Internal carotid artery aneurysms in a 22-month-old boy with Menkes disease: a case report

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Menkes disease (MD) is an X-linked recessive multisystem disorder of copper metabolism. Patients with MD present a wide range of manifestations including kinky hair, dysmorphic faces, osteoporosis, hypothermia, hypoglycemia, feeding difficulties, autonomic dysfunctions, seizures, neurological deterioration, and developmental delay. Patients usually exhibit a progressive clinical course with various adverse events and die within 3 years. Although the early diagnosis is quite challenging because of the subtle clinical presentation, prompt management is crucial to reduce morbidity and mortality. Here, we present a rare case of internal carotid artery aneurysms in a 22-month-old boy with MD. It was found incidentally during a trial of sonography-guided central venous catheter insertion.

Keywords: Menkes kinky hair syndrome; Aneurysm; Genes; X-linked; Pediatrics

INTRODUCTION

Menkes disease (MD) is a fatal multisystem disorder associated with genetically impaired copper metabolism. Mutations in the ATP7A gene result in disturbances of ATP7A functions, including control of copper export, intracellular copper trafficking, and delivery to copper-dependent enzymes [1-4]. Consequently, MD leads to characteristic clinical phenotypes such as progressive neurodegeneration and marked connective tissue dysfunction. Furthermore, patients severely affected by MD experience multiple complications and eventually die, usually before the third year of life [5]. In this report, we describe rare vascular complications in a child with MD.

The requirements for approval of the Institutional Review Board of Asan Medical Center (No. 2024-0727) and informed consent were waived.

CASE REPORT

A 22-month-old boy was admitted to Asan Medical Center Children’s Hospital for a regular nephrostomy tube change. His growth parameters showed a weight of 10.0 kg (5th to 10th percentile) and length 78.7 cm (< 3rd percentile). His medical history was significant for MD. At the age of 60 days, he presented with seizures accompanied by features such as kinky hair, hypotonia, and osteoporosis. Subsequent laboratory findings re-
revealed a serum copper level of 3 µg/dL and ceruloplasmin level of < 3.0 dL. Molecular genetic testing included a whole-exome sequencing study, which identified an ATP7A mutation (c.2323G > T [p.Gly775Ter]), leading to the diagnosis of MD. He was transferred to our hospital to receive copper histidine supplementation at age 3 months. Initial brain magnetic resonance imaging and head angiography were compatible with MD, showing symmetric diffuse increased signal intensity of the bilateral basal ganglia (especially globus pallidus), abnormal gyral swelling with increased T2/fluid-attenuated inversion recovery signal intensity of the bilateral frontal-parietal-temporal lobes, and tortuous intracranial arteries. During follow-up, he developed progressively intractable seizures, multiple fractures, and large bladder diverticula, complicated by obstructive uropathy with obstruction of both ureteropelvic junctions. The management of these complications included left percutaneous nephrostomy (PCN) at age 14 months. Tracheostomy was also performed at age 14 months due to combined severe laryngomalacia and recurrent apnea associated with seizures. Subsequently, the left PCN tube was regularly changed every 4 months. Peripheral intravenous line access was attempted after admission for the second change of the PCN tube. However, due to tortuosity of the vessels, it was difficult to place a proper peripheral intravenous line, and multiple trials resulted in several long bone fractures due to severe osteoporosis. Consequently, it was decided to insert a central line. Before insertion of a sonography-guided central venous catheter into the internal jugular vein, ultrasound evaluation of the neck was performed, which incidentally detected a huge saccular hypoechoic lesion (2.4 cm × 2.8 cm) in the right neck (Fig. 1). A subsequent neck computed tomography scan with angiography showed that tortuous bilateral carotid arteries and markedly dilated vascular aneurysms in the bilateral neck were communicating with the internal carotid arteries (ICAs) (Fig. 2). Concerned about sudden rupture or thrombosis of the ICAs, we consulted an interventional radiologist and a vascular surgeon. However, due to the patient’s small body and vessel size and limited life expectancy, aggressive intervention or surgical management was refused. We decided to provide supportive care and regular follow-up without any other intervention. His PCN change was performed smoothly on hospital day 6. Due to the recurrent vascular access problems and for the regular PCN change procedures, a permanent central venous Broviac catheter was inserted and he was discharged. Five months later, he presented to the emergency room with a chief complaint of color change and enlargement of both sides of the neck. Point-of-care ultrasound showed that both ICA aneurysms were markedly enlarged and measured up to 10 cm on the right side and 6 cm on the left side with an internal echogenic swirling pattern of fluid movement. Blood testing revealed a hemoglobin level of 5.0 g/dL, which was significantly decreased from 8.9 g/dL at the time of his third regular admission for PCN change 1 month earlier. Since his family understood his desperate situation and that it could not be managed, they agreed to a “do-not-resuscitate” status. He was then transfused with packed red blood cells and discharged. Several days later, his mother reported his death, likely due to upper airway compression by the bilateral

