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Clinical note

Long surviving classical Menkes disease treated with weekly intravenous copper therapy

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ABSTRACT

Menkes diseases (MD) is an X-linked recessive neurodegenerative disorder of copper metabolism, characterized by progressive multisystemic involvement. Death in the early childhood is usually observed in classical patients. Although a definite cure has not been established, copper replacement therapy administered parenterally may modify the severity of MD and permitted survival into adolescence. Subcutaneous copper-histidine supplementation is the current choice of therapy, and long-term administration is not desirable because of the expected nephrotoxicity. We report here the case of a 29-year-old male with MD who tolerated long-term intravenous copper therapy initiated at 2 months. Molecular analysis revealed hemizygous deletion mutation of *ATP7A* previously reported in classical MD. Although neurodevelopement is poor, no major event of central nervous system is observed, and he enjoys a good social life by interacting using gestures. Optimum management is unknown, and closed follow-up is mandatory for clarification of this phenotype.

1. Introduction

Menkes disease (MD) is an infantile onset inherited metabolic disorder of copper homeostasis. This neurodegenerative disorder is caused by dysfunction of the X-linked *ATP7A* gene, which encodes a highly conserved copper-transporting ATPase [1]. The typical clinical course of MD is progressive with multisystemic involvement in nature, and death in early childhood is usually seen in classical MD patients [2].

As features of MD are consistent with the reduced activities of copper-requiring enzymes, providing exogenous copper might theoretically restore the normal intracellular copper metabolism. Early parenteral supplementation may correct some of the neurological symptoms [1]. We herein report a case of surviving classical MD adult patient who tolerated long-term intravenous copper supplementation. Clinical course, as well as radiographic evaluation and clinical features are described.

2. Patient and results

2.1. Patient

The proband is a 29-year-old male born after 37 weeks of gestation to healthy non-consanguineous parents. His birth weight was 3050 g (+ 0.88SD), and the head circumference was 35.0 cm (+1.70SD). He had an elder brother with MD who died at 8 years of age following a severe neurodegenerative course. Physical examination at neonatal period showed hypotonia, sparse scalp hair, pale skin and expressionless appearance. Low plasma level of copper (12 μg/dL; normal range 78–131) and ceruloplasmin (7 mg/dL; normal range 15–28) led to the diagnosis of MD at 2 months.

Recurrent epileptic spasms occurring in clusters was noted at 6 months, and electroencephalogram demonstrated typical pattern of hypsarrhythmia. A diagnosis of symptomatic West syndrome was made, and administration of pyridoxine and clonazepam was successful in terminating the seizures at 9 months. At 5 years, focal onset seizure with impaired awareness showing eye deviations were observed. Good seizure control was achieved after 9 years after valproate was added.

He was treated for recurrent respiratory infections since 4 years old.

Abbreviations: MD, Menkes disease; CT, computed tomography; MR, magnetic resonance

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Genitourinary evaluation revealed bladder diverticula at age 5, and he was diagnosed as having neurogenic bladder at age 11 necessitating intermittent urinary catheterization and bladder washing. He had chronic diarrhea and experienced paralytic ileus several times during gastrointestinal infection at age 15-17. He was also diagnosed with asthma, and nocturnal noninvasive positive-pressure ventilation was commenced from 23 years. He had fracture of the right humerus bone at age 28 years as a consequence of osteoporosis treated conservatively. Examination at age 29 years shows generalized hypotonia, marked kyphoscoliosis, pale complexion, dry skin, and coarse hair. He had a small stature with body height of 140.0 cm, and body weight of 18.1 kg. He was bedridden, and marked cutis laxa, prominent proximal joints hyperextensibility, and contractures of distal joints with reduced muscle mass and strength was observed. Although verbal communication was not achieved, communication using gestures was possible.

Copper acetate was commenced immediately after diagnosis at 2 months with intravenous copper acetate administered twice a week, which was reduced to once a week after three years of age. There was good biochemical response, judging from the constant monitoring of plasma copper and ceruloplasmin. At 5 years, his treatment regimen was changed to weekly intravenous copper chloride. Constant monitoring of kidney and liver function shows normal findings. Renal function test at 29 years old showed slight renal dysfunction (serum creatinine 0.42 mg/dL, cystatin C 1.04 mg/dL, eGFR 82 mL/min/1.73 m^2), with proteinuria (128 mg/mmol creatinine). Discontinuation of copper supplementation is being considered.

2.2. Results

Routine skeletal radiograph showed profound scoliosis, metaphyseal-diaphyseal flaring, delayed epiphyseal closure and bone age, and severe deformity of the joints with dislocation (Fig. 1A–D). Bladder diverticula (Fig. 1E) and prominent bilateral occipital exostoses (Fig. 1F) can be confirmed from computed tomography (CT). Intracranial magnetic resonance (MR) imaging demonstrated old cerebral infarction in the right frontal lobe and cerebral atrophy (Fig. 1G). Contrast enhanced CT angiography showed the usual reported intracranial cerebral changes (Fig. 2A), increased vascular tortuosity in the carotid arteries (Fig. 2B), and also the major branches of abdominal aorta (Fig. 2C).

