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Findings of metabolic bone disease in infants with unexplained fractures in contested child abuse investigations: a case series of 75 infants

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Abstract

Background: Infants who present with multiple unexplained fractures (MUF) are often diagnosed as victims of child abuse when parents deny wrongdoing and cannot provide a plausible alternative explanation. Herein we describe evidence of specific and commonly overlooked radiographic abnormalities and risk factors that suggest a medical explanation in such cases.
Methods: We evaluated such infants in which we reviewed the radiographs for signs of poor bone mineralization. We reviewed medical, pregnancy and family histories.
Results: Seventy-five of 78 cases showed poor bone mineralization with findings of healing rickets indicating susceptibility to fragility fractures that could result from a wide variety of causes other than child abuse. We found risk factors that could explain the poor bone mineralization: maternal and infant vitamin D deficiency (VDD), decreased fetal bone loading, prematurity and others. Most infants had more than one risk factor indicating that this bone disorder is a multifactorial disorder that we term metabolic bone disease of infancy (MBDI). Maternal and infant VDD were common. When tested, 1,25-dihydroxyvitamin D levels were often elevated, indicating metabolic bone disease.
Conclusions: Child abuse is sometimes incorrectly diagnosed in infants with MUF. Appreciation of the radiographic signs of MBDI (healing rickets), risk factors for MBDI and appropriate laboratory testing will improve diagnostic accuracy in these cases.

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Introduction

Infants with multiple unexplained fractures (MUF) pose a diagnostic challenge: Is the explanation child abuse, an intrinsic bone disorder or an accidental traumatic event? Establishing the correct diagnosis in the infant with MUF is critical, as the diagnosis of child abuse has far-reaching implications: family dissolution, incarceration of the alleged perpetrator, tarnished reputations, personal financial ruin and significant legal/judiciary costs to society.

Radiographic findings almost always drive the diagnosis of child abuse in the infant presenting with MUF. The radiographic findings of classical metaphyseal lesions (CMLs), posterior rib fractures, fractures in different stages of healing and normal bone mineralization are thought to be pathognomonic for child abuse, as emphasized in the most recent American Academy of Pediatrics Committee on Child Abuse and Neglect (AAP-COCAN) [1]. However, recent observations suggest that CMLs and rib fractures are not pathognomonic of child abuse, but rather are more likely indicative of metabolic bone disease [2–5].

Moreover, pediatric radiologists have assumed that radiographs of the bones that show apparent normal mineralization indicate normal infant bone strength, and thus the physical forces that caused these fractures are necessarily excessive and likely violent. However, a bone radiograph cannot reliably evaluate any of the multiple determinants of bone strength; although if osteopenia is present, the bone strength is likely lower than normal [6, 7]. Without knowing the strength of a bone (which an X-ray cannot determine), it is not possible to determine whether a fracture is one caused by excessive forces in a normal strength bone (child abuse) or a fragility fracture caused by minimal forces in an intrinsically weak bone (metabolic bone disorder). Thus, the basis for using

radiographs to unequivocally diagnose child abuse is lacking scientific foundation. Similar circular reasoning has been used in shaken baby syndrome/abusive head trauma cases [8].

Our medical legal review of cases of infants with MUF in which the alleged perpetrator denied wrongdoing has revealed many cases with radiographic findings of healing rickets. This leads us to believe there was likely an alternative medical explanation for these fractures and that these infants had metabolic bone disease. The radiographic findings of healing rickets as opposed to active rickets are well described in the medical literature of the early 1900s, and similar findings were noted in an experimental animal model by Dodds and Cameron [9–16]. This body of work has largely been unappreciated by pediatric radiologists of the present day.

As we studied the clinical findings in these cases, we concluded that metabolic bone disease in young infants is often multifactorial in etiology as there are a number of potentially causative and predisposing factors that are primarily fetal in origin that can lead to a transient fragile bone state in early infancy. Affected infants can incur fractures with physical forces that might not ordinarily cause a fracture compared to an infant with normal bone strength. We have chosen to describe this bone disorder of multifactorial causation as metabolic bone disease of infancy (MBDI) [17]. MBDI encompasses several previously described disorders of transient fragile bone state in young infants, including congenital rickets, temporary brittle bone disease and healing rickets [15, 18, 19].

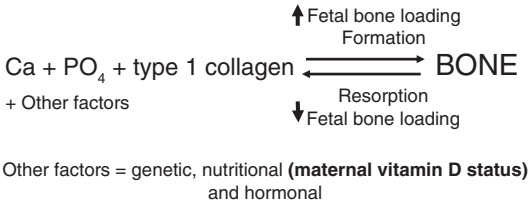

Figure 1: Application of the Utah Paradigm to the fetal time period. The Utah Paradigm envisions bone formation/resorption as a biochemical reaction in which the catalyst for bone formation and strength is bone loading, and the reactants required for this reaction are calcium, phosphate, vitamin D and protein (type 1 collagen). The Utah Paradigm also applies to the fetal skeleton. During pregnancy, fetal movement is the primary determinant of bone loading, and adequate calcium, phosphate, vitamin D and protein (type 1 collagen) must be provided to the fetus for normal bone mineralization. Maternal VDD is an important cause of insufficient provision of calcium to the fetus which would compromise fetal bone strength. This model predicts that decreased fetal bone loading and/or maternal VDD, calcium deficiency or phosphate deficiency can result in diminished bone strength of the fetal skeleton. Vitamin D is essential for both the GI absorption of calcium and for the normal functioning of osteoblasts and osteoclasts to bring about normal mineralization of bone. Bone loading is the catalyst that increases bone strength by increasing bone density and/or altering bone architecture.

When cases of infants with MUF are critically evaluated for explanations other than child abuse, predisposing factors for metabolic bone disease, mostly fetal in origin, are often noted. These factors are consistent with the contemporary model of bone physiology, the Utah Paradigm as shown in Figure 1, and include the following 7 risk factors [20]:

1. Vitamin D deficiency (VDD) in pregnancy
2. Decreased fetal bone loading
3. Prematurity
4. Maternal use of acid lowering drugs during pregnancy that can decrease calcium absorption
5. Maternal use of phosphate binding drugs during pregnancy that can decrease phosphate absorption
6. Gestational diabetes
7. Ehlers-Danlos syndrome/joint hypermobility in parents and/or infant

Vitamin D deficiency (VDD) in pregnancy

There is a global epidemic of VDD that has direct implications for the pregnancies of women with VDD who may not be able to provide adequate calcium to the developing fetal skeleton through gastrointestinal (GI) absorption and may not be able to provide sufficient VD to optimize fetal bone cell function [15, 21]. During pregnancy, maternal absorption of calcium increases by 50% to accommodate the calcium needs of the growing fetus [22]. Thus, maternal VDD during pregnancy can compromise fetal bone mineralization, and the recent case series by Keller supports maternal VDD as a risk factor. Their cases had the same types of fractures as seen in child abuse [15].

Several studies have found a positive correlation between maternal 25-hydroxyvitamin D (25OH-VD) levels during pregnancy and various fetal, newborn and childhood markers of bone health and bone strength suggesting that maternal vitamin D status during pregnancy is an important factor for infant bone strength [23–25]. 25OH-VD levels rapidly increase in the immediate postnatal period, even in breastfed infants, with two important consequences. First, fetal bone hypomineralization from maternal VDD during the third trimester would begin to normalize once the infant is born and 25OH-VD levels began to rise, thus turning the process into a healing phase [26, 27]. Second, blood 25OH-VD taken at the time of presentation with fractures at several months of age

would be much higher than the cord blood level, thus underestimating the true extent of the fetal and early life VDD.

Decreased fetal bone loading

Situations that cause decreased fetal bone loading include decreased fetal movement; various situations of intrauterine confinement including oligohydramnios, twins and malpresentation; and maternal use of drugs during pregnancy that cause decreased fetal immobilization, such as narcotics [17, 28–31].

Bone loading is far greater in the fetus that experiences normal movement than in the fetus in which movement is compromised. Fetal movement and kicking against the maternal uterus is a critical *in utero* event for the fetus to attain normal fetal bone strength [30, 31]. Normal fetal movement requires an intact neuromuscular system in which the intrauterine environment has adequate space for kicking and movement.

Controlled experimental animal studies have confirmed that fetal bone loading is a critical determinant of fetal and young infant bone strength [32–34]. Umbilical cord length is a proxy for fetal movement and thus of bone loading (normal cord length of term infants is 61 cm ± 10 cm = 1 standard deviation [SD]) [35]. Controlled studies using quantitative ultrasound speed of sound (SOS) measurements of the tibia in newborns have shown abnormal bone quality (and thus lower bone strength) in several clinical situations associated with intrauterine confinement and decreased fetal movement including infants with short umbilical cords, twins, infants born in the breech presentation and infants who are large for gestational age [36–41].