Fig. 1. Carotid ultrasonography: (A) B-mode and (B) color Doppler images show bilateral saccular hypoechoic lesions in the neck, indicating aneurysmal dilatation of the internal carotid arteries.

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enlarged ICA aneurysms.

DISCUSSION

MD is a copper metabolism disorder secondary to a mutation in the ATP7A gene located on Xq13.3. This gene encodes ATP7A, a transmembrane active copper transporter protein [3, 6]. A deleterious mutation in this gene results in generalized copper deficiency. Copper is required for the biochemical functions of several enzymes, including those involved in cellular respiration (cytochrome C oxidase), neurotransmitter biosynthesis (dopamine beta-hydroxylase), cross-linking of elastin and collagen (lysyl oxidase [LO]), melanin production (tyrosinase) and free-radical scavenging (superoxide dismutase) [1, 2, 5, 7]. As these enzymes are abundantly expressed, their dysfunction characteristically manifests with multisystemic symptoms. However, until age 2 months, there are often nonspecific symptoms such as cephalohematoma, hypoglycemia, hypothermia, and prolonged jaundice, which frequently delay the diagnosis [5]. Neurologic manifestations such as seizures and developmental delay usually present within 2 to 3 months. These characteristic symptoms progress following different stages [8]. In addition, connective tissue dysfunction, skeletal problems, and urological complications are very common including tortuous blood vessels, osteopenia, multiple fractures, bony deformities, and bladder diverticula with bladder outflow obstruction, renal rupture, cryptorchidism, urinary tract infections, and vesicoureteral reflux [9-12]. This patient presented with a classic course of MD.

In terms of vascular complications in MD, the pathophysiology is mainly explained by decreased LO function. LO oxidizes lysyl and hydroxylysyl residues in collagen and elastin, as the first step for collagen cross-linkage and stabilization of these extracellular matrix proteins, an essential process for connective tissue maturation [5, 8, 13]. Dysfunction of LO leads to poor integrity of the vessel walls contributing to the tortuosity of vessels, kinking, ectasia, or aneurysms. There are several case reports involving aneurysms in various vessels, including the brachial artery, lumbar artery, iliac artery, splenic and hepatic artery, gastric artery, and internal jugular vein, usually detected incidentally and leading to complications including death [14-19]. Although embolization and surgical control of bleeding with retroperitoneal hematoma evacuation were rarely performed, most cases were not aggressively managed but given supportive care considering the patients’ age, size, underlying disease, and limited life expectancy.

To our best knowledge, our case of ICA aneurysms in a 22-month-old patient with MD, which resulted in death after aggressive intervention was deemed futile, is the first reported in Korea. Due to the rarity of this disease and nonspecific presenting symptoms, early diagnosis is often challenging. However, to avoid irreversible neurodegenerative progress and reduce morbidity, prompt recognition and proper intervention are needed. A multidisciplinary approach and interprofessional consultations that include genetic counseling are also crucial for an optimal management plan and control of complications [13].

Fig. 2. Coronal views of the neck: (A) volume rendering and (B) maximum intensity projection computed tomography angiography images show tortuous bilateral internal carotid arteries and markedly dilated vascular structures (arrows) in the bilateral neck (right > left), communicating with the internal carotid arteries. The right-side lesion measures 3.4 cm × 2.8 cm; the left-side lesion measures 2.9 cm × 1.9 cm.
We reported the first case of ICA aneurysms in a 22-month-old patient with MD in Korea. The aneurysms were associated with impaired vessel integrity caused by underlying copper metabolism dysfunction. As MD is a multisystem disease, it is important to know the various characteristic manifestations for early diagnosis and proper management. Affected patients can suffer from a wide range of morbidities, requiring a meticulous evaluation and multidisciplinary approach.

CONFLICT OF INTEREST

Won Kyoung Jhang is an editor-in-chief of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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Conceptualization: WKJ, JY. Visualization: HYS. Project administration: HYS. Writing - original draft: HYS, WKJ. Writing - review & editing: WKJ.

REFERENCES


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