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Case Report

A severe case of Menkes disease with repeated bone fracture during the neonatal period, followed by multiple arterial occlusion

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Abstract

Menkes disease (MD) is a lethal infantile neurodegenerative disorder with X-linked inheritance, characterized by progressive neurodegenerative symptoms caused by pathogenic variants in the ATP7A. Early diagnosis and treatment are important, although the diagnosis is difficult prior to 2 months of age. We present an unusually severe case of MD with skull fractures at the birth and repeated fractures during the neonatal period, with further examinations leading to diagnosis. The patient died due to hemorrhagic shock, due to multiple arterial occlusion despite initiation of copper-histidine therapy in early infancy. Bone fracture at birth and multiple arterial occlusion are very rare findings in MD. This unusual and severe presentation emphasizes the importance of early diagnosis and treatment. A congenital bone fracture should be considered as a possible presentation of MD, especially in cases without birth complications.

Keywords: Menkes disease; Skull fracture; Bone fracture; Cerebral infarction; Arterial occlusion

1. Introduction

Menkes disease (MD) is a lethal infantile neurodegenerative disorder with X-linked inheritance, characterized by progressive neurodegenerative symptoms caused by pathogenic variants in the ATP7A transporter. The clinical features include developmental delay, seizures, marked muscular hypotonia and hair abnormalities including kinky hair. A lack of copper-induced lysyl oxidase leads to unstable connective tissues structures such as bladder diverticula, osteoporosis, skin and joint laxity, arterial abnormalities, and bone fracture [1,2]. Only a few reports have described patients presenting with fractures at birth, and previously reported patients were diagnosed with MD at 3 months of age or later [3–5]. We describe herein an unusually severe case of MD with skull fracture at birth. The diagnosis was made due to repeated fractures during the neonatal period, followed by multiple arterial occlusion.

2. Case report

The male child was born (2960 g) by normal vaginal delivery at 39 weeks of gestation with no complications during pregnancy. His 4-year-old brother was healthy.

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He was admitted to the neonatal intensive care unit (NICU) of our hospital at 1 day of age because of a cephalohematoma that was found immediately after birth and that gradually increased. On admission, the head CT showed a left parietal skull fracture and a right parietal–occipital skull fracture with a subdural hematoma (Fig. 1). The blood tests, including serum chemistry analysis, complete blood count, and coagulation test, were normal. Physical and neurological findings were normal except for the hematoma. After admission, conservative follow-up care was performed. Poor movement of the right upper extremity was observed at 12 days of age, and a fracture of the right humerus was revealed (Fig. 1). Additional examinations performed to identify a cause for the repetitive fractures showed low serum copper (16 μg/dl (normal: 68–128 μg/dl)) and ceruloplasmin levels (11 mg/dl (normal: 21–37 mg/dl). Serum lactate and pyruvate levels were elevated (36.0 mg/dl and 1.46 mg/dl, respectively). The presence of pale skin and kinky hair were also noted (Fig. 1). The diagnosis of MD was confirmed by the high copper concentration in the fibroblasts (68.8 ng/mg protein (control 19.43 ± 0.97 ng/mg protein)) and a high urine homovanillic acid/vanillylmandelic acid ratio (12.8 (control: <4.0)) [6]. However, ATP7A gene analysis showed no mutation in any exon of the ATP7A gene.

Ophthalmologically, strabismus, abnormal retinal vessels, and blue irides were absent. Electroencephalography was normal; clinical seizures were absent. Ultrasound did not reveal bladder diverticula. No Wormian bones and no rib fractures were evident, although metaphyseal spurring of the lower ends of the femur, ulna, and radius were apparent on radiography. We noted no inguinal or umbilical hernia.