Prematurity

Prematurity is associated with an increased risk for developing a transient fragile bone state and incurring fractures, often asymptomatic and incidental, typically in the first 6 months of life. The bone disease of prematurity is a well-described and well-accepted condition with multiple case series and controlled studies that provide evidence that there are multiple, contributing risk factors: inadequate provision of mineral (calcium and phosphate) in the diet, decreased bone loading compared to the term infant, prolonged hyperalimentation, immobilization from prolonged ventilator therapy and calcium wasting from use of hypercalciuric drugs such as Lasix and caffeine [42–45]. Physical therapy which increases bone loading in the premature infant increases bone strength [46].

Maternal use of acid lowering drugs during pregnancy that can decrease calcium absorption

The use of proton pump inhibitors, H2 blockers, such as lansoprazole and ranitidine, can lower the acid content of the stomach and can lead to decreased calcium absorption as calcium is better absorbed in an acid environment [47–49]. Thus, the use of acid lowering drugs during pregnancy could decrease calcium availability to the fetus, a hypothetical consideration that is consistent with the Utah Paradigm [20].

Maternal use of phosphate binding drugs during pregnancy that can decrease phosphate absorption

Calcium carbonate in the form of Tums is a commonly used drug for heartburn during pregnancy. The calcium can bind phosphate and cause phosphate wasting through the GI tract [50]. Thus, the use of phosphate-binding drugs during pregnancy could decrease phosphate availability to the fetus, a hypothetical consideration that is also consistent with the Utah Paradigm [20].

Gestational diabetes

Controlled studies have shown that infants born to mothers with gestational diabetes have decreased bone mass compared to infants born to non-diabetic mothers [51, 52]. It is not known if this is related to a biochemical phenomenon, such as abnormal glycosylation of critical fetal bone proteins, or to decreased fetal movement which can be seen in diabetic pregnancies [53, 54].

Ehlers-Danlos syndrome/joint hypermobility in parents and/or infant

Case series have shown that joint hypermobility and the joint hypermobile form of Ehlers-Danlos syndrome (EDS-type 3) are overrepresented in the parents of infants with MUF and in the infants themselves [55, 56].

The most recent AAP-COCAN related to the evaluation of infants with fractures recommends that in the infant

with MUF the following commonly ordered blood tests related to bone metabolism be performed: calcium, phosphate, alkaline phosphatase, parathyroid hormone (PTH) and 25OH-VD [1]. It is not known if these recommendations are strictly followed.

Herein is a case series of 75 infants with MUF in which child abuse was diagnosed by the conventional approach with the putative "pathognomonic" radiographic findings that were previously noted, but in which we find abnormal radiographs indicating MBDI. The objectives of this case series analysis are threefold: to present our interpretation of the radiographs, to present the risk factors for MBDI and to present the lab findings related to bone metabolism.

Materials and methods

Ascertainment of cases

Between 2007 and 2015, author MM, a forensic pediatrician and clinical geneticist, was asked by parents/caregivers or their attorneys to evaluate the radiographs and pertinent medical records of infants with MUF as part of medical-legal proceedings in which child abuse was alleged against the parents/caregivers and denied by the accused. The infants were born between September 2006 and March 2015. In almost all of the cases, the radiology report raised the strong possibility of child abuse based on four radiographic findings that are generally considered to be specific for child abuse: CMLs, posterior rib fractures, fractures in different stages of healing and normal bone mineralization.

Infants were included in our case series if our review of the radiographs demonstrated at least one radiographic abnormality of bone mineralization as described below. In some instances the infant was physically examined by MM, in other instances there was no physical examination, only review of the records and radiographs.

Review of clinical information

A. Demographic information regarding location and season of birth, race and gender of the infant was noted.
B. Pregnancy and newborn records were reviewed for evidence of decreased fetal bone loading as indicated by any of the following:
    1. history from mother [57]
    2. comparison with another pregnancy, if such existed [57]
    3. disclosure to the obstetrician of decreased fetal movement [57]
    4. short umbilical cord (40 cm or less) [35]
    5. deformation at birth [28]
    6. twin pregnancy with obligatory intrauterine confinement [17]
    7. breech or transverse presentations which are associated with intrauterine confinement [28]
    8. oligohydramnios with obligatory intrauterine confinement [28]
    9. third trimester use of maternal medications that cause decreased fetal movement, such as opioids [29].
C. Pregnancy records of the mother were reviewed for the presence of gestational diabetes and the use of medications that might interfere with calcium absorption such as proton pump inhibitors and histamine antagonists or with phosphate absorption such as phosphate binders (for example, calcium carbonate in Tums) [47–52, 54].
D. Medical history of the infant was reviewed for the presence of any medical conditions such as failure to thrive, use of any drugs that might interfere with calcium absorption, age of presentation with fractures, bruising noted at fracture sites or internal organ injury [47–49, 58]. We specifically noted if there was any thoracic injury in infants with rib fractures.
E. Records were reviewed for blood biochemical tests of bone metabolism including:
    1. the four commonly tested analytes (calcium, phosphate, alkaline phosphatase and PTH)
    2. 25OH-VD
    3. 1,25-dihydroxyvitamin D (1,25DiOH-VD) and
    4. testing for osteogenesis imperfecta (OI)
F. Family history was evaluated for genetic disorders that predispose to fragility fractures such as OI or EDS-type 3. When available for physical examination, the infant and parents were evaluated for joint hypermobility (Beighton score $\geq$5) and/or EDS-type 3 [59].

Review of radiographs

Radiographs were reviewed and reinterpreted by radiologist DA. These included skeletal surveys in all infants and head computed tomography (CT) scans in some infants when done. We evaluated seven radiographic findings of abnormal bone mineralization:

1. Periosteal mineralization abnormality (subperiosteal new bone formation [SPNBF]) [9–11]
2. Growth plate mineralization abnormality [9–11]
3. Ulnar cupping [9–11]
4. Skull mineralization abnormality (craniotabes and/or parasutural hypomineralization) [9–11]
5. Rib mineralization abnormality [9–11]
6. Vertebral mineralization abnormality [14]
7. Looser zones [9–11, 15]

An infant was included in this series if there was at least one of the aforementioned abnormal radiographic findings. We evaluated the radiographs for osteopenia which was not noted in any of the radiology reports and is a subjective finding.

SPNBF secondary to mineralization of excess osteoid was differentiated from SPNBF secondary to trauma by the absence of a fracture, its uniform thickness and its lack of extension beyond the tapered cortical termination in the mid metaphysis. Vertebral body mineralization abnormalities were based upon the presence of a bone-in-bone appearance [15].

The study was approved by the Dayton Children's Hospital's Institutional Review Board (IRB), #2010-009.

Results

Of 78 cases that we reviewed in which parents/caregivers were accused of child abuse and the accused denied wrongdoing, 75 had radiographic findings of healing rickets when we reviewed the imaging studies and three had normal radiographs. Of the 75 cases, 19 infants were clinically evaluated by MM in his clinic and 56 cases were evaluated by available medical records and imaging studies. The mothers of 11 infants were examined by MM, and records of parents related to possible EDS-type 3 were available in 22 cases.

The analysis of the 75 cases is shown in Tables 1–5:

Table 1 describes the demographics of 75 cases. Noteworthy is the high frequency of twins. There were 16 twins, and the co-twin of each twin had a skeletal survey to evaluate for possible fractures. In these 16 co-twins, there were six normal skeletal surveys and 10 that showed fractures. These 10 co-twins with fractures, all asymptomatic, are not included in the present series, only the original twin that presented with fractures.

Table 1: Demographics of 75 infants with MBDI.

1. Singleton vs. twin pregnancy
   Singleton pregnancy – 59 (78.7%)
   Twin pregnancy – 16 (21.3%)
2. Sex
   Male – 47 (62.7%)
   Female – 28 (37.3%)
3. Race
   White – 60
   Black – 6
   Hispanic – 7
   Biracial – 2
4. Gestational age (GA): 59 singleton pregnancies

GA, weeks	Number
28–32	1
32–37	10
>37	48

5. Gestational age: 16 twin pregnancies

GA, weeks	Number
32–37	13
>37	3

6. Mean birth weight ± 1 SD
   = 3064 g ± 646 (Range: 1650–4200 g)
7. Mode of presentation with fractures
   Symptomatic extremity fracture – 53
   Minor injury – 4
   Cutaneous abnormality – 4
   Incidental finding of rib fractures on chest radiograph – 14

Table 2: Fracture profile from skeletal surveys of 75 infants with MBDI.

