Clinical manifestations of nutritional copper deficiency in infants and children¹,²

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ABSTRACT A series of reports in the 1960s highlighted nutritional copper deficiencies in infants and children recovering from malnutrition in Peru; since that time, a cascade of additional cases in premature infants, in patients receiving total parenteral nutrition, and in those receiving special diets or unmodified cow milk have been reported. The identification by Danks that Menkes syndrome, a genetically determined defect in copper absorption and utilization, is responsible for the observed clinical manifestations provided further insight into the physiopathologic effects of copper deficiency. New information on the metabolism and physiologic role of copper, plus the identification of additional copper metalloenzymes and improvement in how to determine copper status, has fueled interpretation and speculation on how and why the classic signs of copper deficiency occur, as well as on the possible effects of mild deficiencies. Also under scrutiny are potential interactions between other elements and the effects of other elements, even when given in acceptable amounts, on copper status. There should be no constraints in thinking on other possible effects of impaired copper status in humans. I review some of the history of nutritional copper deficiency in infants and children and attempt to interpret some of the clinical manifestations in light of newly acquired information. Am J Clin Nutr 1998;67(suppl):1012S–6S.

KEY WORDS Copper deficiency, infants, children, prematurity, malnutrition, Menkes syndrome, copper status

INTRODUCTION

The existence of copper deficiency in humans was debated for many years from the time Josephs (1) suggested in 1931 that copper deficiency would account for instances of anemia in milk-fed infants who were refractory to iron treatment. A series of reports were made in the late 1950s on infants with anemia, hypoproteinemia with peripheral edema, hypoferremia, and hypocupremia who were suffering intestinal losses of copper as a result of enteropathies (2–5).

Our group in Peru first characterized the classic clinical signs of this deficiency in the 1960s (6–9): hypocupremia; low ceruloplasmin; neutropenia; anemia (hypo chromia with various degrees of anisocytosis), with the bone marrow showing signs of maturation arrest of the myeloid series; some cytopenia vacuolation and in some cases early megaloblastic changes; and bone lesions that include fraying and cupping of the metaphysis with spur formation, osteoporosis with a ring-like appearance of the epiphyses, and fracture of long bones. Most of these clinical signs were found in previously severely malnourished infants who had been rehabilitated for several months with a modified high-energy (by the addition of oil and carbohydrate), milk-based infant formula containing vitamins and iron.

Because of anemia, in three of the four cases that were first reported (6), therapeutic doses of oral iron were given for several weeks, which, retrospectively, may have contributed to further deterioration of copper status. The signs of copper deficiency developed although there was absolutely no evidence of malabsorption and total serum protein and albumin concentrations were normal. In two cases, the response to copper supplementation was prompt and dramatic, whereas in the other two, responses obtained with vitamin B-12 administration were slow but good and the addition of copper resulted in a complete response. These cases are striking examples of growth imbalance copper deficiency, resulting from growth acceleration due to a high-energy, low-copper intake by infants whose copper stores were low because of multiple episodes of diarrhea (8–10 in this population during the first year of life) coupled with early weaning, intermittent starvation, and prolonged use of diluted milk feedings (which is still a common practice for diarrhea management in many developing countries.)

The initial report of those four infants led us to review the records of 173 former patients admitted to the nutritional unit of the British American Hospital in Lima, Peru, and to a regular screening of all newly admitted malnourished infants for evidence of copper deficiency (7). Sixty-two instances of copper deficiency were identified at the time of admission or during the course of rehabilitation with milk diets. In several cases that were diagnosed retrospectively, we were fortunate to have stored frozen serum samples, thus allowing the measurement of serum copper and ceruloplasmin concentrations.

Forty-four of the 62 infants were estimated to be copper deficient at admission on the basis of the rapidity (< 50 d) with which they developed signs of copper deficiency when consuming the low-copper diet based on cow milk formula. The peak incidence was at 7–9 mo; younger infants apparently were protected by their prenatal copper stores. Most of the infants estimated to be deficient experienced spontaneous remissions when they were switched to other diets with mineral supplementation. Those few

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who remained copper deficient were treated promptly and their response to copper administration observed. Subsequently, when infants were placed on the same modified cow milk formula, 2.5 mg Cu/d was routinely added.

