Copper Deficiency Presenting as Metabolic Bone Disease in Extremely Low Birth Weight, Short-Gut Infants

abstract

Copper deficiency can cause bone lesions in infants, which might be confused with child abuse. Two extremely low birth weight preterm infants had complicated medical courses requiring prolonged parenteral nutrition for short-gut syndrome, which led to the development of cholestasis. Both had spent their entire lives in the hospital. They had been on prolonged ventilator support for chronic lung disease. They developed signs of copper deficiency between 5 and 6 months of age, initially raising child abuse concerns. Musculoskeletal discomfort led to the recognition of radiographic findings of metabolic bone disease. Included were osteoporosis, metaphyseal changes, and physseal disruptions. Copper levels were low; both low copper parenteral nutrition and gut losses from refeeding diarrhea likely contributed to their deficiency. Therapeutic supplementation with copper corrected their deficits and clinical and radiologic findings. The information from these cases, in particular, their radiologic findings, indicate the need to monitor copper status in at-risk premature infants. These findings may aid prevention and earlier recognition of copper deficiency. Their specific radiologic and clinical findings should aid differentiation of such children from abused infants.

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KEY WORDS

Copper deficiency, short bowel, metabolic bone disease, child abuse, pediatric radiology

ABBREVIATIONS

CML—classic metaphyseal lesion
CT—computed tomography
PN—parenteral nutrition
ZPC—zone of provisional calcification

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Copper deficiency has been recognized to cause bony lesions that could be confused with child abuse. Copper is an essential trace element and important enzyme cofactor. Deficiency prevents enzymes from functioning properly and explains clinical and radiologic deficiency findings: anemia, neutropenia, growth failure, hair depigmentation, apnea, edema and hypothermia. Bone abnormalities include metaphyseal changes and fractures, similar to abusive injuries. Commonly affected are very low birth weight infants and children requiring long-term parenteral nutrition (PN). Other predispositions include low-copper formulas or unmodified cow milk, malabsorption syndromes, and previous malnutrition and its repletion. The primary excretory route for copper is bile; reduced cholestasis and high tissue levels in patients with Wilson disease occur; concerns arose that elevated levels and/or body copper endowment might cause bile duct toxicity and inflammatory cholestasis. Copper may be reduced or omitted for PN patients with cholestasis to minimize toxicity. Appropriate dosages to prevent toxicity, yet avoid insufficiency, are unknown. It may be patient dependent. Copper testing requires large blood volumes for small infants (4 mL), which discourages routine monitoring.

We describe clinical, laboratory, and radiologic features of 2 compromised premature infants, who developed copper deficiency. They had previously reported clinical and laboratory deficiency features and classic radiologic findings. Their metaphyses were similar to classic metaphyseal lesions (CMLs) of abused infants, leading to abuse consultation. However, skeletal changes were sufficiently unique to be recognized to reflect metabolic bone disease, which led to diagnosis by copper assay.

**PATIENT PRESENTATIONS**

**Case 1**

A 27-week-gestation girl weighed 625 g, small for gestational age. Her course was complicated by surgical necrotizing enterocolitis, leaving 80 cm of bowel and an ileostomy. Her chronic PN contained 20 μg/kg per day copper. On half-volume Neocate (124 μg/100 Cal copper), she had refeeding diarrhea. She developed cholestasis (conjugated bilirubin 3.7 mg/dL, aspartate transaminase 65 U/L, alanine aminotransferase 97 U/L). Images at 5 months for “new lower extremity tenderness” showed distal femur, proximal tibia and fibula, proximal humerus, and distal radius changes similar to CMLs (Fig 1). Metaphyseal lesions raised questions of in-hospital abuse by her mother or hospital staff. Her left proximal femur was displaced superiorly and laterally from her acetabulum (Fig 2).

**Case 2**

A former 24-week-gestation, 720-g boy needed increasing pain medicine. He had received prolonged steroids for chronic lung disease and had necrotizing enterocolitis at 2½ months, leaving 32 cm of bowel, including residual cecum. On
Although his hair had been thick, evident left physeal separation (Fig 4). Profuse periosteal reaction, and more changes like scurvy: fragmentation, undermineralized, with poorly mineralized ZPCs. Yet metaphyses at proximal humerus and hips were occasionally injured abusively,9 or metaphyses at proximal humerus and hips are occasionally injured abusively,9 all proximal humeri and hips were abnormal. Metaphyses showed severe metabolic bone disease, with somewhat poorly calcified ZPCs. Yet metaphyses remained better preserved than rickets with less flaring and cupping. Osteomalacia, as in rickets, results from inadequate protein matrix formation, resulting in wide-spaced, “ground glass” trabecular pattern, but normally mineralized ZPC. Osteomalacia, as in rickets, results from
inadequate mineralization of normal protein matrix. It causes loss of ZPC and fuzzy, generalized reduction in bone density. Our patients had changes more typical of osteoporosis than osteomalacia and also had periostial reactions reminiscent of scurvy. Neither infant had rib fractures, common in abuse, but mild rib end flaring was present. Neither had skull or diaphyseal fractures, common in abuse, but skulls were poorly mineralized. Both children had cytopenias typical of copper deficiency. Metabolic bone changes were so widespread and severe that it is unlikely that they would be missed or confused for long with abuse.

The index epiphyseal separation in the first child was initially thought to represent hip dislocation. Early recognition of epiphyseal separation is difficult owing to the absence of ossification centers in young infants. Liberal use of ultrasound, CT, or MRI can exclude pyarthrosis or congenital dislocation. They can localize nonossified epiphyses in joint spaces, separate from displaced diaphyses. Despite widespread metaphyseal abnormalities and 4 epiphyseal separations, the results of the second child’s nuclear scan were normal, except for 1 hip.

It should not be surprising that copper, which participates in production of bony matrix, not its calcification, when deficient, would result in osteoporosis more than osteomalacia. Likewise, insufficient protein matrix connections between epiphyses and metaphyses could predispose to epiphyseal separation. The periosteum is normally attached to infant diaphyses by collagenous fibers. Deficient collagen production from lack of copper could predispose to abundant periosteal new bone, similar to calcification of subperiosteal hemorrhage of vitamin C deficiency. At 3 months of age, a similar pattern developed in 3 premature infants fed low-copper formula during the 1960s. Two had epiphyseal separations, and all had osteoporosis and prominent periosteal new bone. One infant had low postmortem hepatic copper.

CONCLUSIONS

Conventional practice may reduce or eliminate copper supplementation in infants with cholestasis. However, Frem et al found 20 μg/kg per day of copper did not increase toxicity or worsen cholestatic liver disease; yet, it prevented clinical deficiency. It may not be necessary to reduce total parenteral nutrition copper in cholestasis, and reduction might risk deficiency.

Some infants, particularly small premature infants with gut disease receiving prolonged low-copper PN, risk deficiency. Their history, hematologic changes, diffuse osteoporosis, and synchronous, widespread metaphyseal disease should allow easy differentiation from child abuse.

These cases emphasize that copper deficiency should be considered in the differential diagnosis of metabolic bone disease in premature infants if they have clinical and/or nutritional histories, such as PN and/or enteral disease, that place them at risk. Copper levels should be obtained on high-risk infants, but are not warranted in routine evaluation of infants presenting with fractures who have benign nutritional and clinical histories and typical child abuse radiologic findings.

REFERENCES

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