Fracture type	Number (%)
1. Rib	55 (74)
2. CML	50 (67)
3. Long bone diaphysis	49 (65)
4. Clavicle	15 (20)
5. Skull	14 (19)
6. Small bones of hands	4 (5)
7. Small bones of feet	2 (3)
8. Scapula	1 (2)
9. Acromion	1 (2)
10. Vertebrae	1 (2)

Table 3: Radiographic signs of metabolic bone disease in 75 infants with MBDI.

Sign	#	(%)
1. Growth plate mineralization abnormality	68	(91)
2. Skull mineralization abnormality (craniotabes)	55	(73)
3. Rib mineralization abnormality	44	(59)
4. Vertebral mineralization abnormality	43	(57)
5. Ulnar cupping	37	(49)
6. Periosteal mineralization abnormality	29	(39)
7. Looser zones	24	(32)

The most common presenting issue that led to a skeletal survey was a symptomatic extremity fracture. There were four infants who had cutaneous abnormalities that led to a skeletal survey being performed – one with unexplained bruising that parents noted to the pediatrician, one with a burn, one with scalp swelling secondary to a fall and one with scalp swelling not associated with any trauma.

Table 2 details the types of fractures in the 75 cases as reported by the reading radiologist of each case. The average age of presentation with fractures was 12 weeks (SD = 6 weeks; median age = 11 weeks; range: 2–32 weeks). The average number of fractures per infant as indicated by the interpretation of the reading radiologist on the original skeletal radiographs was 10 fractures (SD = 8 fractures; range: 1–36 fractures) and this included CMLs. Rib fractures and CMLs were the most common fractures. Most CMLs were clinically silent and healed without callus or periosteal reaction. There were 36 infants who had four or more rib fractures, and none of these infants had internal thoracic injury on chest X-ray, or signs of significant respiratory distress. In the 75 infants, there was no significant bruising at or near the fractures. Diaphyseal fractures of the long bones were usually symptomatic and were often

Table 4: Frequency of risk factors in 75 infants with MBDI.

1. Vitamin D deficiency (25OH-VD <30 ng/mL)	
a. Mother (n =34, mean ± 1 SD = 19.9 ng/mL ± 9.4, range: 5–51)	30/34 tested = 88%
<10 ng/mL: 4 (12%)	
10–19.9 ng/mL: 18 (53%)	
20–20.9 ng/mL: 8 (23%)	
≥30 ng/mL: 4 (12%)	
b. Infant (n = 54, mean ± 1 SD = 28 ng/mL ± 12, range: 3–55)	30/54 tested = 56%
<10 ng/mL: 5 (9%)	
10–19.9 ng/mL: 7 (13%)	
20–29.9 ng/mL: 18 (33%)	
≥30 ng/mL: 24 (45%)	
2. Decreased fetal bone loading (decreased fetal movement)	63/75 = 84%
a. Historical appreciation with no other pregnancies – 8	
b. Compared to other pregnancy(ies) – 1	
c. Complained to obstetrician – 17	
d. Twins – 16	
e. Deformations/oligohydramnios/malpresentation/short umbilical cord – 29	
f. Maternal use of narcotics during entire pregnancy – 4	
3. Prematurity (<37 weeks of gestational age)	19/75 = 25%
4. Drugs that interfere with maternal calcium absorption	23/75 = 40%
5. Drugs that interfere with maternal phosphate absorption	17/75 = 23%
6. Gestational diabetes	6/75 = 8%
7. Joint hypermobility/EDS-type 3 in either parent or infant	15/75 = 20%

the reason that the parents sought medical attention, because the infant was fussy and perceived to be in pain or not moving the fractured extremity.

Figure 2 shows a plot of the age of presentation of each infant versus the number of fractures each infant had on the initial skeletal survey as determined by the reading radiologist.

Table 3 shows the frequency of the seven major bone mineralization abnormalities that we evaluated. Noteworthy, nearly 90% of infants displayed highly characteristic features of healing rickets at one or more growth plates. There were three infants who had one radiographic sign of healing rickets, seven who had two, 14 who had three, 24 who had four, 20 who had five, six who had six and one who had all seven. Most CMLs were without pain, swelling or functional impairment and on follow-up radiographs healed without callus and by filling in. There were no signs of active rickets as evidenced by the absence of metaphyseal fraying.

Figures 3–12 show representative radiographic findings of the seven abnormalities listed in Table 3 through eight representative clinical vignettes obtained from the 75 cases. The radiographic findings are consistent with healing rickets.

Figures that illustrate each of the seven radiographic signs are given below:

1. Periosteal mineralization abnormality – Figure 9
2. Growth plate mineralization abnormality – Figures 7 and 12
3. Ulnar cupping – Figure 3
4. Skull mineralization abnormality – Figures 4 and 5
5. Rib mineralization abnormality – Figures 10 and 11
6. Vertebral mineralization abnormality – Figure 6
7. Looser zones – Figures 8 and 11

We noted osteopenia in 19 (25%) of the cases.

Table 4 lists the frequency of the seven fetal risk factors for MBDI previously noted. Sixty-three of the 75 infants had evidence of decreased fetal bone loading, and the specific findings that indicated this are given as subheadings; some infants had more than one such finding to indicate decreased fetal bone loading. In 15 cases, the mother had EDS-type 3 or joint hypermobility. The diagnosis of EDS-type 3 was made by author MM by history and physical examination in nine mothers and by history alone in one mother. The diagnosis of EDS-type 3 was made in three other mothers by other physicians. The diagnosis of joint hypermobility (Beighton score ≥5) was made by author MM in two mothers by physical examination. Of these 15 cases, author MM examined eight of the infants and found joint hypermobility in six of them and normal joint mobility in two of them.

Table 5: Biochemical testing[a] in 75 infants with MBDI.

Outcome	Number
A. Blood biochemical profiles of four common tests (Ca, PO4, AP, PTH)	
i. No testing done	16
ii. Normal test result(s) for:	23
– Ca, PO4, AP, PTH – 4	
– Ca, PO4, AP – 7	
– Ca, AP, PTH – 3	
– Ca, PO4, PTH – 3	
– Ca, PO4 – 2	
– Ca, AP – 2	
– Ca, PTH – 1	
– Ca – 1	
iii. Abnormal test result in any of the four tests	36
B. Specific analyte tests	
– Ca (n = 52)	
a. Normal – 46	
b. High – 1	
c. Low – 5	
– PO4 (n = 36)	
a. Normal – 27	
b. High – 8	
c. Low – 1	
– AP (n = 44)	
a. Normal – 21	
b. High – 23	
c. Low – 0	
– PTH (n = 24)	
a. Normal – 15	
b. High – 6	
c. Low – 3	
C. Blood 1,25DiOH-VD (n = 22; normal range: 15–75 pg/mL)	
Normal – 8	
High – 14	
Low – 0	
D. 25OH-VD see Table 4	

[a]Ca, calcium; PO4, phosphate; AP, alkaline phosphatase; PTH, parathyroid hormone.

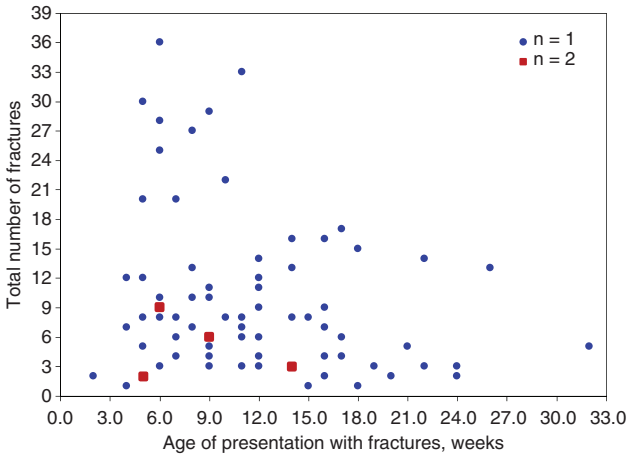

Figure 2: Age of presentation versus total number of fractures in 75 cases of infants with MBDI.
Infants with MBDI typically present in the first 6 months of life, and in the present series 82% (61 of 75) presented at or before 16 weeks of age. Twenty-seven of the 75 infants had 10 or more fractures. The extraordinarily high number of fractures without significant antecedent trauma is not seen at any time period in humans, and coupled with the observation of presentation in a very narrow window of time shortly after birth is consistent with the etiology of MBDI arising, in part, from the fetal risk factors noted in Table 4.