CLINICAL SIGNS OF COPPER DEFICIENCY

Neutropenia was found to be the earliest and most common manifestation of copper deficiency and the most sensitive indicator of the adequacy of treatment. We speculated that besides the observed low number of mature neutrophils in bone marrow, neutropenia could also be the result of decreased survival of polymorphonuclear cells (6). A report by Percival (10) discusses other possible mechanisms of neutropenia and indicates that even if the primary site of impairment is unknown, copper deficiency could damage the cell either in the bone marrow or in the circulation. Copper deficiency may also impair the rate of stem cell proliferation or differentiation or may produce a quicker rate of cellular destruction and clearance. The observation of a normal number of progenitor cells and a low number of mature cells in the bone marrow of copper-deficient humans suggest that there is a delay in the process of cellular differentiation as a result of a lack of copper (11). However, there is also evidence suggesting a shortened cellular life span, and the presence of antibodies to neutrophils (12) suggests an increased clearance of neutrophils in copper deficiency. More research is needed into the mechanism by which copper deficiency results in neutropenia in copper-deficient animal models, focusing on the process of cellular differentiation as well as the viability of neutrophils in both the circulation and the bone marrow.

When serum copper and total neutrophils were analyzed simultaneously in our studies in Peru (8), we found a significant positive correlation between these indexes. Values above the regression line corresponded to clear-cut episodes of infection. Although these copper-deficient infants could respond to infection with neutrophilia and some elevation of serum copper, the latter was much lower than the usual response.

Copper deficiency is regularly associated with hypoceruloplasminemia (13), but the reduction in ceruloplasmin is greater than one would predict from measurements of serum copper concentrations. After the administration of supplementary copper to deficient patients, ceruloplasmin concentrations can rise within 24–48 h. Usually, serum copper concentrations return to normal values before ceruloplasmin concentrations do. It is therefore possible that repletion of ceruloplasmin is not of primary importance in the correction of copper deficiency. This is consistent with the hypothesis that ceruloplasmin is needed to facilitate copper excretion more than transport. Thus, copper-deficient infants to whom copper is given are assumedly in positive copper balance and excrete little or no copper.

A serum copper concentration < 0.90 mg/L and particularly < 0.45 mg/L lends strong support to the diagnosis of deficiency, as does low or absent serum ceruloplasmin concentrations. In most of our patients, when serum copper concentrations were < 0.45 mg/L, ceruloplasmin concentrations were < 20 mg/L. When serum copper concentrations were between 0.45 and 0.90 mg/L, ceruloplasmin concentrations were usually between 20 and 200 mg/L. In a few patients who were in the process of developing copper deficiency, ceruloplasmin concentrations fell below 200 mg/L before serum copper concentrations fell below 0.90 mg/L.

The results of Graham and Cordano (14) lend support to the concept of two effects of copper deficiency on iron metabolism in humans. The first, occurring early, is an adverse effect on iron absorption or mobilization. Untreated iron deficiency that precedes or develops simultaneously with copper deficiency is characterized by hypochromia that persists despite treatment with copper alone. The second and later effect of copper deficiency on iron metabolism relates to inadequate erythropoiesis, even in the presence of abundant iron stores. When iron stores were present, anemia responded promptly to copper supplementation alone.

CASE REPORTS

Because of its exceptional characteristics, I will discuss in some detail the case I presented at the second Western Hemisphere Nutrition Congress in Puerto Rico of a marasmic infant in whom severe copper deficiency was diagnosed a few hours after the infant was admitted to the hospital (A Cordano, GG Graham, unpublished observations, 1968). The laboratory reports indicated that there were no neutrophils in the peripheral blood. This led to an immediate request for measurement of serum copper concentrations, which turned out to be undetectable. As seen in Table 1, copper supplementation (2.5 mg/d, which for this infant was equivalent to 528 μg·kg⁻¹·d⁻¹) was started on the second hospital day. A progressive increase in neutrophils was noted and normal values (> 1.5 × 10⁹/L) were attained by day 15. Serum copper concentrations returned to normal values by day 5, whereas ceruloplasmin lagged behind, normalizing ≈ 2 wk after treatment with copper was started. Hemoglobin and hematocrit values reached 10 g/dL and 0.33, respectively, by day 24.

