Case Report

Iliac Artery Aneurysms in Menkes Disease: A Case Report

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Background: *Menkes disease is a disorder of copper transportation that results in multi-systems involvement including neurological deterioration, seizure, dysmorphic facies and kinky hair. The authors report a case of Menkes disease that was complicated with bilateral iliac artery aneurysms.*
Case Report: *A 6-month-old Thai male infant presented with seizure, global delayed development, hypotonia and sparse, short, lightly pigmented and kinky hair. Light microscopic hair analysis showed pili torti. His serum copper and ceruloplasmin levels were low and were compatible with Menkes disease. Radiological finding from magnetic resonance angiography (MRA) revealed irregular tortuosity of abdominal aorta, a large right internal iliac artery aneurysm and a small left common iliac artery aneurysm. Genetic counseling and supportive treatment were provided for this patient.*
Conclusion: *Iliac aneurysms are a serious complication of patients with Menkes disease. Careful investigation with computed tomographic angiography (CTA) or MRA is helpful in those patients.*

Keywords: *Menkes disease, Iliac aneurysm, ATP7A, Pili torti*

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Menkes disease is a rare X-linked recessive inherited metabolic disorder with incidence of 1: 250,000 live births[1]. It is caused by *ATP7A* mutation that results in copper transportation protein defect. The clinical presentation includes hypotonia, failure to thrive, progressive neurological deterioration, seizure, dysmorphic facies and abnormal pigmentation of skin and hair. Abnormal characteristic feature of hair is pili torti (hair shaft twisting 180°)[2]. Laboratory findings of an affected individual reveal low level of serum copper and ceruloplasmin. Without early treatment, patients with Menkes disease usually die by the age of three years[2]. Arterial tortuosity is a mainly vascular complication, but on the other hand large arterial aneurysm is extremely rare in the disease. The authors describe a case report of Menkes disease with unusual complication of iliac artery aneurysms. This case report was approved by the Ethics Committee in Human Research, Khon Kaen University, with the approval number of HE561229.

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Case Report

A 6-month-old Thai male infant was born at term from a 39-year-old mother by cesarean section due to breech presentation with birth weight of 2,605 g and length of 51 cm. He was the first child from non-consanguineous parents. He developed seizures and nystagmus since he was 3 months old and was diagnosed with symptomatic hyponatremia at the community hospital. After admission for correction of hyponatremia, he still had seizures several times a day and had global delayed development. Then he was referred to our center when he was 6 months old. Physical examination revealed: sparse, short, coarse, lightly pigmented and kinky hair, sagging cheeks, micrognathia, nystagmus and hypotonia (Fig. 1). His growth parameters showed: weight of 6.9 kg (25^{th} centile), length 63 cm (10^{th} centile) and head circumference 41.2 cm (25^{th} centile). Light microscopic hair analysis showed pili torti, trichoclasis and trichorrhexis nodosa (Fig. 2). Laboratory findings revealed markedly low serum copper level: 2.3 µg/dl (reference range: 80-150 µg/dl) and low serum ceruloplasmin level: 5 mg/dl (reference range: 20-46 mg/dl). The laboratory results confirmed the diagnosis of Menkes disease.

He was investigated for the complications.

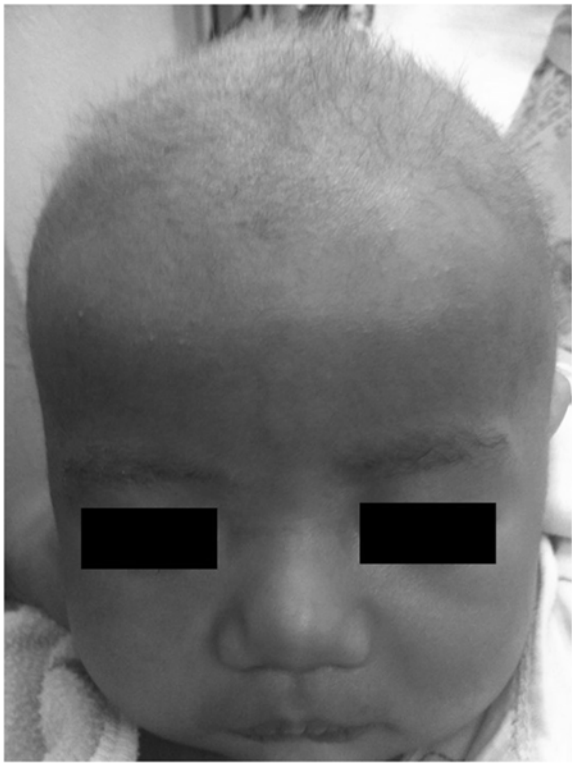

Fig. 1 Short, sparse, coarse, lightly pigmented and kinky hair, sagging cheeks and micrognathia.