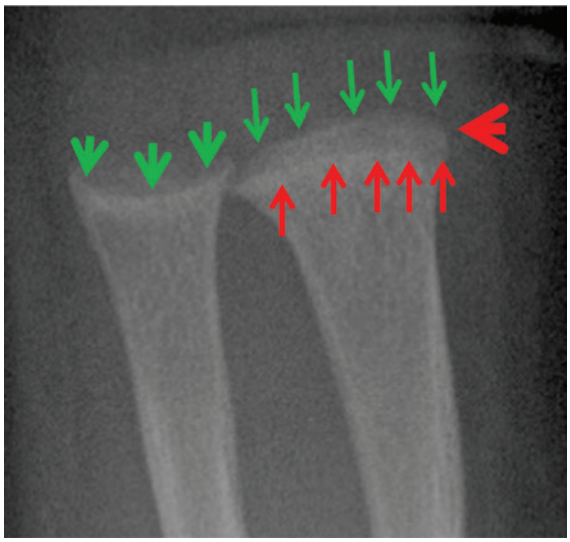

Figure 3: (Case 1) The abnormal growth plate of the distal forearm with cupping of the ulna and clubbing of the radius is shown.
The distal radius shows the original zone of provisional calcification (ZPC, red arrows) and the partial remineralization of the rachitic intermediate zone forming a "cap" (red arrowhead) between the original ZPC and the green arrows, a finding that is often mistaken for a CML fracture. There is significant ulnar cupping (stocky green arrowheads). History of Case 1: This male infant presented at 12 weeks of age with eight fractures including four rib fractures without internal thoracic injury and four CMLs. Risk factors for MBDI included twin pregnancy, mild prematurity (36 weeks of gestational age) and mild maternal VDD (25OH-VD = 25 ng/mL).

There were two infants who had no risk factors, 10 who had one, 28 who had two, 23 who had three, 10 who had four and two who had five.

There were three non-fetal risk factors that could have affected infant bone strength in the immediate postnatal period prior to presentation with fractures. There were eight infants with failure to thrive, 12 infants taking acid lowering drugs for gastroesophageal reflux disease (GERD) and one infant with prolonged postnatal immobilization from being on a ventilator in the pediatric intensive care unit for 2 weeks (see Case 5).

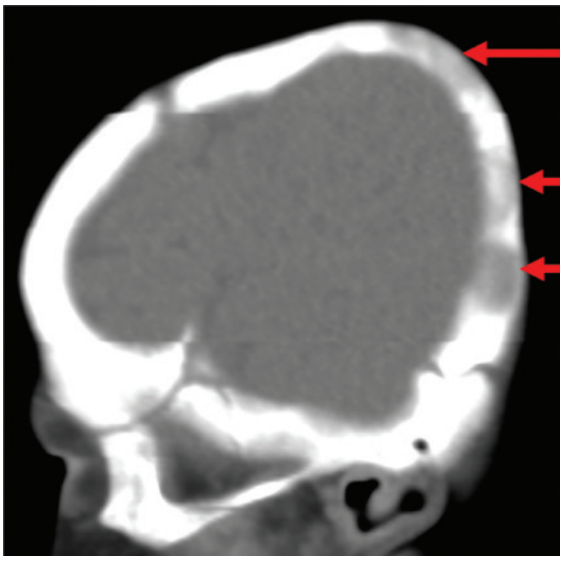

Figure 4: (Case 2) Abnormal skull mineralization on the reconstructed sagittal CT scan with several discrete spherical mineralization defects in the posterior skull (red arrows) is shown. History of Case 2: This female infant presented at 18 weeks of age with a transverse right femur fracture. Risk factors for MBDI included twin pregnancy, breech presentation with a short umbilical cord of 13 cm, Ehlers-Danlos syndrome in the mother, joint laxity in the infant and infant VDD (25OH-VD = 12 ng/mL).

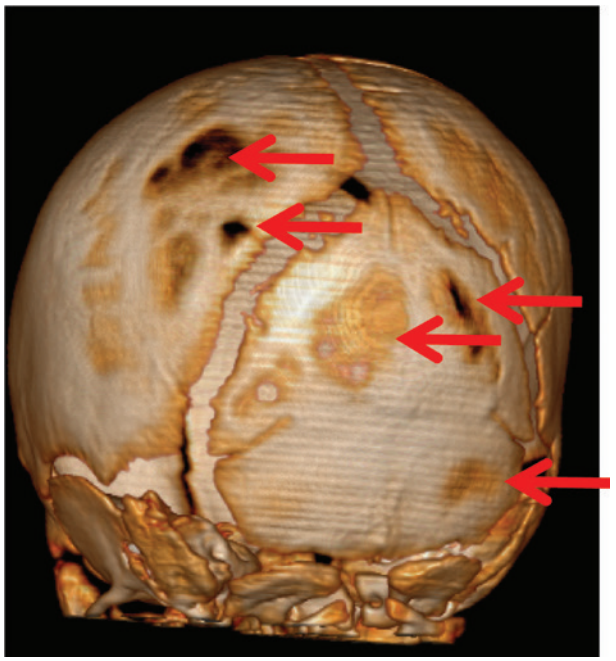

Figure 5: (Case 3) This figure is a three-dimensional (3D) surface rendered head CT reconstruction that shows the isolated posterior and lateral regions of brown and black (red arrows) indicating skull mineralization defects.
The brown edges of the widened sutures shows parasutural hypomineralization. History of Case 3: This female infant presented at 12 weeks of age with acute fractures of the distal left radius, left femur and left fifth rib. There were healing fractures of the right fifth rib, the right radius and ulna and two parietal bone fractures. The day prior to presentation with fractures the father accidentally fell while holding the infant, resulting in her head possibly striking a couch. Risk factors for MBDI included twin pregnancy, prematurity (34 weeks of gestational age), severe infant VDD (25OH-VD = 7.6 ng/mL), high PTH of 97 pg/mL, low phosphate of 3.3 mg% and high alkaline phosphatase of 783 U/L, maternal use of omeprazole in the second and third trimesters and maternal EDS-type 3.

Table 5 shows the results of the biochemical testing in the 75 cases. There was great variation in the battery of tests ordered.

Table 5A shows the profile results of the four commonly tested analytes: calcium, phosphate, alkaline phosphatase and PTH. In 16 cases no testing was done, in 23 cases the testing was normal (the various normal profiles are shown) and in 36 cases one or more of the four analytes was abnormal. Blood alkaline phosphatase was ordered in 44 cases and was elevated over half of the time, a finding consistent with either fractures or VDD. Blood calcium was the most commonly ordered of the four analytes and was normal in almost 90% of cases (46/52). PTH was ordered in less than one third of the cases (24/75) and was elevated in 25% of the cases ordered, a finding consistent with VDD.

Table 5B shows the specific outcomes of the four individual analytes, when tested. For example, in 52 of the 75 cases blood calcium was tested and in 46 cases it was normal, in one case it was high, and in five cases it was low.

Table 5C shows the results of the blood 1,25DiOH-VD testing which was the test least ordered (22/75 = 29%), and yet it had the highest frequency of abnormality with 14 of the 22 (64%) being elevated, and none being low. Table 4 shows the 25OH-VD test results.

Regarding osteogenesis imperfecta testing, 31 had negative DNA tests for *COL1A1* and *COL1A2* genes only, two had negative tests using skin biopsy biochemical testing for type 1 collagen, five had no testing and the status of 37 was unknown.

Discussion

Our analysis of this case series of 75 infants with MUF indicates that some were diagnosed as victims of child abuse based on conventional diagnostic criteria – namely pathognomonic radiographic findings – despite convincing evidence of an alternative explanation. Specifically, our review shows evidence of healing rickets in the radiographs, plausible risk factors for MBDI from the histories and sometimes abnormal lab findings that are also consistent with MBDI.

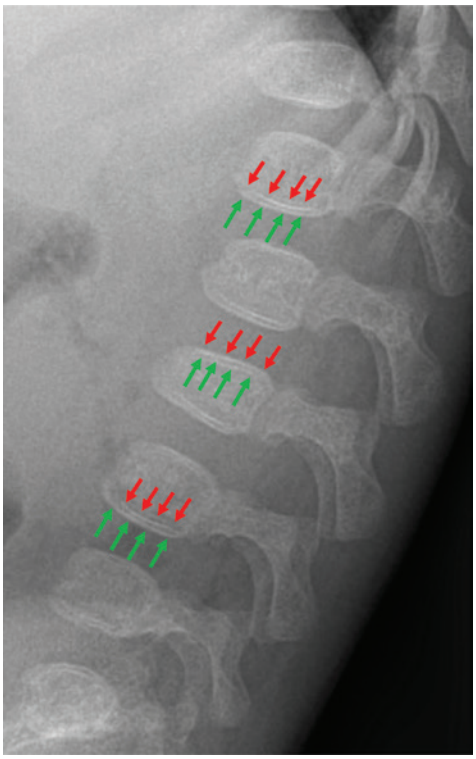

Figure 6: (Case 3) Abnormal vertebral bone mineralization with "bone in bone" in multiple vertebrae.
The thin black region sandwiched between two lines of calcified bone (between red arrows and green arrows) is nonmineralized osteoid. Normally, only the outer cortical bone is seen. History of Case 3: Please refer Figure 5 caption.