An additional interesting observation, showing the marked sensitivity of neutrophil response to copper administration in patients who may have poor copper stores, was noted on day 16, when the copper supplement was inadvertently not provided and neutrophils dipped to only 0.770 × 10⁹/L. We realized that insufficient copper was being provided and the dose was increased to 785 μg·kg⁻¹·d⁻¹; the neutrophil count increased rapidly to 3.696 × 10⁹/L in 24 h and remained normal afterward. Although examination of this patient’s bone marrow at admission showed maturation arrest of the myeloid series with a predominance of promyelocytes and myelocytes, after 8 d of copper treatment, bone marrow showed normal maturation with abundant polymorphonuclear cells.

Because of the uniqueness of a neurologic disorder not reported previously, I will discuss in some detail a case of chronic, severe diarrhea and maldigestion beginning in early infancy, possibly due to primary lactase deficiency, that was published in 1966 (9). At the age of 19 mo the patient had anemia, neutropenia, osteoporosis, and pathologic fractures. At that time and again at 60 mo of age, she was hospitalized in the United States; later on, between the ages of 73 and 76 mo, she received 20 blood transfusions because of severe anemia unresponsive to treatment. Around that time, the case came to my attention and copper supplementation was initiated. The hematologic data before copper treatment and how these indexes normalized after only a few weeks of supplementation with 2.5 mg Cu/d are shown in Table 2. The patient never required another transfusion and the rapid recovery of the anemia was undoubtedly the result of a pronounced response to copper in the presence of more than adequate iron stores from the multiple transfusions received and normalization of the erythrocyte survival rate.

What came as a welcome surprise was a striking improvement in the malabsorption syndrome, with progressive tolerance for
COPPER DEFICIENCY IN PREMATURE INFANTS

As in the 1960s in Peru (6–9), in the 1980s Uauy and his group (15–17) in Chile also recognized copper deficiency in malnourished infants and children being renourished with a cow-milk-based diet with relatively low copper content. They reported that red cell superoxide dismutase (SOD) was a good indicator of copper nutrition (16) and speculated that if a parallel decrease were to occur in polymorphonuclear SOD, this could be a possible mechanism for neutropenia and that increased destruction of phagocytes might result in poor bactericidal capacity. A higher prevalence of severe respiratory infections was described in copper-deficient infants (17). Additionally, a group of infants recovering from malnutrition and with evidence of copper deficiency increased their energy intake and showed better weight gain after being supplemented with copper compared with a control group (15). The cow-milk-based diet still being used during recovery from malnutrition in most developing countries does not provide optimal amounts of copper. Castillo-Duran and Uauy (15) suggest supplementation with 80 μg Cu·kg⁻¹·d⁻¹, which is similar to the requirement suggested by Cordano et al (6): > 42 but < 135 μg Cu·kg⁻¹·d⁻¹.

COPPER DEFICIENCY IN MALNOURISHED INFANTS

In 1960 Wilson and Lahey failed to induce copper deficiency in a group of seven premature infants (average weight: 1238 g) and concluded that the daily requirement for copper in early infancy can be met by an intake of 15 μg Cu·kg⁻¹·d⁻¹ (18). This trial, which was limited in the number of subjects studied and in duration (7–10 wk), led to a very low estimate of the infant requirement, different from estimates of requirements in other mammals such as pigs (77–110 μg·kg⁻¹·d⁻¹) (19). My interest in the possibility of the occurrence of copper deficiency in premature infants was expressed in an interview printed in JAMA in 1968 (20), 3 y before the early reports by Griscom et al (21) and Al Rashid and Spangler (22). The interview stated, “Prematures or LBW [low-birth-weight] infants requiring an exclusive milk diet for more than 4 months may also become copper deficient. While the copper reserve in the liver of a normal newborn can carry him through the first four months of life

