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CLINICAL REPORT

Guidance for the Clinician in Rendering Pediatric Care

Evaluating Infants and Young Children With Multiple Fractures

Carole Jenny, MD, MBA, FAAP, for the Committee on Child Abuse and Neglect

ABSTRACT

Infants and toddlers with multiple unexplained fractures are often victims of inflicted injury. However, several medical conditions can also cause multiple fractures in children in this age group. In this report, the differential diagnosis of multiple fractures is presented, and diagnostic testing available to the clinician is discussed. The hypothetical entity "temporary brittle-bone disease" is examined also. Although frequently offered in court cases as a cause of multiple infant fractures, there is no evidence that this condition actually exists.

INTRODUCTION

When infants and toddlers present with multiple unexplained fractures, the differential diagnosis can be difficult. Although child abuse is the most frequent cause of multiple fractures in children in these age groups, bone diseases associated with increased bone fragility can be subtle or difficult to diagnose. These children are usually preverbal and cannot give a cogent history of their experiences. If abuse has occurred, caregivers of young children may not be forthcoming with a truthful history. On the other hand, family members of a child having an undiagnosed bone disorder may not be able to explain any mechanism of injury and may be completely bewildered by the injuries. Many parents of children with genetic or metabolic bone disease report that they were initially accused of abusing their children.[1]

DIFFERENTIAL DIAGNOSIS OF MULTIPLE FRACTURES IN INFANTS

Child Abuse

Any type of fracture can be caused by child abuse, although some fractures, such as metaphyseal fractures and posterior rib fractures, are more frequently found in abused children.[2] A careful review of the clinical history and a careful examination for other signs of abuse or neglect are important when child abuse is suspected.

Osteogenesis Imperfecta

Osteogenesis imperfecta is a heterogeneous family of diseases, usually caused by mutations of the genes *COL1A1* and *COL1A2*.[3] These genes encode the chains of type I collagen, which forms the structural framework of bone. Although it is a genetic disease, the presentation of the disease within the same family can be quite variable. Phenotypic expression of the disease depends on the nature of the mutation, its relative abundance resulting from mosaicism, and its expression in target tissues.[4] Some types of osteogenesis imperfecta involve slow production of

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collagen, and the symptoms resolve or lessen after bone growth stops.[5] In addition, spontaneous mutations are common, so there may be no family history of bone disease. Table 1 lists the various signs and symptoms that can be present in a case of osteogenesis imperfecta.

The diagnosis of osteogenesis imperfecta usually can be made by obtaining a careful medical and family history, performing a physical examination, and interpreting the results of appropriate biochemical and radiographic analyses. Many patients with osteogenesis imperfecta will have obvious diagnostic signs such as osteopenia, bone deformities, and wormian bones of the skull on radiographs. In addition, the classic metaphyseal lesions (planar microfractures through the primary spongiosum) that are often seen in abused children are not likely to be seen in children with osteogenesis imperfecta in the absence of obvious demineralization.[6] In some cases, the diagnostic signs of osteogenesis imperfecta can be quite subtle, and blue sclera (a sign found in many but not all cases of osteogenesis imperfecta) can also be seen in normal children with thin sclera.[7]

Osteogenesis imperfecta can be diagnosed by culturing of fibroblasts obtained from a skin biopsy. The cell culture is analyzed to determine if normal amounts and types of procollagen molecules are synthesized by the cells.[8] Eighty-seven percent of patients who are suspected to have osteogenesis imperfecta on the basis of clinical presentation will have abnormal collagen production that is identified by using this method.[9]

The authors of a recent study examined results of fibroblast cultures from skin biopsies that were obtained in cases of suspected child abuse.[10] In 138 children with fractures, osteogenesis imperfecta was identified in 9 cases. In an additional 6 cases, osteogenesis imperfecta could not be ruled out. Three of the 9 children with osteogenesis imperfecta were not suspected to have the disease before the collagen test was obtained. Rare cases of spontaneous subdural hematomas have been reported in children with osteogenesis imperfecta, presumably because of abnormally fragile blood vessels resulting from defective collagen.[11] In children, retinal hemorrhages have been documented in the posterior portion of the retina in nonabused children with osteogenesis imperfecta after accidental head trauma.[12] These hemorrhages have been described as small, intraretinal, and localized to the posterior pole of the retina. In contrast, retinal hemorrhages seen in abusive head trauma are often extensive, multilayered, and found from the posterior pole of the retina extending out to the ora serrata.[13]