Genetic analysis was carried out after obtaining parental written informed consent. Direct sequencing of all 23 exons of *ATP7* was conducted as previously reported [3]. A hemizygous 4011_4013delTCT mutation in exon 21, reported in classic MD was detected [3].

3. Discussion

This case presented clinical features and radiologic findings of a surviving adult classic MD patient, describing valuable adult phenotype of a neurodegenerative disorder in which death at the early childhood is usually inevitable. Despite prominent involvement of bones and soft tissues, central nervous system is relatively spared without major ischemic or hemorrhagic events, with only one asymptomatic cerebral infarction of unknown period observed. Although he shows severe physical and mental retardation, no development regression is observed and he enjoys a good social life by interacting using gestures. It might be possible that central nervous system reacted favorably to copper replacement.

The prominent vascular and skeletal abnormalities noticed in the adulthood reflected MD as a progressive connective tissue disorder. Vascular tortuosity was confirmed in major vessels, indicating a generalized systemic involvement. Neuroradiological and skeletal characteristics of MD had been comprehensively reported, however, most of these are of the infantile and early childhood findings [4]. Our radiographic evaluation showed that disease progression in the adulthood causes more severe bone deformity and higher index of vessels tortuosity. Delayed epiphyseal closing is a prominent radiological feature observed. Inadequate favorable reaction to copper replacement to correct the enzymatic dysfunction of lysyl oxidase needed in elastin and collagen cross-linking might have cause these observations [1].

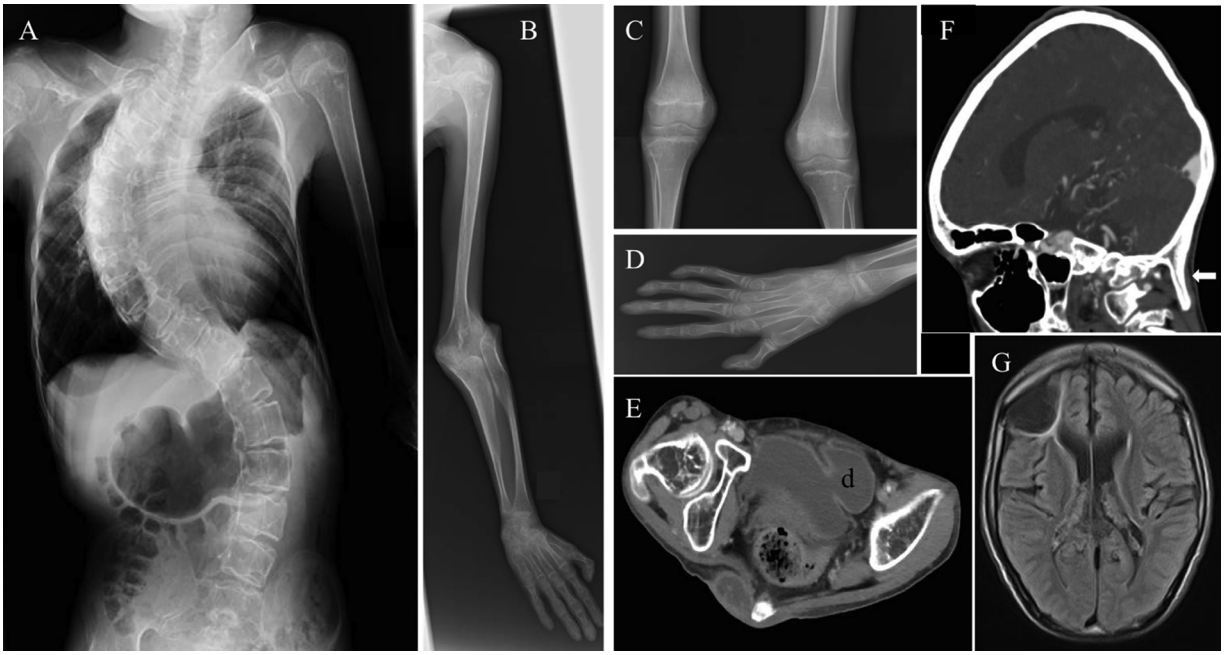

Fig. 1. Radiographic evaluation of the patient at the age of 29 years old. **A,** severe scoliosis, chest wall and clavicle deformity, with widening of the distal ends. **B,** long bones of the arms show areas of uneven sclerosis, and significant metaphyseal and diaphyseal flaring of ulna and radius causing severe joint deformity. **C,** epiphyseal plates seen in long bones of the lower limbs indicating delayed epiphyseal closure and delayed bone age. **D,** delayed epiphyseal closure of the hand bones indicating delayed bone age. **E,** Abdominal CT showing diffuse bladder wall thickening with diverticulum (d). **F,** Cranial CT showed prominent occipital exostoses (arrow). **G,** Intracranial MRI (axial T2-FLAIR with motion correction image) showing old cerebral infarction in the right frontal lobe with generalized cerebral atrophy.

