Brief Report

Hypocupremia and Neutropenia in Copper Deficiency

By Angel Cordano, Robert P. Placko and George C. Graham

We have previously reported the development of copper deficiency in 4 marasmic infants rehabilitated on Cu-poor, calorie-rich milk diets. Neutropenia developed before or simultaneously with anemia, and the bone marrow revealed granulocytic maturation arrest and erythroid hypoplasia. Even when neutropenia was severe, there was a normal neutrophilic response to infection. Response to oral Cu therapy was evident within 36 hours as a prompt rise in peripheral neutrophils and a marked mature granulocytic hyperplasia of the bone marrow. We reported the serum Cu levels when hematologic and osseous manifestations were most marked and after treatment; we had not determined serum Cu at the time of admission.

We are now reporting 93 simultaneous determinations in 21 marasmic infants of serum Cu and total neutrophils in peripheral blood taken on admission, during the development of Cu deficiency, or after therapy.

Methods

Infants suffering from severe marasmus and chronic diarrhea, some of them with complicating kwashiorkor, are admitted for treatment and study. Nearly all of them receive modified cow’s milk initially and some continue to receive it as the only source of protein for many months, with cane sugar and cottonseed oil added to provide supplemental calories. We estimate that in these diets they receive 28 to 42 μg. of Cu/Kg. of body weight/day, and as we assume that their previously poor diets and chronic diarrhea have resulted in depletion of Cu stores, that this intake is not then adequate to keep up with their accelerated growth during recovery, resulting in overt deficiency.

One of the infants in the present study was 41 months of age on admission, and the remaining 20 were between 4 and 19 months of age, with an average age for the whole group of 11 months. The 21 infants were marasmic, and 2 of them had complicating kwashiorkor; all received modified cow’s milk until persistent neutropenia developed, with or without anemia, or until the diet was changed, for other reasons, to one containing adequate copper.

Serum Cu was determined in 15 of the 21 infants within 1 week of admission by a micromodification of the method of Natelson. In 20 of 21 it was determined when persistent neutropenia was present, with or without anemia, and in 17 of these 20 it was repeated 1

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HYPOCUPREMIA AND NEUTROPENIA IN COPPER DEFICIENCY

Fig. 1.—Evolution of serum Cu in 11 marasmic infants receiving exclusive milk diets during recovery. The broken line in the evolution of patient E. S. indicates 40 days of oral Cu supplementation.

or more times after blood cell values had returned to normal following adequate supplementation equivalent to more than 150 μg. of elemental Cu/Kg. of body weight/day. In 14 of the 21 we measured serum Cu on admission, during the development of hypocupremia, and after its correction.

RESULTS

The mean serum Cu of 15 infants on admission was 111, with a range of 43 to 204 μg./100 ml. Although 2 of the infants had severe hypoalbuminemia, their serum Cu values were not lower than the mean. The 1 infant, aged 17 months, whose serum Cu was 43 μg./100 ml. on admission had a total neutrophil count of 1034/mm.³ and a long history of diarrhea, and for many weeks before admission had been alternated between a milk diet and long periods of therapeutic starvation. One infant was changed to a different diet before significant hypocupremia or neutropenia developed.

In the remaining 19 subjects hypocupremia and persistent neutropenia were evident 23 to 106 days after admission (median = 44 days). The mean serum Cu at that time, when serum albumin and total protein were normal, was 35 μg./100 ml. (range 11–89). Following Cu supplementation and hematologic response, the mean of 27 determinations in 17 subjects was 143 μg./100 ml. (range 102–210).

Figure 1 depicts the evolution of serum Cu in 11 of the 14 infants on whom values were available during the first hospital week and who subsequently developed significant hypocupremia. Three of the infants, whose evolution was...
Fig. 2.—Scattergram depicting relation of peripheral neutrophil count to serum Cu in 93 simultaneous determinations in 21 marasmic infants taken at the time of admission, while receiving a Cu-poor milk diet and after Cu supplementation. The straight line corresponds to the regression equation: Neutrophils/mm$^3 = 16.5 \times $ (serum Cu in $\mu g.$ 100 ml.) + 900.

very similar to the others, have not been included. One infant, E. S., developed hypocupremia on day 23 with moderate neutropenia, and was given supplemental Cu, 250–300 $\mu g.$/Kg./day, during the next 40 days. On the 43rd hospital day serum Cu was 118/$\mu g.$/100 ml., but on the 63rd day Cu was inadvertently discontinued; 43 days later serum Cu had fallen to 50 $\mu g.$/100 ml. and total neutrophils to less than 500/mm$^3$.

Figure 2 is a scattergram of the relation of peripheral neutrophil count to serum Cu in 93 simultaneous determinations made at the time of admission, while receiving the Cu-poor milk diet and after supplementation. The correlation coefficient of +0.61 is significant and the regression equation is: Neutrophils/mm$^3 = 16.5 \times$ (serum Cu in $\mu g.$) + 900. Most of the neutrophil counts which are at some distance above the regression line correspond to clear-cut episodes of infection. Although these Cu-deficient children were able to respond to infection with neutrophilia and some elevation of serum Cu, this latter was much less than the usual response.

DISCUSSION

Although naturally occurring or induced Cu deficiency has been observed in many species, neutropenia as a manifestation has been reported only in the
We have found it to be the earliest and most constant manifestation of Cu deficiency in man, and the most sensitive indicator of the adequacy of treatment. A number of cases of unexplained neutropenia reported from Mexico in recovering malnourished infants on almost exclusive milk diets are possibly due to Cu deficiency.

**Summary**

Copper deficiency was often found in severely malnourished infants rehabilitated on exclusive milk diets. Marked, persistent neutropenia was its earliest and most constant manifestation.

**Summario in Interlingua**

Carentia de cupro esseva constatatate frequentemente in severmente malalimentate infantes rehabilitate exclusivemente con dietas de lacte. Marcate e persistente neutropenia esseva su manifestation le plus precoce e le plus constante.

**REFERENCES**

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