Recent phone conversations (March 1996) with members of the patient’s family allowed me to explore her progress over the past 30 y. She apparently experienced some learning disabilities at school and has some speech difficulties, particularly with the English language. Despite some errors, she manages to write in Spanish. She has a high-pitched voice and has suffered from masticatory problems, which could be related to the fact that she received a special semielemental diet and few baby foods during her first 7 y of life. She has minor difficulties with fine movements of her hands and walks with a gait problem because of a moderate stiffness of her right lower leg and foot. She is said to be tenacious with her tasks, to have a good disposition, and to love children; she is working as a volunteer in a child-care center, with expectations of finding a permanent position in the same field. Except for occasional bouts of diarrhea (she also still suffers from some food intolerance), she has been quite healthy. She married at the age of 33 y and except for minor help is managing to perform her household duties.

In summary, this young woman’s case is the only described case of prolonged, severe copper deficiency complicating severe malabsorption and malnutrition, with evidence of neurologic compromise. How much of the developmental and neurologic damage was due to malnutrition and how much to copper deficiency is difficult to distinguish. Note, however, that in none of the other reported cases of copper deficiency in Peru were signs of neurologic damage shown during the routine 10–15-y follow-up program for recovered malnourished infants and children (6–9; A Cordano, GG Graham, unpublished observations, 1968). The reason may well be that in those patients copper deficiency was not as severe or as prolonged as in the case described (9).

**TABLE 1**

<table>
<thead>
<tr>
<th>Hospital day</th>
<th>Neutrophils</th>
<th>Serum Cu</th>
<th>Ceruloplasmin</th>
<th>Hb</th>
<th>Hct</th>
<th>Reticulocytes</th>
<th>Fe intake</th>
<th>Cu intake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>× 10⁹/L</td>
<td>μg/L</td>
<td>mg/L</td>
<td>g/L</td>
<td>0.25</td>
<td>0.002</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>66</td>
<td>0.26</td>
<td>—</td>
<td>7</td>
<td>528</td>
</tr>
<tr>
<td>2</td>
<td>0.200</td>
<td>0</td>
<td>0</td>
<td>66</td>
<td>0.26</td>
<td>—</td>
<td>7</td>
<td>528</td>
</tr>
<tr>
<td>3</td>
<td>0.242</td>
<td>290</td>
<td>—</td>
<td>66</td>
<td>0.26</td>
<td>—</td>
<td>7</td>
<td>528</td>
</tr>
<tr>
<td>4</td>
<td>0.244</td>
<td>680</td>
<td>80</td>
<td>65</td>
<td>0.26</td>
<td>—</td>
<td>7</td>
<td>528</td>
</tr>
<tr>
<td>5</td>
<td>1.330</td>
<td>1010</td>
<td>130</td>
<td>65</td>
<td>0.25</td>
<td>0.001</td>
<td>9</td>
<td>535</td>
</tr>
<tr>
<td>6</td>
<td>1.120</td>
<td>960</td>
<td>240</td>
<td>65</td>
<td>0.25</td>
<td>0.001</td>
<td>9</td>
<td>535</td>
</tr>
<tr>
<td>8</td>
<td>1.100</td>
<td>—</td>
<td>—</td>
<td>72</td>
<td>0.28</td>
<td>0.013</td>
<td>9</td>
<td>535</td>
</tr>
<tr>
<td>10</td>
<td>1.192</td>
<td>1770</td>
<td>210</td>
<td>—</td>
<td>0.28</td>
<td>0.013</td>
<td>9</td>
<td>535</td>
</tr>
<tr>
<td>15</td>
<td>1.712</td>
<td>1420</td>
<td>280</td>
<td>97</td>
<td>0.32</td>
<td>0.003</td>
<td>9</td>
<td>42</td>
</tr>
<tr>
<td>16</td>
<td>0.770</td>
<td>—</td>
<td>—</td>
<td>94</td>
<td>0.32</td>
<td>0.006</td>
<td>9</td>
<td>785</td>
</tr>
<tr>
<td>17</td>
<td>3.696</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.32</td>
<td>0.004</td>
<td>9</td>
<td>785</td>
</tr>
<tr>
<td>23</td>
<td>2.548</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.33</td>
<td>—</td>
<td>9</td>
<td>535</td>
</tr>
<tr>
<td>24</td>
<td>2.210</td>
<td>1360</td>
<td>300</td>
<td>100</td>
<td>0.33</td>
<td>0.006</td>
<td>9</td>
<td>535</td>
</tr>
</tbody>
</table>