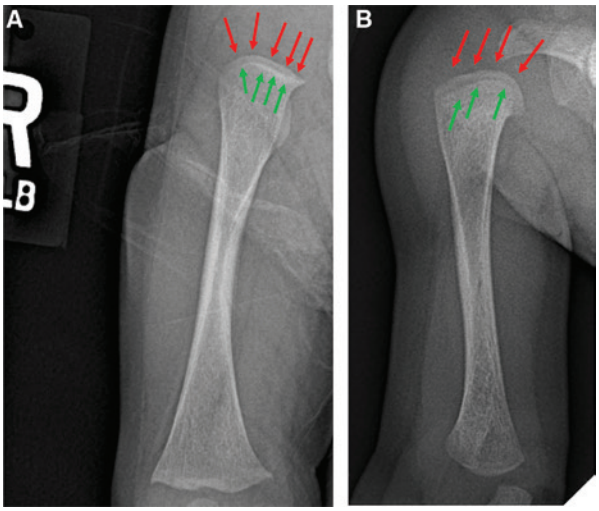

Figure 7: (Case 3) (A) A submetaphyseal band of the proximal femur. (B) A submetaphyseal band of the proximal humerus, represented by the thin black band sandwiched between the original ZPC (green arrows) and the new ZPC (red arrows) that has formed during the healing phase. The region between the green and red arrows is the rachitic intermediate zone of nonmineralized osteoid which can be confused for a CML.
History of Case 3: Please refer Figure 5 caption.

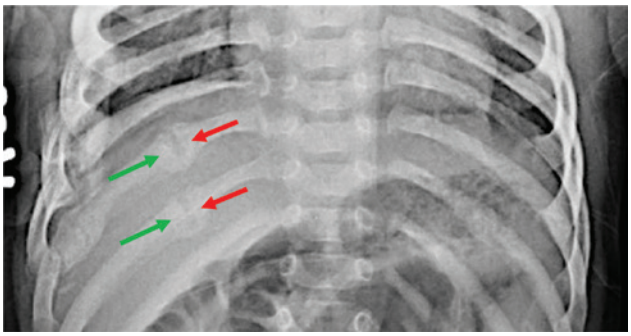

Figure 8: (Case 4) Multiple Looser zones that represent transverse seams of nonmineralized osteoid are shown, illustrated in two ribs between the red and green arrows.
The markedly elevated 1,25DiOH-VD and the lack of severe internal thoracic injury in the setting of 14 rib fractures is most consistent with these fractures being fragility fractures. History of Case 4: This male infant presented at 16 weeks of age with apparent tenderness of the ribs and was found to have four acute rib fractures, 10 healing rib fractures and bilateral acromion fractures. There was no internal thoracic injury. His mother noted decreased fetal movement and had EDS-type 3. Infant blood studies showed a 25OH-VD = 19.6 ng/mL (normal: 30–100) and a 1,25DiOH-VD >190 pg/mL (normal: 10–75). Risk factors for MBDI included decreased fetal movement, infant VDD and maternal EDS-type 3.

The radiographic findings in MBDI

The radiographic abnormalities of MBDI listed in Table 3 are those of healing rickets. Rickets is a mineralization deficiency that can be related to inadequate vitamin D, calcium and/or phosphate during pregnancy or early infancy. When any of these deficiencies are present in a mother during the third trimester or in early infancy, the detrimental effects of these deficiencies on bone strength are accentuated by the rapid skeletal growth rates seen in the last trimester of pregnancy and the first few months of life. As a result of impaired mineralization, there is accumulation of excessive amounts of nonmineralized osteoid/matrix in the growth plates, along trabeculae and within the periosteum/perichondrium. This affects bones with fastest growth rates such as the ribs, skull and metaphysis of long bones.

When deficiencies are restored after birth through treatment, increased oral intake, sun exposure, supplements or slowing of the growth rates, the mineralization of excessive osteoid/matrix results in exaggeration of these structures and the radiographic abnormalities presented in Table 3: SPNBF, perichondrial thickening, the appearance of a second zone of provisional calcification (ZPC) that produces a submetaphyseal band, trabecular thickening, skull mineralization defects and rib mineralization defects.

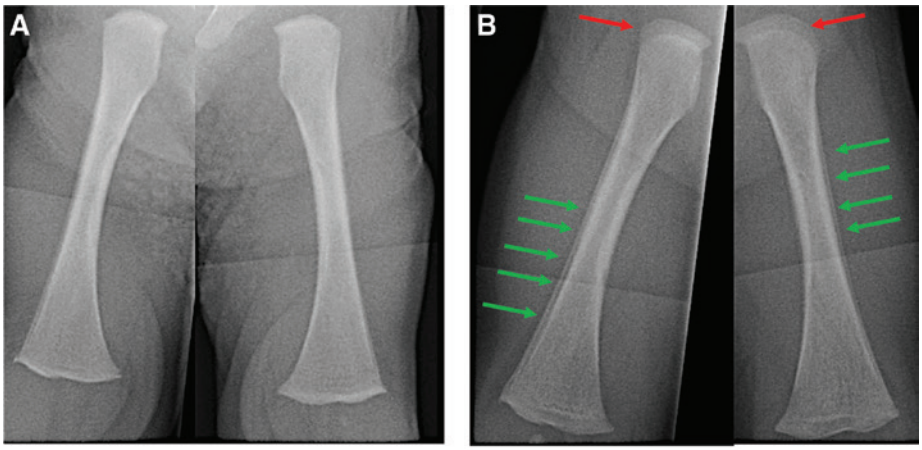

Figure 9: (Case 5) (A) No subperiosteal new bone formation (SPNBF) of the femurs at the time of presentation with MUF at 61 days of age. (B) At 77 days of age now symmetric SPNBF of the outer aspects of both femurs (green arrows) along with new caps of mineralized cartilage on the proximal growth plates (red arrows) is shown. These dramatic changes indicate there was excessive subperiosteal osteoid and growth plate matrix on the admission films at 61 days of age, becoming visible only after initiation of healing at 77 days of age.
History of Case 5: This male infant presented at 4 weeks of age with an apparent life threatening event and spent 27 days in the pediatric intensive care unit (PICU) and was intubated for 2 weeks. At 8 weeks of age, his dad was changing his diapers and heard a pop, and the infant would not use his right arm. Skeletal survey showed a mid-shaft right humerus fracture and three CMLs of the legs. Risk factors for MBDI include mild prematurity (35 weeks of gestational age), nutritional compromise from placental insufficiency and immobilization for 2 weeks while intubated in the newborn intensive care unit.

Osteopenia is the hallmark of decreased bone loading and can also be seen in rickets. It is a subjective and nonspecific finding, but when found indicates significant loss of bone mass and thus is associated with decreased bone strength. The radiographic findings of healing rickets are thus more specific, apparent and dramatic than those of osteopenia in our cases.

Once a fetus that experiences an environment of decreased fetal bone loading and/or insufficient calcium, phosphate or vitamin D is born, these factors tend to normalize over the first year of life, and especially in the first 6 months of life. Infant 25OH-VD levels usually rise from birth through 15 months of age [26, 27]. Fetal immobilization and intrauterine confinement that leads to decreased fetal bone loading ceases once the infant is born, and insufficient calcium, phosphate or vitamin D from the mother during pregnancy often tend to improve as the infant is given calcium, phosphate and vitamin D in their diet or as a supplement [30, 31]. As illustrated in Figure 13, this is why the major radiographic findings of MBDI are those of healing rickets and is likely the basis of the transient nature of MBDI with affected infants usually not fracturing after 6 months of age. Decreased linear growth rates after 6 months of age may further contribute to the recovery of more normal mineralization.

Thus, the recovery process of rickets affects the radiographic appearance of the periosteum to produce SPNBF, the growth plate to produce a second ZPC (the submetaphyseal band is the darker region between the original and new ZPC and mimics a CML) and the perichondrium to produce a spur as illustrated in Figure 13C. Most noteworthy is that the submetaphyseal band is almost always diagnosed as a CML and the SPNBF is likewise almost always diagnosed as a healing fracture, thus confusing child abuse for healing rickets.

We believe the radiographic abnormalities noted in Table 3 were often likely either not appreciated or dismissed by the reading radiologist for two reasons. First, pediatric radiologists have unwittingly accepted the previously noted, alleged pathognomonic radiographic findings of child abuse without question. This unwavering acceptance of child abuse in these cases has led to complacency and thwarted critical thinking in the determinants of infant bone strength.

