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Case Report

Imaging findings of Menkes disease, a radiographic mimic of abusive trauma

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ABSTRACT

Menkes disease is a rare X-linked recessive disorder caused by impaired copper absorption and transport. Presented here is a case of a 12-week-old male who presented with hypotonia and multiple metaphyseal fractures. Further imaging and workup revealed a diagnosis of Menkes disease. While nonaccidental trauma is a much more common cause of metaphyseal bone fractures, encephalopathy, and subdural hematomas in infants, Menkes syndrome should be considered in the setting of corroborating signs and symptoms, as early diagnosis and treatment can delay progression of the disease.

Introduction

Menkes disease is a lethal X-lined-recessive disorder of copper metabolism. The disease was first described in 1962 by John Menkes in 5 related male patients with failure to thrive, progressive neurologic deterioration, and peculiar hair [1]. All 5 patients exhibited abnormal hair and developmental delay during early infancy, and all 5 died between the ages of 7 months and 42 months of age. The condition results from a mutation in the transport protein which mediates copper uptake from the intestine, encoded by the ATP7A gene which is located at the Xq21.2 position. This results in severe copper deficiency, epilepsy, and growth retardation. The disease typically progresses to death in early childhood. Most children with Menkes disease present by age 3 months with failure to thrive, developmental delay, or seizures. Affected children have characteristic "kinky hair," skeletal abnormalities, and hypopigmentation of the skin. Other possible complications include subdural hematomas, cerebrovascular accidents, and bladder diverticula.

The diagnosis is typically made with clinical, imaging, and laboratory findings which include low copper and ceruloplasmin levels. The classic radiographic findings seen in

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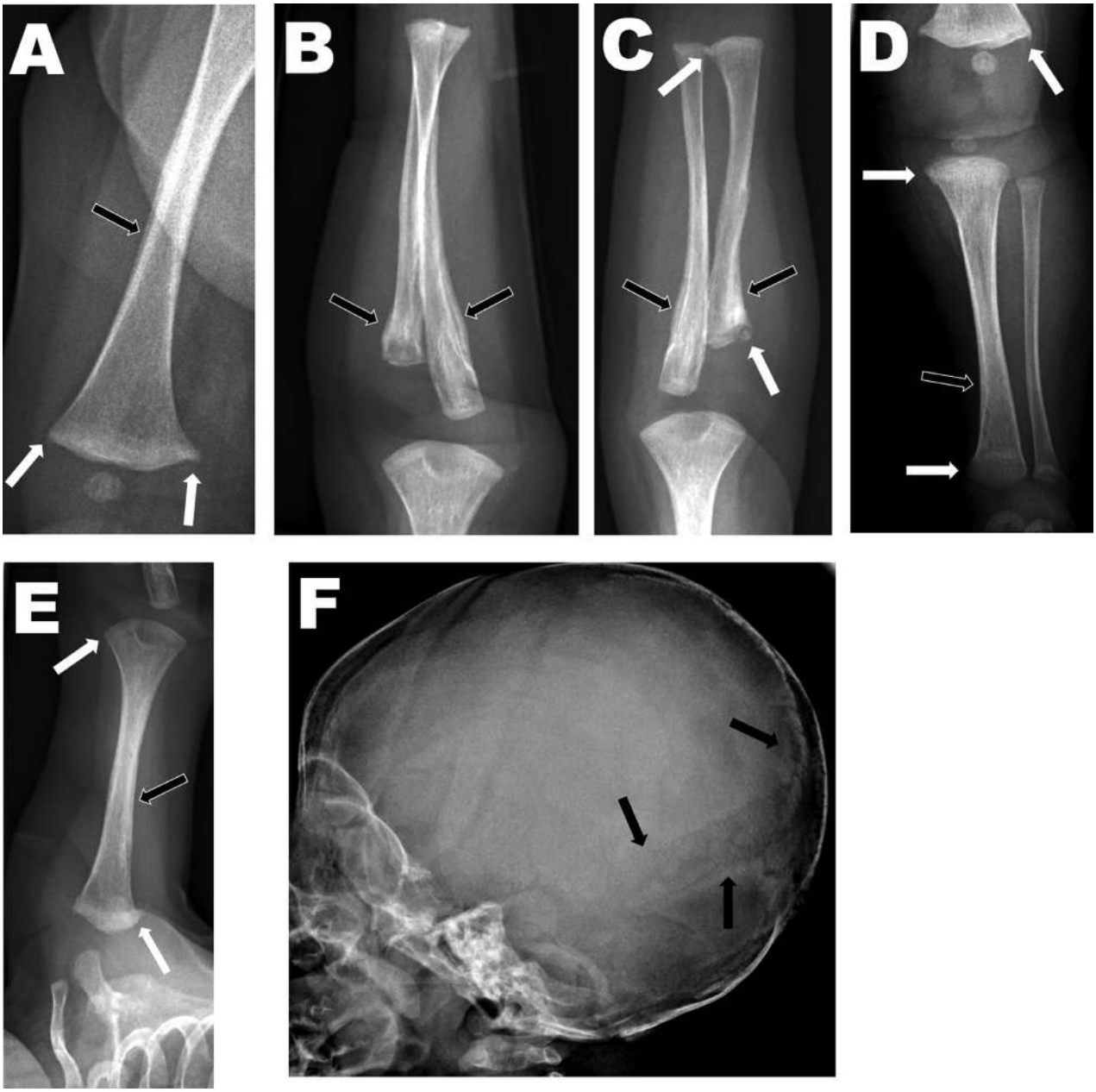