with almost no dietary copper, the premature infant has a much reduced reserve. Copper should be added to the milk diet of these infants\(^1\) (20).

The steady decrease in liver copper content with age in full-term infants suggests that the increase in serum copper is due more to production of ceruloplasmin and mobilization of liver stores than to increased copper absorption (23). Apparently, the concentration of copper in the liver of premature infants is not low, but total stores are limited by the smaller liver size. More than two-thirds of liver copper accumulates during the last 10–12 wk of gestation, rising from 2.5 to 9 mg Cu in the total organ (24). Two prospective studies showed convincingly that it is likely that any infant born at < 34 wk postconceptional age would have markedly reduced circulating concentrations of copper and ceruloplasmin (25, 26).

These concentrations do seem to be related to natural maturation processes involving a developmental delay in liver function. The rise in serum copper appears related to postconceptional rather than postpartum age and in very-low-birth-weight (VLBW) infants serum copper concentrations increase until 4 mo of age (27). Serum copper values in preterm infants in the first week of life are not related to gestational age or to birth weight (28) and are similar to values reported for full-term infants (29). Measurement of serum copper by itself is not adequate for defining a copper-deficient state; such measurements failed to distinguish 5 of 15 infants with symptomatic copper deficiency from other growing preterm infants (28). Deficiency was defined when the neutrophil count was < 1.5 \times 10^9/L, when serum copper was < 0.25 mg/L, and when all values returned to normal after the infants were supplemented with copper.

Burns et al (30) note that a low serum copper value at 12 wk merits closer investigation and that this analysis is still the most applicable for investigating copper status. They add that erythrocyte SOD activity and erythrocyte copper concentration are of little value in preterm infants because of frequent blood transusions in these infants. In a long-term study in VLBW infants fed different amounts of copper, L’Abbe and Friel (31) showed that erythrocyte SOD activity does not follow the physiologic three-fold increase during the first year that is observed for serum copper and also found that dietary copper intake was positively associated with erythrocyte Cu/Zn-SOD activity. This suggests that erythrocyte SOD activity is a more appropriate indicator of copper status in VLBW infants than is serum copper. Their results suggest that up to one-third of the formula-fed VLBW infants may have had suboptimal copper status between 6 and 12 mo of age. However, because the period from 6 to 12 mo coincides with the time when breast-fed and formula-fed infants are switched to cow milk, which has a low copper content, the authors suggest that the use of copper supplements or a formula with supplemental copper for > 6 mo may benefit copper status.

After the early reports in 1971, at least a dozen cases of severe nutritional copper deficiency in VLBW infants have been reported and in two-thirds of these cases deficiency was diagnosed by the age of 15 wk. These findings emphasize the importance of assessing copper status in early life as well as the provision of special infant formulas for premature infants to cover the requirements of such rapidly growing infants.

Our efforts toward communicating the need for increasing the copper content of formulas used for premature infants were reflected in a letter to the editor published in Pediatrics in 1974 (32): “Most manufacturers of infant formulas now include copper at about 60 \(\mu\)g/100 kcal. However, to assure a minimum of 100 \(\mu\)g/kg/day, infant formulas fed to prematures should contain not less than 90 \(\mu\)g/100 kcal (0.6 mg/L); this will provide the estimated requirement when fed at the usual 110 to 120 kcal/kg/day.”

Although some manufacturers of infant formulas for premature infants in the United States provided adequate copper concentrations in the mid or late 1970s, it took years before the Canadian Pediatric Society and the American Academy of Pediatrics recommended the suggested concentrations of 900 \(\mu\)g Cu/L (90 mg/100 mL; 1981 and 1985). Now, all premature formulas produced in the United States contain this amount of copper or more.

