Published in final edited form as:

Pediatr Radiol. 2012 November ; 42(11): 1301–1304. doi:10.1007/s00247-012-2457-4.

Cervical spine anomalies in Menkes disease: a radiologic finding potentially confused with child abuse

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Abstract

Background—Menkes disease is an X-linked recessive disorder of copper transport caused by mutations in ATP7A, a copper-transporting ATPase. Certain radiologic findings reported in this condition overlap with those caused by child abuse. However, cervical spine defects simulating cervical spine fracture, a known result of nonaccidental pediatric trauma, have not been reported previously in this illness.

Objective—To assess the frequency of cervical spine anomalies in Menkes disease after discovery of an apparent C2 posterior arch defect in a child participating in a clinical trial.

Materials and methods—We examined cervical spine radiographs obtained in 35 children with Menkes disease enrolled in a clinical trial at the National Institutes of Health Clinical Center.

Results—Four of the 35 children with Menkes disease had apparent C2 posterior arch defects consistent with spondylolysis or incomplete/delayed ossification.

Conclusion—Defects in C2 were found in 11% of infants and young children with Menkes disease. Discovery of cervical spine defects expands the spectrum of radiologic findings associated with this condition. As with other skeletal abnormalities, this feature simulates nonaccidental trauma. In the context of Menkes disease, suspicions of child abuse should be considered cautiously and tempered by these findings to avoid unwarranted accusations.

Keywords

Menkes disease; Cervical spine; Bone abnormalities; Copper metabolism

Introduction

Menkes disease, also known as kinky hair or steely hair disease, is an infant-onset, X-linked, neurodegenerative and connective tissue disorder caused by deficiency of a copper-transporting ATPase associated with mutations in the ATP7A gene [1, 2]. Deficiencies in copper-requiring enzymes account for distinctive clinical and biochemical abnormalities in affected individuals [3–7].

Previously described radiographic features of Menkes disease include two major groups of findings. The first is attributed to bone and vascular dysplasia; it includes wormian bones, flared clavicles, deformed elbows, occipital horns, pectus deformities, and dolechoectatic changes of extra- and intracranial vessels [5, 8–13]. Findings in the second group are attributed to weakening of bone and may be confused with the results of nonaccidental trauma (e.g., fractures of the skull, ribs and long bones, with metaphyseal corner changes and cupping simulating fractures) [14–16].

Cervical spine anomalies may occur in genetic syndromes including skeletal dysplasias [17, 18]; however, such defects have not been described previously in Menkes disease. Here, we report a newly identified developmental skeletal abnormality in Menkes disease, C2 cervical spine anomalies, detected by radiologic studies in children participating in a clinical trial of copper replacement. Since this abnormality mimics a “hangman’s fracture,” our observation adds to the list of radiographic bone lesions associated with Menkes disease that may be confused with child abuse [19].

Materials and methods

Patients

Thirty-five children with Menkes disease between 10 days and 4 years of age underwent posteroanterior and lateral skull radiographic imaging in the Radiology and Imaging Sciences Department of the Clinical Center, National Institutes of Health. They met clinical, biochemical and/or molecular criteria for the diagnosis [2, 14]. NIH institutional review boards and the NIH Radiation Safety Committee approved the studies.

Results

We found cervical spine defects involving the second cervical vertebra (C2) in four children. They ranged in age from 4.5 months to 3 years and had no history of accidental or nonaccidental trauma, although suspicion was raised in the youngest infant. Their condensed case histories, emphasizing relevant clinical, biochemical and molecular findings are presented below.

Case 1

A 4.5-month-old boy with known Menkes disease due to ATP7A mutation R547X was admitted to his local hospital for evaluation of new-onset seizures. He was receiving copper histidine (Investigational New Drug #34,166; SG Kaler IND holder) 250 µg twice daily injected subcutaneously as a participant in a phase III NIH-sponsored clinical trial (ClinicalTrials.gov Identifier: NCT00811785). After routine radiographs disclosed healing fractures of the third, fourth and fifth left ribs, a small periosteal reaction in the proximal right humerus, and a possible fracture of the second cervical vertebra (Fig. 1), he was referred to the County Department of Family Services and removed from the custody of his mother. Following a detailed investigation, which formally excluded nonaccidental trauma, the infant was returned to his family.