Fig. 1 – Skeletal survey performed at 2 months, 26 days of age. Metaphyseal irregularities (white arrows) and periosteal reaction (black arrows with white outlines) are seen on these radiographs of the right femur (A), left radius and ulna (B), right radius and ulna (C), left tibia and fibula (D), and left humerus (E). The lateral skull radiograph reveals multiple wormian bones (solid black arrows).

Menke's disease have been documented and include wormian bones, diaphyseal and metaphyseal bone fractures, subdural hematomas, and tortuous intracranial arteries [2].

Case report

A 12-week-old male presented to his primary care provider with a 2-day history of fussiness and vomiting. His parents noticed that he was more somnolent and reported a subjective fever. A sepsis workup was performed including blood, urine, and CSF cultures. Intraosseous access was obtained due to inability to obtain intravenous access. A radiograph of the right tibia and fibula was obtained to evaluate the intraosseous line. The radiograph revealed healing metaphyseal fractures which prompted a skeletal survey. The skeletal survey showed periosteal reaction, metaphyseal lesions, and wormian bones in the skull (Fig. 1). The patient was transferred to a tertiary children's hospital for further evaluation, and the child abuse pediatrics team was consulted. A CT of the head was then acquired which confirmed the wormian bones (Fig. 2). The

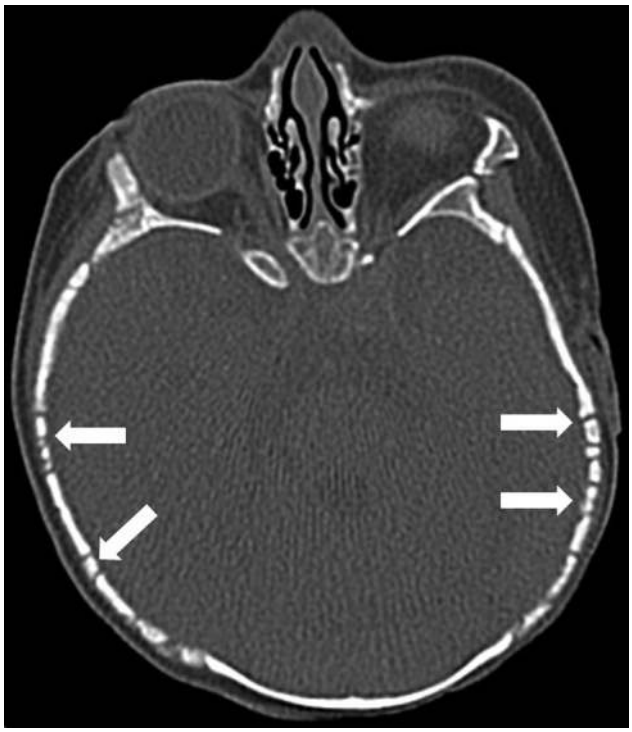

Fig. 2 – Axial CT of the head at presentation (age 2 months, 26 days) demonstrates wormian bones (arrows).

attenuation of the brain parenchyma was normal on this initial CT.

Physical exam demonstrated an enlarged anterior fontanelle, high arched palate, poor suck response, hypertonia, and fine hair. Seizure activity was observed on day 2 of the admission. MR Angiography revealed marked tortuosity of the intracranial arterial structures with multifocal ectasia and narrowing of the upper cervical segments of the internal carotid arteries and vertebral arteries (Fig. 3).

The patient had very low ceruloplasmin and copper levels suggestive of Menkes disease. The disease was confirmed with genetic testing of the ATP7A gene which identified a mutation involving intron 11 (c.2499-1F>A) which is the "classic" mutation of Menkes.

The patient later developed encephalomalacia throughout the brain and large low attenuation subdural hematomas which had accumulated by age 1 year, 3 months. (Fig. 4). He passed away shortly thereafter.