Subcutaneous copper-histidine injection was started at 37 days after birth. The serum levels of copper reached normal levels (Fig. 2), and the hair abnormalities improved upon copper-histidine injections. At 84 days, facial pallor and decreased activity with no clinical cause were noted after he was discharged at 75 days of age. He was admitted to the ICU due to decreased consciousness (GCS score 5/15 (E1V1M3)) with an extremely distended abdomen and peripheral coldness. The blood examination showed remarkable anemia at Hb 5.3 mg/dl. Abdominal CT showed a retroperitoneal hematoma, which was considered to have led to hemorrhagic shock. On enhanced CT, multiple arterial occlusion or stenosis of the superior mesenteric, left renal,

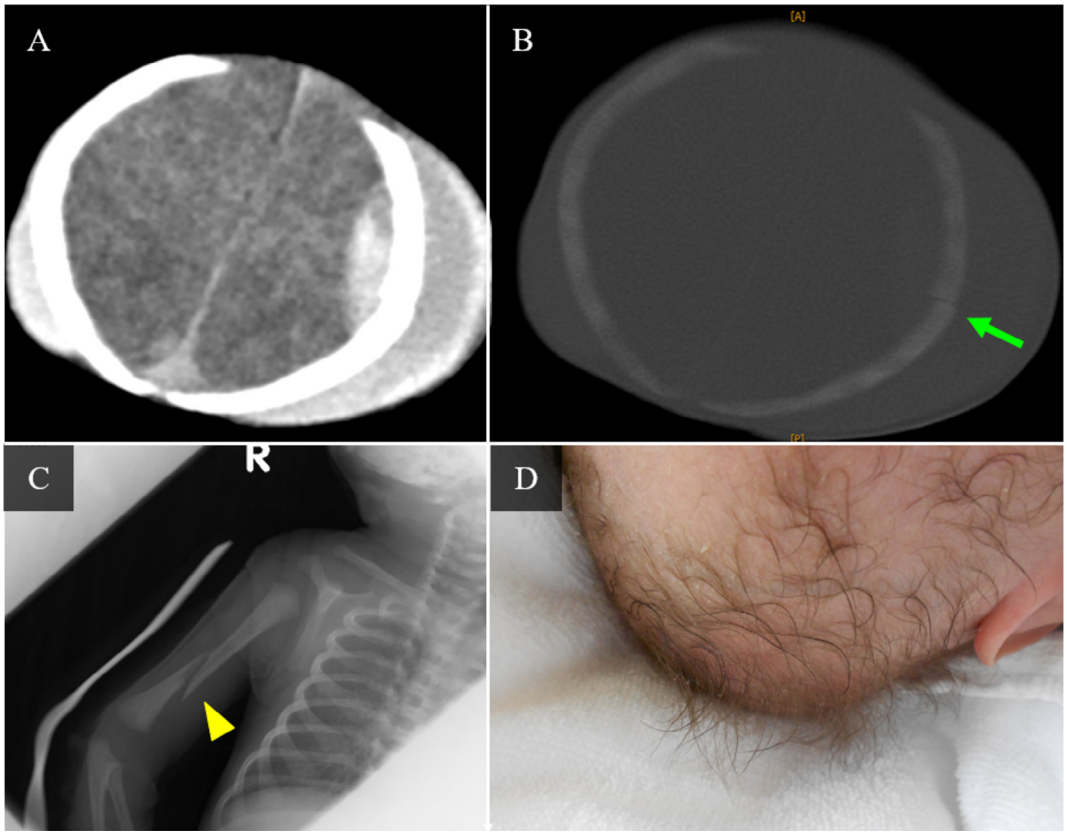

Fig. 1. Brain CT at 1 day of age shows cephalohematoma and subdural hematoma (A) and left parietal and right parietal–occipital skull fracture (arrow) (B). Frontal right humerus radiograph (C) at 12 days of age. Note the apparent right humerus fracture (arrow head). Kinky hair of the patient at 28 day of age (D).

