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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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 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).

**FIGURE 1**

Case 1: Corner fracture CML-like lesion of distal femur (arrow). Bucket handle CML-like lesion of proximal tibia (arrowhead). Bones demonstrate severe osteoporosis and irregular metaphysis.

**FIGURE 2**

Case 1: Bones are poorly mineralized demonstrating osteoporosis, but with reduced definition of the zones of provisional calcification. Hips are separated through the physes, resulting in displacement of the metaphyses from the epiphyses, which remain in joint spaces (arrows). Metaphyses are fragmented (arrows).

Femoral heads remained unossified. Because immobilization precluded ultrasound evaluation, computed tomography (CT) was done to differentiate epiphyseal disruption from hip dislocation. Femoral heads were in her acetabulae, but displaced from irregular metaphyses. Zones of provisional calcification (ZPC) were undermineralized. Chest, spine, clavicles, ribs, and skull were normal, except for generalized osteoporosis.

She had anemia, red blood cell fragments and spherocytes, neutropenia and thrombocytopenia, and normal levels of iron, calcium, zinc, parathyroid, and alkaline phosphatase. Copper level was 10 µg/dL (normal, 30–150).

After diagnosis, she received a week of 50 µg/kg per day copper; then 30 µg/kg per day. Six weeks later she had dramatic periosteal new bone formation around proximal humeri and femurs, similar to scurvy. By 9½ months, copper level was 178 µg/dL, and metaphyses were healing.

**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 fraying and cupping, generalized demineralization, flaring, and prominent beaking (Fig 3). Epiphyseal separation was delayed. ZPCs were poorly mineralized. Metaphyseal changes led his neonatologists to seek abuse consultation. Radionuclide bone scan results were normal, except for increased left hip activity. Proximal femur physeal disruptions and flared rib ends were present on CT scan. Skull was undermineralized, with poorly visualized orbital rims and widened sutures. He had thrombocytopenia, normal hematocrit, but abnormal red blood cell morphology. Iron studies, ionized calcium, phosphorus, alkaline phosphatase, and parathyroid were relatively normal, whereas 25-OH vitamin D was low normal (30 ng/dL). Copper level was below detection limit (<20 μg/dL) (laboratory standards changed in the 8 years between patients).

One month later, his shoulders had changes like scurvy: fragmentation, profuse periosteal reaction, and more evident left physeal separation (Fig 4). Although his hair had been thick, straight, and black, it became sparse, curly, thin, and lightly pigmented, like Menke syndrome hair.

His daily dose of PN copper was increased to "normal" (20 μg/kg per day), but after 1 month remained undetectable. He received 50 μg/kg per day for 1 week, then 30 μg/kg per day. Subsequent level was 71 μg/dL, and skeletal changes healed.

DISCUSSION
Copper deficiency causes clinical and radiologic abnormalities. Most fetal stores (85%) are accumulated in the last trimester. Half is bound to hepatic metallothionein. Term infants’ endowment can be sufficient for several weeks without dietary copper. Unmodified cow milk has low copper content (11 μg/dL). Healthy infants fed exclusively unmodified cow milk beyond 4 to 6 months risk deficiency. Current formulas are adequately supplemented. Premature infants born with decreased copper reserves and increased growth requirements risk deficiency earlier postnatally. Sick newborns and premature infants often require PN. American Society for Clinical Nutrition’s vitamin and trace elements guidelines recommend 20 μg/kg per day copper for preterm and term infants. Patients with higher copper levels might risk bile duct toxicity and inflammatory cholestasis. It is unclear whether elevated copper levels are the cause, consequence, or both of cholestasis. PN, itself, causes cholestasis. To prevent toxicity and liver damage, patients may receive less copper, but this could risk deficiency. Copper is primarily excreted in bile, but some is reabsorbed lower in the intestine. Children with short-gut lose copper through diarrhea. Appropriate supplementation probably is patient dependent. Copper should be measured frequently to prevent deficiency and toxicity, however, 4-mL blood samples discourage measurement.

Although abuse initially was considered in these infants, metabolic bone disease of copper deficiency was rapidly suspected. Any of their metaphyses could have been confused with an abused infant’s CMLs. However, several clinical and radiologic findings should allow differentiation. Both were severely ill small premature infants who never left the hospital. Both had prolonged PN for short gut, developed cholestasis, and had ongoing gut losses. Despite widespread bone disease, calcium, phosphate, alkaline phosphatase, vitamin D, and parathyroid hormone concentrations were remarkably normal. Widespread, symmetric metaphyseal involvement appeared of relatively synchronous onset, unusual for abuse, but common with metabolic bone disease. Metaphyses, particularly about knees, had prominent metaphyseal beaks similar to Menke syndrome. However, beaks were not separate from adjacent metaphyseal margins, as with CMLs. Although physis or metaphyses at proximal humerus and hips are occasionally injured abusively, 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. Osteoporosis results from inadequate protein matrix formation, resulting in widespread, “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 periosteal 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 physeal separation is difficult owing to the absence of ossification centers in young infants. Liberal use of ultrasound, CT, or MRI can exclude pyarthrosis, secondarily 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 bone matrix, 1 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 15 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.

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