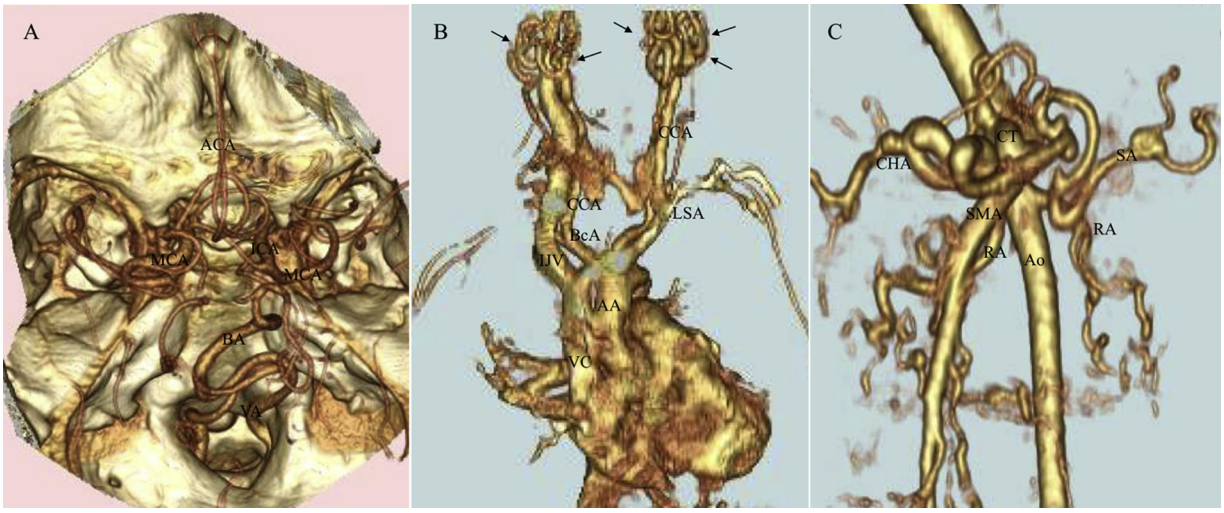

Fig. 2. Computer-generated three-dimensional reconstruction by volume rendering of major vessels obtained by contrast-enhanced CT at 23 years old. **A,** intracranial artery tortuosity was prominent. **B,** marked vascular tortuosity observed in bilateral carotid arteries (arrows). **C,** significant arterial tortuosity observed in branches of abdominal aorta (Ao), centered on celiac trunk (CT). ACA, anterior cerebral artery; ICA, internal carotid artery; MCA, middle cerebral artery; BA, basilar artery; VA: vertebral artery; CCA, common carotid artery; LSA: left subclavian artery; BcA: brachiocephalic artery; IJV: internal jugular vein; AA: aortic arch; VC: vena cava; CHA: common hepatic artery; SA: splenic artery; SMA: superior mesenteric artery; RA: renal artery.

Recent research showed favorable response to copper replacement treatment with better neurological outcomes in patients with *ATP7A* mutations retaining some capacity for copper transport [2,5]. Genetic analysis of our classic MD patient showed previously reported 4011_4013delTCT mutation, with predicted skipping of exons 20 and 21 [3]. It might be possible that skipping of exons producing in-frame deletions resulting in truncated protein variants might result in better treatment response [1], dictating some residual activity for copper transport at least observed in the brain. In contrast, the progressive connective tissues involvement indicated that enzymatic copper replacement in lysyl oxidase might not be present. Functional analysis should be considered in future for prediction of mutation effect on the clinical phenotype.

Copper-histidine supplementation is the most preferred treatment agent currently. Several reports had shown that positive neurologic outcome is dependent on early initiation and *ATP7A* mutations with retained capacity for copper transport [2,5]. More than 3 years of copper administration is usually not desirable because of the expected nephrotoxicity [2]. This patient was treated with weekly intravenous copper chloride and tolerated the procedure well with no major adverse effects. The relationship of his survival into the adulthood with the unconventional treatment regimen remains to be controversial. Discussion on discontinuation of therapy is on-going.

4. Conclusion

We presented the phenotype of a long-surviving adult classical MD patient who tolerated long-term intravenous copper supplementation. Radiologic evaluation showed marked abnormalities of the skeletal and vascular system, substantiating MD as a progressive connective tissue disorder, even after treatment with normalization of copper level. The reason for his long survival is unknown, however genotype and the effects of long-term weekly supplementation might offer possible hints. Optimum management of long-term survival of classical MD patients is currently unknown, and closed follow-up is mandatory for clarification of this phenotype.

Conflict of interest

The authors declare no conflict of interest.

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Transparency document

The Transparency document associated with this article can be found in the online version.

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