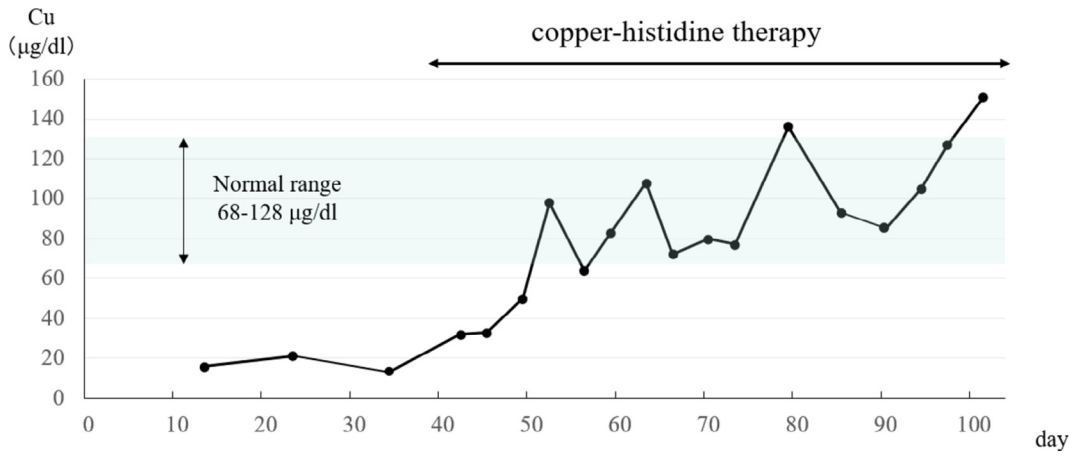

Fig. 2. The value of serum copper level shows copper-histidine therapy normalized serum copper levels.

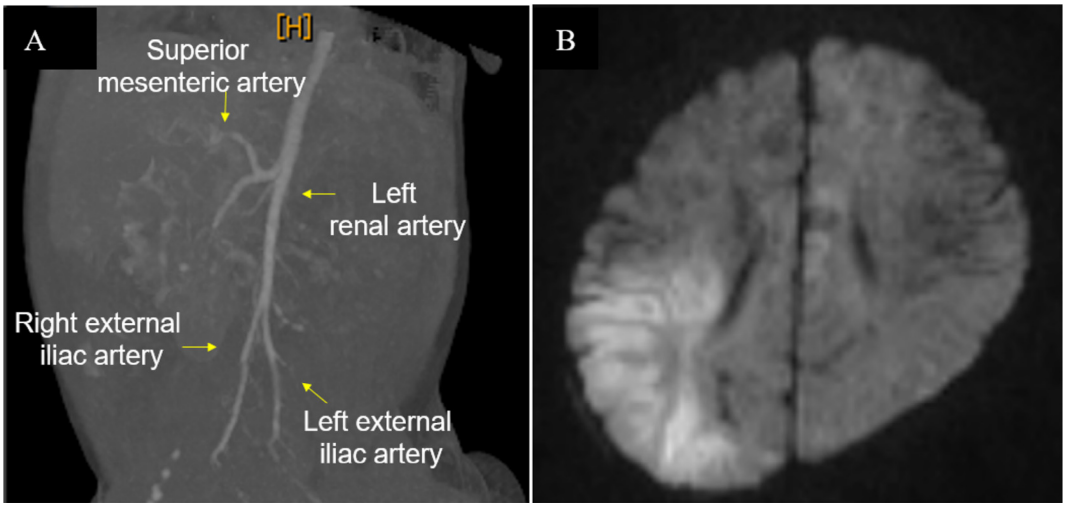

Fig. 3. At 85 days after birth, 3-dimensional CT image (A) shows occlusion and stenosis of the superior mesenteric, left renal, and bilateral external iliac arteries. On DWI MRI images, a right median cerebral artery infarction is visible (B).

and bilateral external iliac arteries were observed (Fig. 3). A right median cerebral artery infarction was identified on the brain MRI (Fig. 3). Although cardiovascular and respiratory care were performed, he died due to hemorrhagic shock by abdominal re-bleeding at 103 days of age. Informed consent was obtained from the patient's parents for publication of this report.