Case 2

A 19-month-old boy with Menkes disease with a splice acceptor site mutation in ATP7A (IVS11, SA -1, G to A) [19] and no history of accidental or nonaccidental trauma was found on a lateral skull radiograph to have a defect of C2 ossification (Fig. 2). Follow-up at 35 months of age (Fig. 2) demonstrated improved ossification.

Case 3

A 20-month-old boy with Menkes disease with a deletion of ATP7A exons 20–23 [13, 19] and no history of accidental or nonaccidental trauma showed a prominent defect in C2 (Fig. 3).

Case 4

A 3-year-old boy with Menkes disease who had no history of accidental or nonaccidental trauma and a single base deletion in the coding sequence of ATP7A (3936/7 delT) was found to have a prominent defect in the C2 posterior arch and subluxation of the C2 vertebral body (Fig. 4) [13, 19].

Discussion

We describe a previously unappreciated skeletal abnormality in Menkes disease: posterior neural arch defects of the cervical spine. Congenital clefts in the neural axis arch are rare [20]. The failure of chondrification centers containing embryonic mesenchymal cells at each side of the posterior arch to fuse with chondrification centers in the vertebral body results in the defect (Fig. 5). In a review summarizing 31 reported cases of an absent pedicle in the cervical spine, the most common locations were from C4 to C6 [21]. Only ten prior cases of nonsyndromic C2 arch defects have been reported [21, 22]. Atlantoaxial instability, C2 to C3 subluxation and C2 spondylolysis have been noted in various genetic disorders, including Down syndrome, Marfan syndrome, Morquio syndrome and pyknodysostosis [17, 18].

Evidence in support of a congenital basis for posterior arch defects includes the smooth corticated margins of the resulting pedicular wings and a frequent association with other birth defects [21]. The known tendency for vascular abnormalities such as tortuosity and aneurysm to occur in Menkes disease [3–5], as well as in mouse models of this illness [6], may be relevant to the developmental mechanism of cervical spine anomalies.

MR and CT images of the cervical spine were not obtained in the children with Menkes disease on which we report here; thus, it is possible that the gaps between the C2 posterior arches and the vertebrae may have represented delayed ossification of cartilaginous bone, rather than congenital bone defects. The diminishing size of the defect observed in serial radiographs in one child at 19 and 35 months of age (case 2, Fig. 2) supports this hypothesis. The alternative explanation of a complete bone defect perhaps is most convincing in patient 4 in whom the C2 vertebral body appeared anteriorly displaced despite normal alignment of the C2 and C3 posterior arches (Fig. 4). To further evaluate these issues, we suggest screening additional patients with Menkes disease with lateral c-spine (flexion/ extension) views.

Radiographic signs of nonaccidental head [23] and body trauma in children overlap with several manifestations of Menkes disease and may pose awkward problems for the parents and care providers of infants with this inherited disease. Subdural hematomas, rib fractures and metaphyseal spurs are all common findings in classic Menkes disease [2, 14]. In

addition, the cervical spine defects that we describe may occur in otherwise healthy children as a consequence of nonaccidental trauma [23].

Conclusion

Pediatric radiologists, when noting any of the above findings in a male infant or young child, should include the possibility of Menkes disease in the differential diagnosis. Physicians, social workers, Child Protective Services personnel and other child welfare advocates also should be cognizant of the direct overlap between the skeletal features of these two entirely different conditions.

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Fig. 1. Lateral cervical spine radiograph in a 4-month-old boy with classical severe Menkes disease in whom maternal child abuse was suspected. Note the apparent C2 posterior arch ossification defect (*arrow*)

Fig. 2. Radiographs in a boy with Menkes disease. **a** Radiograph at 19 months of age shows a C2 posterior arch ossification defect (*arrow*). **b** Radiograph at 35 months of age shows interval ossification (*arrow*)

Fig. 3.
Radiographs in a 20-month-old boy with Menkes disease with an apparent C2 posterior arch defect (*arrow*)

Fig. 4.
Radiograph in a 3-year-old boy with Menkes disease with an apparent C2 posterior arch defect (*arrow*) and anterior displacement (subluxation) of the C2 vertebral body

Fig. 5. Diagrams of normal posterior neural axis closure (*left*), and the defects that result (*arrows*) when chondrification centers fail to fuse (*right*)