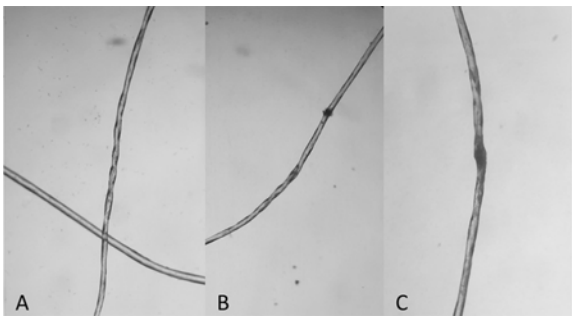

Fig. 2 Microscopic hair analysis showed (A) pili torti (hair shaft twisting 180°), (B) trichoclasis (transverse fractures of the hair shaft), (C) trichorrhexis nodosa (nodes along the hair shaft).

Wormian bones were found on skull radiography (Fig. 3). Urinary bladder diverticulum was not found on ultrasonography of the KUB system but there was evidence of arterial aneurysm at right lower abdomen. Magnetic resonance angiography (MRA) of abdominal aorta was further investigated and revealed a large right internal iliac artery aneurysm and a small left common iliac artery aneurysm (Fig. 4A). Magnetic resonance imaging (MRI) of brain showed tortuous

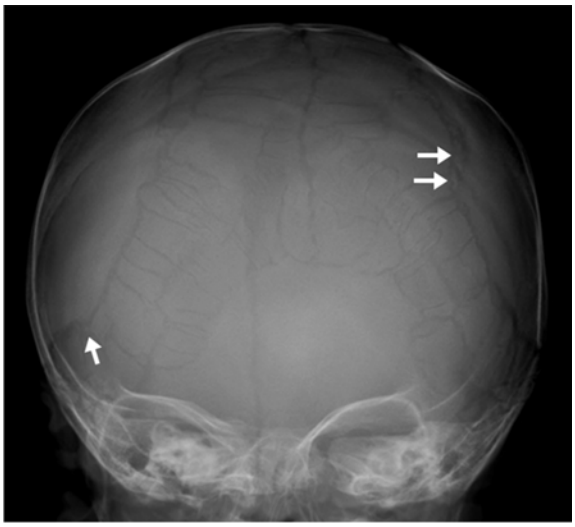

Fig. 3 Skull radiography showed wormian bones.

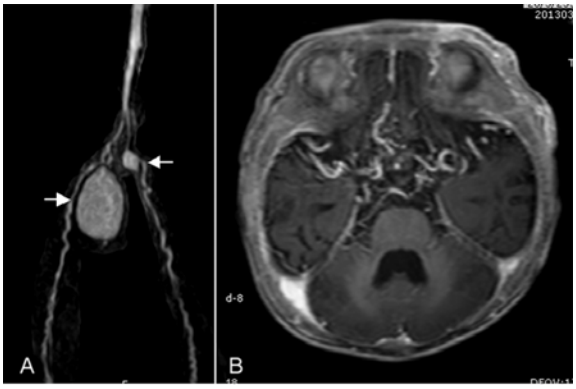

Fig. 4 (A) Contrast Enhanced Magnetic Resonance Angiography (CE-MRA) of infra-renal abdominal aorta revealed two abnormal outpunching lesions which are a larger right internal iliac arterial aneurysm and a smaller left common iliac arterial aneurysm, (B) Contrasted Magnetic Resonance Imaging (MRI) showed abnormal morphological change with tortuousity and dilatation of the circle of Willis.

and dilated vessels within circle of Willis and diffused brain atrophy (Fig. 4B). Regarding poor clinical outcome due to late diagnosis in this patient, management was supportive treatment and follow-up without any surgery. The patient suffered from several episodes of aspiration pneumonia and died when he was 1.5 years old.

Discussion

Menkes disease is an inherited metabolic

disorder that has a defect of copper metabolism. It is caused by mutation in *ATP7A* gene that regulate copper exportation from intestinal cells and results in copper deficiency. Copper is required for cuproenzymes such as cytochrome-c-oxidase, superoxide dismutase, ceramidegalactosyl transferase, dopamine beta-hydroxylase, tyrosinase, phenylalanine hydroxylase and lysyloxidase that plays an important role in many cellular functions in several organ systems especially brain[2,3]. Thus, reducing of cuproenzymes activities due to copper deficiency is a pathogenesis of many clinical presentation including developmental delayed, seizure, failure to thrive, hypotonia, abnormal skin and peculiar hair.

It is difficult to make a diagnosis of Menkes disease during neonatal period because of non-specific signs and symptoms. It should be considered in a male infant with hypotonia, failure to thrive, seizure and neurological deterioration. Seizure and neurological deterioration are usually developed around 3 months of age[3]. Skin laxity and dysmorphic facies including micrognathia, sagging cheeks and frontal bossing are also presented. Radiographic findings of bones including generalized osteoporosis, flaring metaphyses of the long bones, short clavicles, rib fractures and wormian bones in the cranial sutures are observed[4]. The specific characteristic of hair including short, coarse, sparse, silver, pili torti (hair shaft twisting 180°), monilethrix (varying diameters of the hair shaft), trichorrhexis nodosa (nodes along the hair shaft), trichoclasis (transverse fractures of the hair shaft) and trichoptilosis (longitudinal splitting of the hair shaft) on microscopic hair analysis is very helpful to determine the diagnosis[2,5]. Serum copper and ceruloplasmin levels are useful biochemical markers that support the diagnosis of Menkes disease. Detection of mutation in *ATP7A* gene is used to confirm the diagnosis and also helpful for prenatal diagnosis and genetic counseling.