Second, while pediatric radiologists are familiar with the radiographic findings of active rickets in which metaphyseal fraying is a hallmark, they are unfamiliar with the radiographic findings of healing rickets/MBDI in which metaphyseal fraying is absent. The clinical and radiographic features of healing rickets were well described in standard pediatric textbooks (Nelson, 4th edition, 1946) and pediatric radiology textbooks (Caffey, 1st edition, 1945) of the 1940s [60, 61]. However subsequent editions of each of these respected textbooks contained less commentary and fewer X-ray examples to the point that neither the most current Nelson nor Caffey textbook mentions healing rickets.

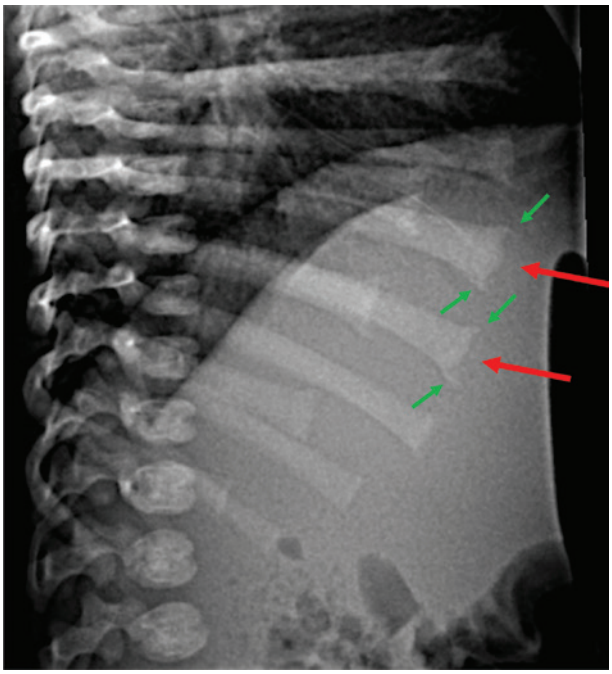

Figure 10: (Case 6) This figure is a lateral chest X-ray at 5 weeks of age that shows two ribs that are cupped and flared (red arrows) with perichondrial spurs (green arrows) at the costochondral junction, consistent with a rachitic rosary.
History of Case 6: This male infant presented at 5 weeks of age with facial petechiae and a subconjunctival hemorrhage that were likely related to extreme coughing from a respiratory infection. This prompted a skeletal survey which showed a possible CML and a safety plan was put in place. Follow-up X-rays then showed additional fractures in the care of multiple different caretakers. This suggested these were fragility fractures. Risk factors for MBDI included decreased fetal movement which the mother noted to her obstetrician, maternal administration of six calcium carbonate tablets (Tums)/day during the entire pregnancy for heartburn.

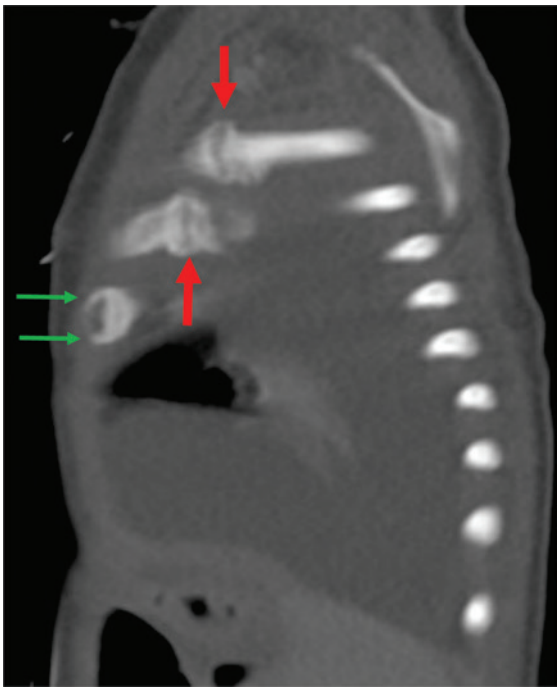

Figure 11: (Case 7) This figure is a sagittal reconstruction CT of the chest that shows vertical lucencies through callus of rib fractures (red arrows), findings again consistent with Looser zones.
The image shows a prominent rachitic rosary with thickened perichondrial spurs (green arrows). History of Case 7: This male infant presented at 11 weeks of age with severe congestion. A chest X-ray was performed which showed consolidation in the lingula and left lower lobe with a left pleural effusion that was drained. A skeletal survey showed multiple, bilateral, healing posterior and lateral rib fractures, greater than 30 in number, healing fractures of the distal left tibia and fibula and a nondisplaced fracture of the proximal left ulna without visible callus. A CT scan of the chest was also performed. The infant 25OH-VD was normal with an elevated 1,25DiOH-VD = 119 pg/mL (normal: 15–75). Risk factor for MBDI included maternal use of omeprazole during the third trimester and maternal EDS-type 3 (five recurrent dehiscences of her two cesarean delivery incisions, joint laxity, easy bruisability, joint pains of her knees, temporomandibular disorder, orthostatic hypotension and recurrent sprains; examined by MM).

It is not surprising that MBDI has been overlooked. Pediatric radiologists seem to require metaphyseal fraying to consider the diagnosis of rickets. However, while metaphyseal fraying is found in active rickets, it is not present in healing rickets, which is what our 75 cases represent. Infants with healing rickets typically present before 6 months of age, whereas infants with active rickets typically present after 12 months of age. Infants with healing rickets typically present with fractures, whereas infants with active rickets typically present with bowing of the lower legs and/or hypocalcemic seizures.

The risk factors for MBDI

In most infants, we found multiple predisposing risk factors that could explain the underlying basis of the MBDI, most of which had their effects during the third trimester of pregnancy, and thus were of fetal origin. The pathogenesis of MBDI and healing begins once the fetus is born. There were three postnatal risk factors operating between birth and the time of presentation with fractures that may have also contributed to the metabolic bone disease – use of acid lowering drugs, failure to thrive and prolonged postnatal immobilization from being on a ventilator [20, 49, 58].

The Utah paradigm is the contemporary model for understanding bone mineralization and bone strength [20]. The Utah paradigm applies to both the fetal and early postnatal time periods, and the predisposing factors we

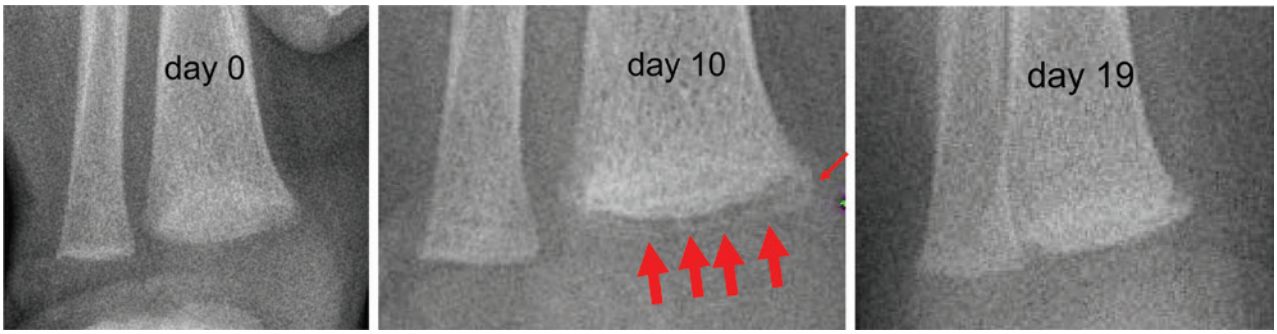

Figure 12: (Case 8) This figure shows the radiographic progression of healing rickets mimicking a CML.
The admission image (left) of the right ankle appears normal. On day 10 (center), a classic bucket-handle-like fracture (CML) appears (red arrows) representing mineralization of a new ZPC (thick arrow) above the radiolucent rachitic intermediate zone and a new thickened perichondrial spur (thin arrow). By day 19 (right), the rachitic intermediate zone has now almost completely remineralized without evidence of periosteal reaction indicating this was not a fracture, but rather mineralizing of previously nonmineralized osteoid. History of Case 8: This female infant presented at 12 weeks with knee discolorations. X-rays of the knees showed metaphyseal irregularities of both distal femurs with normal distal tibias. Follow-up skeletal survey 10 days later showed healing, bilateral metaphyseal fractures of the distal femurs and a healing bucket-handle fracture of the distal right tibial metaphysis that was not seen on the prior study. Follow-up X-rays of the legs 19 days after the initial skeletal survey described the distal right tibial CML as being in stable alignment. Risk factors for MBDI were maternal VDD with 25OH-VD = 14 ng/mL (normal: 30–100) and decreased fetal movement. The infant had an elevated 1,25DiOH-VD level = 106 pg/mL (normal: 15–75).

evaluated in the pathogenesis of MBDI as listed in Table 4 are thus logical and are in accord with this model of bone physiology.

