and NP#2. LoF: loss of function.