A patient's DNA can also be sequenced to locate mutations of the *COLA1A* and *COLA2A* genes. This method can detect abnormal alleles in up to 96% of cases of serious osteogenesis imperfecta, but a genetic abnormality will be detected in only 60% of mild cases. In addition, approximately 5% of subjects without clinical osteogenesis imperfecta will have a sequence variation identified.[14]

In cases of osteogenesis imperfecta that are identified clinically, some patients who have abnormalities identified on analysis of their collagen will have a normal result on DNA sequencing, and some patients with abnormalities found on DNA testing will not have abnormal collagen test results. Both tests are expensive (approximately $2000 for collagen analysis and $3000 for DNA analysis). Although the collagen test requires a skin biopsy, the DNA sequencing can be performed on venous blood. Obtaining collagen test results takes 6 weeks to 3 months, and the DNA test results take up to 6 months to obtain. When testing for osteogenesis imperfecta, the better test to order is not always obvious, and each case should be considered individually. Consultation with a pediatric geneticist may be helpful in deciding which children to test and which test to order.

In cases where abuse is obvious (eg, when other abusive injuries are present or when abuse is witnessed), testing for osteogenesis imperfecta is not usually necessary.

TABLE 1 **Signs and Symptoms of Osteogenesis Imperfecta**

Fragile bones, with few, some, or many of the following findings:
Poor linear growth
Hypoplastic, translucent, carious, late-erupting, or discolored teeth
Blue sclera
Easy bruisability
Limb deformities
Scoliosis and/or kyphosis
Hyperextensible joints
Wormian bones
Hearing impairment as a result of otosclerosis
Inguinal and/or umbilical hernias
Triangular-shaped face
Macrocephaly
Demineralized bones

Preterm Birth

Preterm infants have decreased bone mineralization at birth, but after the first year of life, bone density normalizes.[15] Osteopenia of prematurity has been well described as a complication in low birth weight infants, particularly when prolonged parenteral nutrition is required.[16] Osteopenia of prematurity is multifactorial. Contributing factors can include inadequate calcium and phosphorus stores, inadequate mineral intake to support rapid growth, effects of medications used to treat complications of preterm birth, and limited patient mobility.[17–21] Osteopenia commonly presents between 6 and 12 weeks of postnatal age. The issue of multiple fractures in preterm infants is complicated by the fact that these infants have been reported to be at an increased risk of abuse.[22]

Rickets

Vitamin D deficiency is an uncommon condition that can be seen in infants who are solely breastfed and not receiving vitamin supplements or in dark-skinned children who are not exposed to adequate sunlight because of lifestyle or geographic location. The American Academy of Pediatrics recently recommended that all breastfed infants receive daily vitamin D supplementation.[23] Rickets can be diagnosed by typical changes on radiographs, including cupping and fraying of the costochondral junctions and epiphyses, demineralization, widened epiphyses, and cortical thinning. Serum concentrations of vitamin D metabolites are low, and alkaline phosphatase concentration is usually elevated. Other metabolic diseases can also cause rickets.

Osteomyelitis

Osteomyelitis in infants can present as multiple lesions at the metaphyses of the long bones, initially resembling the classical metaphyseal lesions found in abused children.[24] Over time, the sites of infection change in appearance to lytic lesions of the bone. Other signs of infection will be present, such as fever, increased erythrocyte sedimentation rate, elevated C-reactive protein concentration, and elevated white blood cell count.

Copper Deficiency

Preterm infants are born with lower stores of copper than term infants.[25] With their rapid rate of growth, copper deficiency can occur, usually in the second 6 months of postnatal life. Copper deficiency can cause pathologic fractures. Children with copper deficiency also have severe sideroblastic anemia and often have neutropenia. Obvious radiographic bone changes will occur before fractures occur, including symmetrical cupping and fraying of the metaphyses, osteopenia, subperiosteal new bone formation, and delayed bone age. Copper deficiency is not likely to occur in term infants of normal birth weight in the absence of a severely restricted diet or in the absence of an underlying genetic or metabolic disease.