Discussion

It is estimated that 7% of children thought to have physical signs of child abuse have a medical explanation for their injuries instead [3]. Diseases of connective tissue such as Ehlers Danlos or osteogenesis imperfecta may lead to easy bruising and multiple fractures which may also be misinterpreted as nonaccidental trauma. Disorders that affect bone mineralization or skeletal dysplasias can mimic abusive fractures [4]. In this case, the combination of failure to thrive, metaphyseal

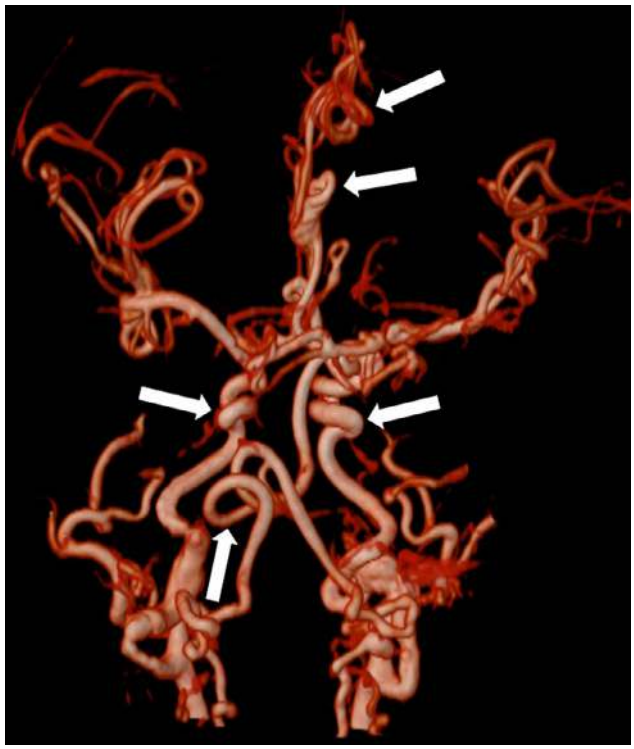

Fig. 3 – MRA of the head with 3-dimensional reconstruction obtained at 2 months, 27 days shows extensive tortuosity of the vasculature (arrows).

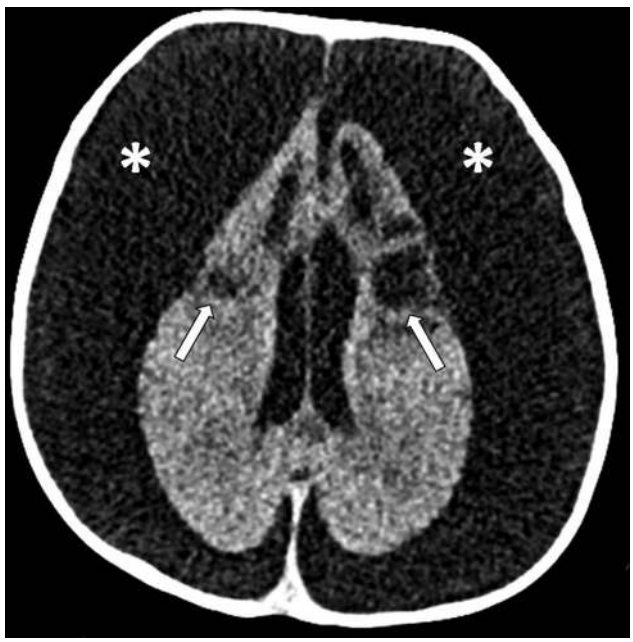

Fig. 4 – Axial CT of the head performed at age 1 year, 3 months depicting large bilateral subdural fluid collections (*) and bifrontal encephalomalacia (arrows).

lesions, and seizures raised the possibility of nonaccidental trauma. A more comprehensive evaluation of all radiologic findings suggested a syndromic etiology for the presentation and guided the medical team to the cause.

ATP7A is a transmembrane protein responsible for copper transport. Mutations in the gene thus result in improper copper metabolism which thus has a downstream effect on copper-dependent enzymes. For example, lysyl oxidase is an important copper-dependent enzyme in the formation of elastin and collagen [5]. Mutations thus lead to connective tissue dysfunction which accounts for the bone abnormalities and vessel tortuosity. Tortuous carotid arteries, as seen in this case, have been associated with brain ischemia [6]. The disease is most commonly inherited but arises from a spontaneous mutation in approximately 30% of cases.

The prognosis for affected children is poor. Most children with Menkes disease pass away in early childhood from progressive neuronal degeneration [7]. There is no effective treatment for Menkes disease, though patients with partial function of ATP7A may benefit from copper histidine if started shortly after birth [8].

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