3. Discussion

MD is a congenital copper metabolism disorder with characteristic clinical features including severe neurological degeneration, abnormal hair, hypothermia, and connective tissue disorders. Because clinical abnormalities are absent or subtle in affected newborns, the diagnosis is difficult prior to 2 months of age when copper deficiency becomes advanced [1,2]. In our case, the diagnosis of MD was made due to bone fractures during NICU hospitalization. Only three papers have previously reported MD patients with fractures at birth; two underwent normal vaginal deliveries, and one was born by caesarian section. However, each case was subsequently diagnosed with MD due to other symptoms. Clinical findings of "seizures, abnormal skin, sparse hair, and hypothermia", "intractable seizures and growing wiry hair", and "seizure, bladder diverticula, and hair abnormalities" in addition to bone fractures at birth have been reported as features leading to a diagnosis of MD at 3 months [3], at over 20 weeks [5], and at 10 months [4], respectively (Table 1). These cases suggest that it is difficult to diagnose, or even to consider, MD based only on clinical findings of fracture at birth. Although skull fracture may occur even with spontaneous vaginal delivery, linear skull fracture is an unusual complication in normal neonates, occurring in only 0.06 cases per 1000, making it very rare compared with cephalohematoma (15.7 per 1000) [7].

Table 1
MD patients exhibiting fractures at birth.

	Our case	Ubhi et al. (2000)	Freidl et al. (2015)	McPherson et al. (2018)
Gestational age (weeks)	39	Term	38	35
Birth weight (kg)	2.96	N/D	2.79	2.3
Sex	Male	Male	Male	Male
Form of delivery	Vaginal delivery	Vaginal delivery	Cesarean section	Vaginal delivery
Chief complaint	A marked cephalohematoma	Abnormally shaped head and hands; 'tissue-paper' skin; micrognathia; bilateral positional talipes; hypotonia; low-set ears	Crepitation of the cranium; contour disruption with a hematoma	Occipital swelling
Fracture findings	Left parietal and right parieto-occipital skull fractures with a subdural hematoma	Parietal fracture with an underlying hematoma and extensive extracranial soft-tissue swelling	Right parieto-occipital fractures with intracerebral bleeding	Extensive comminuted and displaced skull fractures with extensive subgaleal bleed
Symptoms prior to diagnosis of MD	–	Seizures	Seizures, pathologies of the trabecular urinary bladder, and diverticula	Seizures
Age of diagnosis with MD	About 2 weeks	3 months	10 months	Later than 20 weeks
Diagnostic pointers	Repetitive fractures	Abnormal skin, sparse hair, hypothermia	Lusterless wiry hair resistant to combing	Wiry hair

-, Absent; N/D, no data; MD, Menkes disease.

Arterial abnormalities have been reported as reflecting connective tissue changes in MD [1,2]. In our patient, multiple arterial occlusion and stenosis were recognized, and sudden hemorrhagic shock occurred. Although the cause of such episodes is unclear, spontaneous retroperitoneal hemorrhage has been described previously in patients with MD [8]. This report postulated that the formation of the hematoma was caused by intermittent bleeding of the friable and tortuous abdominal vessels over time. We speculated that multiple arterial occlusion and stenosis happened due to the spontaneous occurrence of retroperitoneal hemorrhage. Connective tissue disorders, which are attributed to decreased activities of lysyl oxidase, the key copper-dependent enzyme that works in elastin and collagen cross-linking, are a major part of MD symptomology. Subcutaneous copper-histidine therapy cannot improve the activities of lysyl oxidase because the administered copper is not transported to the Golgi apparatus, where lysyl oxidase combines with copper to function [1,2].

Although a genotype–phenotype correlation was reported upon ATP7A genetic analysis, 4 of 62 (6%) MD patients had no detectable mutations in the ATP7A gene [9]. ATP7A genetic analysis revealed no previously reported mutation, although our patient presented with a more severe phenotype than is commonly encountered. It may be that mutation of the promoter or an intron caused the complete absence of ATP7A activity.

Hemorrhagic shock and multiple arterial occlusion could not be prevented, even though copper-histidine therapy was started at 37 days of age. Treatment must be initiated before 2 months of age to improve neurological outcomes, as copper can be transported to neurons through the immature blood–brain barrier during this period [10]. Thus, early diagnosis of the disease is crucial. A congenital bone fracture should be considered as a possible presentation of MD, especially in cases without birth complications.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2019.06.005.

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