We must be optimistic that except for rare cases, there should be no more reports of severe nutritional copper deficiency in the literature. The proper application of old and new indicators of copper status, such as neutrophil counts, Cu/Zn-SOD activity,

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**TABLE 2**

Effects of copper supplementation on a child with prolonged severe malnutrition and copper deficiency\(^2\)

<table>
<thead>
<tr>
<th>Date (month-day-year)</th>
<th>Age</th>
<th>Hct</th>
<th>Hb</th>
<th>Leukocytes</th>
<th>Neutrophils</th>
<th>Reticulocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-27-59</td>
<td>1.7</td>
<td>0.24</td>
<td>73</td>
<td>8.2</td>
<td>0.13</td>
<td>—</td>
</tr>
<tr>
<td>1-15-60</td>
<td>1.9</td>
<td>—</td>
<td>103</td>
<td>4.95</td>
<td>0.26</td>
<td>0.052</td>
</tr>
<tr>
<td>7-09-62</td>
<td>4.2</td>
<td>—</td>
<td>47</td>
<td>5.1</td>
<td>0.05</td>
<td>0.011</td>
</tr>
<tr>
<td>10-23-62</td>
<td>4.6</td>
<td>—</td>
<td>72</td>
<td>4.4</td>
<td>0.34</td>
<td>0.03</td>
</tr>
<tr>
<td>5-17-63</td>
<td>5.1</td>
<td>0.39</td>
<td>125</td>
<td>8.0</td>
<td>0.25</td>
<td>0.04</td>
</tr>
<tr>
<td>6-25-64</td>
<td>6.2</td>
<td>—</td>
<td>52</td>
<td>5.4</td>
<td>0.30</td>
<td>0</td>
</tr>
<tr>
<td>7-14-64</td>
<td>6.3</td>
<td>0.08</td>
<td>27</td>
<td>8.3</td>
<td>0.24</td>
<td>0.001</td>
</tr>
<tr>
<td>8-24-64</td>
<td>6.4</td>
<td>0.10</td>
<td>36</td>
<td>3.9</td>
<td>0.09</td>
<td>0.002</td>
</tr>
<tr>
<td>8-30-64</td>
<td>6.4</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>9-05-64</td>
<td>6.4</td>
<td>—</td>
<td>58</td>
<td>12.4</td>
<td>0.45</td>
<td>0.045</td>
</tr>
<tr>
<td>9-28-64</td>
<td>6.5</td>
<td>0.32</td>
<td>100</td>
<td>10.5</td>
<td>0.67</td>
<td>0.02</td>
</tr>
<tr>
<td>10-26-64</td>
<td>6.6</td>
<td>0.39</td>
<td>110</td>
<td>13.9</td>
<td>0.71</td>
<td>0.03</td>
</tr>
<tr>
<td>4-08-65</td>
<td>7.0</td>
<td>0.41</td>
<td>127</td>
<td>14.75</td>
<td>0.44</td>
<td>0.012</td>
</tr>
</tbody>
</table>

\(^1\)Hct, hematocrit; Hb, hemoglobin.

\(^2\)Copper therapy started with 2.5 mg/d.
platelet cytochrome-c oxidase activity, platelet copper concentrations, glutathione peroxidase activity, clotting factor VIII concentrations, and others, should help research in this field. It is hoped that such tests will be economically and practically feasible and applied to different age groups for their benefit and to prevent deterioration of copper status. The effects of minor differences in dietary intakes of copper or imbalances of other nutrients (such as zinc and iron) may be more important than the few cases of obvious nutritional copper deficiency that may occur.

Research efforts should continue in relation to the involvement of copper in antioxidant protection, carbohydrate metabolism, and host defense mechanisms and to identify alterations of noncopper enzymes that are or may be copper responsive. Continued research on Menkes syndrome, mouse mutants, and site-directed mutagenesis will further clarify the different effects of copper deficiency in different species.

REFERENCES