Of the seven risk factors that can predispose to MBDI, the three that are most common are maternal VDD, decreased bone loading and prematurity. Maternal VDD and decreased bone loading are present in the fetal time period and then begin to normalize at birth. Likewise, the bone disease of prematurity tends to normalize during the first year of life. Several of the other risk factors including gestational diabetes and maternal use of medications during pregnancy that could impair bone mineralization would also cease their effects once the infant is born.

Using historical controls, several of the risk factors appear common:

1. VDD was present in 88% of the mothers tested with a background frequency of 46% [62]. VDD frequency was present in 56% of the infants tested with a background frequency of 40% [63]. Newborns are born with 25OH-VD levels that are approximately 70% of the mother's blood 25OH-VD, and then slowly increase after birth, even in breastfed infants, to levels that are approximately twice that of the newborn level at 2 months of age [26, 27, 62]. That maternal 25OH-VD is significantly lower than infant 25OH-VD in our cases suggests that maternal 25OH-VD during pregnancy (and thus the level that the fetus experiences) is likely the critical issue in these infants.
2. Decreased fetal bone loading as evaluated by any of several measures as listed in Table 4 was present in 84% of the cases. A history of decreased fetal movement was noted in 26 of the 59 (44%) singleton pregnancies, compared to the background frequency of 7% [57].
3. Premature infants were present in 11 of the 59 (19%) singleton pregnancies compared to the background frequency of 12% [64].

(A) Normal. There is minimal nonmineralized matrix in the growth plate and nonmineralized osteoid along trabeculae and along the subperiosteum/subperichondrium. The ZPC is normally a thin, uniform dense band of bone at the chondro-osseous junction. The perichondrial ring is often too small to detect radiographically. The trabeculae are thin and uniform. In normal mineralization, the nonmineralized matrix in the growth plate and the nonmineralized osteoid along the periosteum (red lines) are rapidly mineralized to form the ZPC and the cortex, respectively. (B) Active rickets. There is proliferation of nonmineralized osteoid in the perichondrial ring, under the periosteum and along trabeculae during the active phase of rickets, along with excessive growth plate matrix and hypertrophic chondrocytes. The original ZPC is usually preserved in acute rickets that is of short duration illness as seen in young infants, but may be absent in chronic illness as seen in older children. (C) Healing rickets. The mineralization of the excessive matrix/osteoid produces exaggerated new bone that can mimic a CML-like lesion, either a corner fracture (thick perichondria ring) or a bucket handle injury (new ZPC). The periosteal healing can mimic a traumatic injury or physiological SPNBF. In late healing of severe disease, the cortical and trabecular bone can appear markedly thickened.

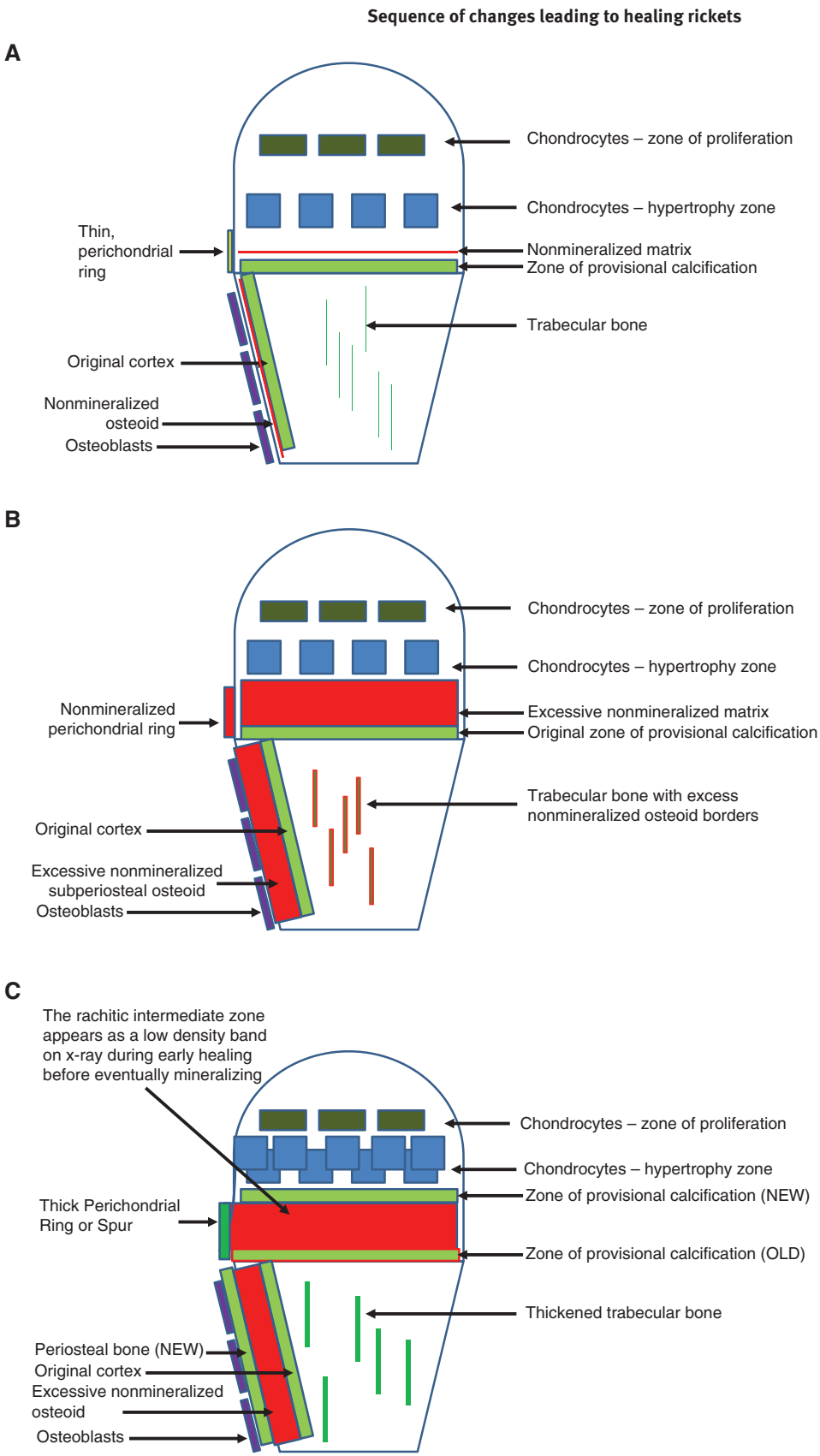

Figure 13: The sequence of changes in infantile bones during normal development and in active and healing stages of rickets can mimic traumatic injury.

4. The most dramatic finding was the marked over-representation of twins with a frequency of 21.3% compared to the background frequency of 3.3% [64]. Given the aforementioned three risk factors, this is not unexpected as twins are always confined and thus have decreased bone loading, are almost always premature and often have VDD *in utero* [17, 65]. In some populations, twins have a 25 times greater relative risk for developing rickets than singletons [17].

There is no known single gene that causes the EDS-type 3 which is the most common form of EDS, so EDS-type 3 is not typically evaluated by genetic testing [66]. EDS-type 3 is thus diagnosed by clinical examination and family history.

The association between joint hypermobility and EDS-type 3 may be that it causes an intrinsic weakness in bone [67, 68]. Another possible explanation for the association of EDS/joint hypermobility with fragility fractures in young infants is decreased fetal bone loading secondary to decreased strain on bones from the joint hypermobility during intrauterine movement.

Biochemical findings in MBDI

There was no uniformity in the biochemical testing ordered. Some cases had minimal testing, while others had a complete battery of tests related to bone physiology. There was no consistent profile or abnormality of blood analytes related to bone metabolism. Blood 25OH-VD levels, however, suggested a relatively high frequency of VDD in those mothers who were tested for vitamin D status which was greater than that found in the group of infants tested. This suggests that fetal VDD is an important factor in some cases of MBDI. Of infants tested for OI, none were affected.

While hypocalcemia was occasionally found, it is not unexpected that the blood calcium levels in MBDI tend to be normal, as a robust compensatory mechanism exists to maintain the blood calcium level in the normal range with 1,25DiOH-VD playing a critical function in this homeostasis [69]. The most dramatic finding in the analysis of lab studies was that, when tested, 1,25DiOH-VD was elevated in 64% of cases. An elevated 1,25DiOH-VD is consistent with underlying metabolic bone disease, and yet the most recent AAP-COCAN related to infants with fractures does not recommend that 1,25DiOH-VD be tested in infants with unexplained fractures. We believe 1,25DiOH-VD should be tested in all infants with MUF, because an elevated level suggests a disorder in bone mineralization.