An individual with Menkes disease can be complicated with bladder diverticulum, umbilical hernia and vascular abnormalities. Among vascular abnormalities, vascular tortuosity is the vast majority complication, while arterial and venous aneurysms are extremely rare. Pathogenesis of vascular abnormalities is a reduction of tensile strength of blood vessels wall due to defects in collagen and elastin cross-linking. This is a consequence from insufficiency of lysyl oxidase activity[3]. Arterial aneurysms are a serious complication and a significant leading cause of death[6,7]. They have been reported in various vessels including brachial, hepatic, iliac, lumbar and splenic arteries[6-10]. Venous aneurysm or phlebectasia is another rare vascular complication that is also found in Menkes disease[11]. This evidence supports that either computed tomographic angiography (CTA) or MRA is needed to investigate for aneurysm in an individual with Menkes disease. Early recognition of arterial aneurysms that leads to early treatment may result in a better outcome. Apart from monitoring and follow-up of the aneurysm, aggressive treatment modalities either surgery or intervention radiology were reported previously. Indication for the aggressive treatment is not established; however, aggressive treatment of large aneurysm seems to be necessary for avoiding serious complications such as rupture or thrombosis[7]. Currently, it is still unclear which modality has a better outcome but surgery is preferred in a large aneurysm while intervention radiology for the smaller one[7]. Without any treatment, the patient will be at risk of fatal hemorrhage. So risk and benefit of each treatment modality should be considered case by case. The long-term clinical outcome of Menkes disease is not good. Without treatment with copper-histidine, most patients usually die within 3 years. Although, early treatment with copper-histidine intravenous or subcutaneous injection during the utero or neonatal period may have a better neurological outcome in some patients[12,13]; but it cannot improve vascular, skeletal and other connective tissues abnormalities[4]. Due to the lethal nature of this disease, genetic counseling is highly recommended to prevent recurrence of the disease in the family.

Conclusion

Menkes disease should be considered in an infant with neurological deterioration and abnormal hair. The authors report bilateral iliac artery aneurysms as rare complications of this disease. Investigation with CTA or MRA is necessary for early detection of this complication.

What is already known on this topic?

Menkes disease is a rare X-linked recessive inherited metabolic disorder of Copper transportation. The clinical presentation includes hypotonia, failure to thrive, progressive neurological deterioration, seizure, dysmorphic facies and kinky hair. Individual with Menkes disease has low levels of serum copper and ceruloplasmin. Some patients have arterial tortuosity, a vascular complication, due to decreased lysyl oxidase activity.

What this study adds?

The authors report an atypical case of Menkes disease with unusual complication of bilateral iliac artery aneurysms.

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Potential conflicts of interest

None.

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หลอดเลือดแดงอิลิแอกโป่งพองในโรค Menkes: รายงานผู้ป่วย

กุณฑล วิชาจารย์, วรานนท์ มั่นคง

ภูมิหลัง: *โรค Menkes disease เป็นโรคที่มีความผิดปกติของการขนส่งทองแดงทำให้เกิดอาการในหลายระบบ ได้แก่ การเสื่อมถอยของระบบประสาท ชัก ลักษณะใบหน้าผิดปกติ และเส้นผมหยิก ผู้นิพนธ์รายงานผู้ป่วยโรค Menkes disease ที่มีภาวะแทรกซ้อนจากหลอดเลือดแดงอิลิแอกโป่งพองทั้งสองข้าง*

รายงานผู้ป่วย: *เด็กชายไทยอายุ 6 เดือน มีอาการชัก พัฒนาการช้ารอบด้าน กล้ามเนื้ออ่อนนิ่ม ผมบาง สั้น ติดสีจางและหยิก การวิเคราะห์เส้นผมด้วยกล้องจุลทรรศน์พบลักษณะ pili torti ผู้ป่วยมีระดับทองแดงและระดับโปรตีนเซอรูโลพลาสมินในซีรัมต่ำและได้รับการวินิจฉัยเป็นโรค Menkes disease ภาพเอ็มอาร์หลอดเลือดพบหลอดเลือดแดงเอออร์ตามีลักษณะไม่เรียบและคดเคี้ยว หลอดเลือดแดงอินเทอร์นอลอิลิแอกข้างขวาโป่งพองขนาดใหญ่ และหลอดเลือดแดงคอมมอนอิลิแอกข้างซ้ายโป่งพองขนาดเล็ก ผู้ป่วยได้รับคำปรึกษาทางพันธุศาสตร์และรักษาแบบประคับประคอง*

สรุป: *หลอดเลือดแดงอิลิแอกโป่งพองเป็นภาวะแทรกซ้อนที่รุนแรงในผู้ป่วยโรค Menkes disease การตรวจเพิ่มเติมด้วยเอกซเรย์คอมพิวเตอร์หลอดเลือดหรือการตรวจด้วยภาพเอ็มอาร์หลอดเลือดมีประโยชน์ในผู้ป่วยกลุ่มนี้*