Fractures Secondary to Demineralization From Paralysis

Any child with paralysis of the limbs can be at risk of fractures secondary to disuse demineralization, even with normal handling.[26] Often, these fractures are reported to occur during physical therapy and range-of-motion exercises. It can be difficult to distinguish between fractures caused by abnormally rough handling and fractures that occurred accidentally in these fragile children. When multiple fractures are recurring in disabled children, rarely a trial change in caregivers may be indicated to determine if the fractures can be prevented. This is an extreme intervention and should be reserved for very unusual circumstances.

Other Rare Conditions That Mimic Child-Abuse Fractures

Other conditions that can be confused with child abuse include Menkes syndrome (kinky hair syndrome), scurvy, osteopetrosis, hypophosphatasia, congenital syphilitic periostitis, leukemia, vitamin A toxicity, and metabolic and kidney diseases that cause calcium wasting and demineralization. Prolonged administration of prostaglandins, glucocorticoids, or methotrexate also can lead to bony changes that resemble child abuse. These conditions have very distinctive clinical presentations and radiographic findings.[27] Careful history, physical examination, and consultation with a pediatric radiologist may avoid mistaking these conditions for child abuse.

HYPOTHESIZED CONDITIONS PRESENTED IN MULTIPLE-FRACTURE CASES

A few articles in the literature have hypothesized the existence of a condition referred to as "temporary brittle-bone disease." One proponent of this theory claims that an infant's bones can be especially vulnerable to fractures for a short period of time because of some unknown metabolic abnormality, perhaps involving copper metabolism.[28] Another proposed explanation is that the bones are fragile because of decreased fetal movement in utero.[29] Neither of these theories are supported by any clinical or laboratory studies. The very nature of bone maturation and development make it unlikely that bones would quickly change from fragile to normal. Temporary brittle-bone disease is neither clinically validated nor generally accepted by expert professionals and should not be invoked to explain multiple fractures in an infant.[22]

DIAGNOSING CHILD ABUSE WHEN A CHILD PRESENTS WITH MULTIPLE FRACTURES

Child abuse is many times more common in the population than osteogenesis imperfecta.[30] Although osteogenesis imperfecta and other conditions should be considered, clinicians should not hesitate to report suspected child abuse and institute protective measures even before the diagnostic workup is complete. When multiple or suspicious fractures are detected, a complete skeletal survey should be performed on any child younger than 2 years.[31] Computed tomography or MRI of the head as well as a careful retinal examination by an ophthalmologist should be considered. A complete blood cell count and serum calcium, phosphorus, and alkaline phosphatase concentrations should be obtained, although the alkaline phosphatase concentration may be elevated as a result of the fractures. A serum 25-hydroxy-vitamin D concentration can be obtained if rickets is suspected because of radiographic findings or history. Serum copper and ceruloplasmin concentrations should be obtained if radiographic findings suggest copper deficiency.

In any case of suspected child abuse, liver-function studies should be performed and amylase and lipase

concentrations should be obtained to evaluate for possible occult abdominal injury.[32] A urinalysis should be performed to screen for occult blood. A careful physical examination should be performed to document bruising or other skin injury. If fractures stop occurring when the child moves to a protected environment, the diagnosis of bone disease is most likely ruled out, especially if the child has begun walking and falling without refracturing.

Bone densitometry might prove to be helpful in the future, but at this time, no age-adjusted reference values have been determined by studying a large population of infants and children. The threshold level of decreased mineralization that leads to increased fracturability is unknown. Differences in bone size and shape in the pediatric age group make densitometry results difficult to interpret.[33]

If a child has an underlying bone disorder or disability, child abuse can still coexist with the disease. Children with disabilities have been shown to have an increased risk of child abuse.[34]

Distinguishing child abuse from other conditions that cause multiple or suspicious fractures requires the clinician to have an open mind. Thoughtful and objective evaluation of the clinical evidence is required. It is critical to remember that child abuse occurs in all racial and socioeconomic groups. Physicians should not hesitate to comply with state laws that require reporting of suspected abuse.

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