Fetal and infant bone strength is a multifactorial characteristic

The skeletal bone strength of a newborn infant is the final bone strength of the fetus, and diminished fetal bone strength may be revealed by fragility fractures in the young infant, typically less than 6 months of age.

Our analysis of the present series of infants with MUF suggests that multiple fetal factors, predominantly environmental in origin, are major determinants of fetal and young infant bone strength. Other environmental factors include copper deficiency, prolonged magnesium exposure and vitamin C deficiency. Genetic factors that influence young infant bone strength are revealed through several monogenic disorders associated with fragility fractures including OI (type 1 collagen genes [*COL1A1* and *COL1A2*] and their modifying genes associated with autosomal recessive OI), hypophosphatasia (*ALPL* gene), Menkes disease (*ATP7A* gene) and others [70].

Given the multiple environmental and genetic factors that influence fetal bone strength (and thus young infant bone strength), we believe that newborn and young infant bone strength is a multifactorial characteristic.

The magnitude of effect of any adverse environmental factor that affects bone strength is directly related to the rate of growth of the skeleton at that particular time. The most rapid period of bone growth is in the third trimester of pregnancy during which fetal linear bone growth is about 100 cm/year. Neonatal linear bone growth is about 50 cm/year [71]. It is during times of most rapid bone growth that the human skeleton is at greatest risk to become undermineralized if one of the critical factors that determines mineralization is compromised [72]. As previously noted, the Utah Paradigm posits that bone loading and calcium, phosphate and vitamin D availability are critical factors that determine normal bone strength. Thus, during the most rapid period of skeletal growth, the third trimester of the human pregnancy, decreased fetal bone loading and insufficient maternal provision of calcium, phosphate and vitamin D to the fetus can result in a weaker skeleton in the fetus and young infant.

Potential misdiagnosis of MBDI for child abuse

The findings herein suggest that over the past four decades some infants who present with MUF may have been misdiagnosed as victims of abuse, when the correct diagnosis was likely MBDI. We believe there are four main reasons

our approach in establishing a diagnosis in infants with MUF yields diametrically different conclusions from the conventional approach:

- First, neither the medical literature nor scientific studies support the unfounded dogma that there are highly specific bone radiographic findings of child abuse in the infant with MUF. Once child abuse is accepted as the diagnosis based on these false premises, no further consideration is given to predisposing factors that might cause a weaker fetal/infant skeleton, and thus an alternative, medical explanation for the fractures. The radiographic claims that are perpetuated by the unfounded dogma include the following:
  1. CMLs are specific for child abuse; – false, they are not [2, 3]. Moreover, they often indicate an underlying bone mineralization disorder that would indicate bone fragility [2, 3].
  2. Posterior rib fractures are specific for child abuse; – false, they are not [4, 5].
  3. The notion that normal bone whiteness on plain X-rays infers normal bone mineralization, and thus normal bone strength; – false, it does not. Up to 30–40% of bone density must be lost before the eye of the radiologist can detect such a loss [73, 74]. Thus, a plain X-ray that appears to have normal bone whiteness can still have considerable loss of bone density (up to 40%). Moreover, bone strength is determined by factors other than bone density including bone geometry and the intrinsic material properties of the bone [6, 7]. Like bone density, these other properties are not evaluated by plain radiographs. Thus, plain radiographs cannot adequately assess bone strength.
- Second, as previously noted, the radiographic findings in MBDI (healing rickets) have not been appreciated, and they are distinct from those of active rickets.
- Third, the multifactorial nature of fetal and young infant bone strength has not been appreciated. Previously only OI was considered as an alternative medical explanation for the infant who presented with MUF [1].
- Fourth, one of the common misconceptions is that if there is a normal blood calcium with normal bone mineralization on the radiographs, then metabolic bone disease is excluded. This is inaccurate, but unfortunately this type of analysis reinforces the diagnosis of child abuse in these cases.

Why child abuse is unlikely in these 75 cases

We believe that child abuse is unlikely in these cases for four reasons:

- First, at the time of presentation and on prior health care visits, there was no evidence of any significant bruising at the site of the fractures. Lack of bruising at the sites of the fractures in an infant with MUF suggests that these are more likely fragility fractures, and that the forces that caused them were likely minor such as those that occur with routine handling of the infant in changing clothes or diapers or in holding for medical procedures [75–77].
- Second, Garcia et al. showed that infants with normal bone strength who incur four or more rib fractures from motor vehicle accidents or violent child abuse always have severe internal lung injury (contusion hemothorax, pneumothorax) [78]. In our series, 36 of the 75 infants (48%) had four or more rib fractures, and none of them had severe internal thoracic injury or respiratory stress. This observation is strong evidence that these are fragility fractures. Some of these rib fractures may have been from the birthing process.
- Third, as illustrated in Figure 2, there are two striking observations about how infants with MBDI present. First, they can present with an extraordinarily high number of fractures (we believe not all the CMLs are necessarily fractures), unlike any other time in the human life span. Second, the presentation is in a very narrow time period that peaks at 12 weeks of age with few cases after 6 months. Series of infants with temporary brittle bone disease show a similar age of presentation distribution [19, 31]. We believe temporary brittle bone disease and MBDI are the same. Child abuse experts insist that the diagnosis of temporary brittle bone disease or congenital/healing rickets is a ruse for child abuse. However, if that were the case, one would expect to see an approximately even distribution of such cases during the first 24 months of life, and this is not observed. The narrow range of presentation with fractures occurring in the first 6 months of life and the high number of fractures suggest that there is a fragile bone state as a result of factors operating in the fetal time period where the growth rate is the highest in the human life span.
- Fourth, Paterson has provided compelling follow-up information on 85 infants with MUF that he believed to have temporary brittle bone disease, but who were diagnosed as battered infants. Paterson testified on behalf of the parents in the legal proceedings in these cases, and 63 of the 85 infants were

returned to the parents. Follow-up of 61 of these 63 infants has been for a mean of 6.9 years (range 1–17 years; median 6 years), and there has been no evidence of child abuse in the 61 infants returned to their parents [79]. Paterson has also provided compelling case histories of infants with temporary brittle bone disease in which the fractures occurred in the hospital [80].

Limitations

The main limitations of this study are that:

1. It is a retrospective and descriptive case series, and selective of only infants with MUF who had abnormal radiographs, and not of the total universe of infants with MUF.
2. Information was obtained from available medical records, and not all infants and parents were examined.
3. There were no controls for the risk factors; historical controls were utilized.
4. A single radiologist interpreted the radiographs, so no inter-observer correlations could be made.

The strength of the study is that we noted radiographic findings that were consistent with poor bone mineralization, and we identified risk factors that are either known to be/can be associated with poor bone mineralization or are consistent with the underpinnings of the Utah Paradigm.

Conclusions

Infants who present with MUF should be evaluated by a child abuse team to ensure the infant is returned to a safe environment and also by a pediatric bone specialist to ensure a comprehensive evaluation for a bone disorder has been done. Such an approach maximizes the likelihood that an infant will not be returned to an unsafe environment and that parents will not be unfairly accused of child abuse when an underlying bone fragility disorder could support a plausible, socially benign alternative explanation for the infant's fractures.

Our analysis of these cases reveals MBDI as a common cause of fractures in young infants that can often be differentiated from child abuse, and we recommend the following in the evaluation of the infant with MUF:

1. Evaluation of the pregnancy history and medical history for the seven risk factors noted in Table 4.
2. Evaluation of infant and maternal blood studies related to bone physiology: Ca, PO4, alkaline phosphatase, PTH, 25OH-VD, 1,25DiOH-VD, comprehensive OI DNA testing (including autosomal recessive forms).
3. Evaluation of the radiographic findings noted in Table 3.

We believe the conventional radiographic approach to establishing the diagnosis in young infants who present with MUF is flawed and has incorrectly diagnosed child abuse in some infants who likely had MBDI. Recognizing both the radiographic findings of MBDI and the predisposing factors to MBDI will lead to a greater likelihood of correct diagnoses of infants presenting with MUF.

Our appreciation of these predisposing risk factors and that infant bone strength is a multifactorial characteristic has developed over the last 20 years. A recent epidemiological study of infant fractures in Sweden from 1997 to 2014 also affirms the multifactorial nature of infant bone strength and similar risk factors that we noted in our 75 infants [81]. Future studies related to understanding infants with MUF should include controls and more than one radiologist to interpret the radiographic findings so that inter-observer correlations can be assessed. It is likely that future research will reveal other factors that relate to young infant bone strength that are unknown to us in 2019.

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