

Symptomatic zinc deficiency in a breast-fed, preterm infant

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SUMMARY A 2-month-old preterm boy who developed symptomatic zinc deficiency while being exclusively breast fed is described. Oral zinc supplements induced a complete remission but mucosal ⁶⁵Zn uptake studies and metabolic balances conducted before and after withdrawal of the supplements excluded the diagnosis of acrodermatitis enteropathica. By age 12 months the boy was well and no longer required zinc supplements. Other possible causes of this patient's symptomatic zinc deficiency are discussed and these should be considered in the immediate and long-term management of preterm infants.

Zinc is essential for optimum growth and development,¹ and although both term and preterm infants may be in negative zinc balance for some time after birth²⁻⁴ the development of the clinical manifestations of zinc deficiency in infancy has not been reported in the absence of factors such as intravenous feeding or the inborn error of zinc absorption acrodermatitis enteropathica. Human breast milk is probably a better source of zinc for the young infant than cows' milk since it may contain a factor, not present in cows' milk, which facilitates zinc absorption.⁵ However the development of acrodermatitis enteropathica in a breast-fed, preterm infant,⁶ and of symptomatic zinc deficiency in 2 preterm infants who had received intravenous feeding for 6 and 3 weeks before the introduction of breast milk,⁷ suggests that human breast milk does not completely protect against symptomatic zinc deficiency.

This paper describes a breast-fed, preterm infant who developed profound zinc deficiency and low plasma copper concentrations in the absence of the above predisposing factors.

Methods

Blood was taken by venepuncture into trace metal-free heparinised tubes, and concentrations of plasma zinc and copper were determined by atomic absorption spectroscopy (Instrumentation Laboratories 751 spectrometer).⁸ A peroral jejunal biopsy was obtained from just distal to the ligament of Treitz under fluoroscopic control; a portion of the biopsy was sent for histology and the remainder was used

for ⁶⁵Zn uptake studies as previously described.⁹ In addition 3-day trace metal metabolic balance studies were performed.¹⁰ During the first balance, while the infant was breast fed, his intake at each feed was determined by test weighing and by collecting equal volumes of fore and hindmilk; aliquots of these samples proportionate to the amount ingested at each feed were pooled for analysis.¹⁰

Case history

A white baby boy was born at 32 weeks' gestation weighing 1.98 kg (50th centile allowing for gestation) to healthy unrelated parents; the neonatal period was uneventful. He was exclusively breast fed, apart from two cows' milk formulae feeds which were offered during the first 5 days of life. At 2 months he developed a progressive facial dermatitis and similar lesions appeared on his fingers and perineum; a month later he developed diarrhoea and was referred to The Hospital for Sick Children, with a provisional diagnosis of acrodermatitis enteropathica. On admission he weighed 3.8 kg (3rd centile) his length and occipitofrontal circumference were 54 cm (3rd centile) and 39.5 cm (50th centile) respectively. He was irritable and difficult to console. He had a severe symmetrical facial dermatitis (Fig. 1) with a similar eruption in the perianal area, and erythema, and slight peeling of skin on the dorsa of the fingers.

Haemoglobin was 9.8 g/dl, with a total white blood count of $10.5 \times 10^9/l$ and a normal differential. Plasma zinc and copper concentrations were



Fig. 1 Patient at presentation (age 3 months) showing severe symmetrical facial dermatitis.

4.7 $\mu\text{mol/l}$ (30.7 $\mu\text{g}/100$ ml) (normal range 11–24 $\mu\text{mol/l}$ (72–157 $\mu\text{g}/100$ ml)) and 8.1 $\mu\text{mol/l}$ (51.5 $\mu\text{g}/100$ ml) (normal range 12–26 $\mu\text{mol/l}$ (76–165 $\mu\text{g}/100$ ml)) respectively. Total serum protein was 0.54 g/100 ml with an albumin content of 0.38 g/100 ml; the plasma alkaline phosphatase activity, a zinc-dependent enzyme, was 78 IU/l (normal range 71–247 IU/l). Plasma calcium, magnesium, inorganic phosphate, amino-acids, immunoglobulins, aspartate and alanine transaminases, and 5' nucleotidase were normal, as was a chest x-ray and skeletal survey; skeletal maturity was compatible with age. Skin swabs grew *Staphylococcus aureus*. A metabolic balance showed net intestinal loss of zinc and copper, and net absorption of iron, manganese, calcium, and magnesium (Table); the maternal breast milk zinc content, measured after

17 weeks' lactation, was 8.86 $\mu\text{mol/l}$ (57.9 $\mu\text{g}/100$ ml), copper content was 5.29 $\mu\text{mol/l}$ (33.6 $\mu\text{g}/100$ ml), and iron and manganese concentrations were 5.7 $\mu\text{mol/l}$ (31.9 $\mu\text{g}/100$ ml) and 0.86 $\mu\text{mol/l}$ (4.7 $\mu\text{g}/100$ ml) respectively. Jejunal biopsy histology was normal on light microscopical examination, and the mucosal uptake of ^{65}Zn achieved a tissue to medium concentration gradient of 13.5 compared with our control values of 4.3–11.0 (mean 7.5 \pm 0.8 SE).⁹

The patient was exclusively breast fed for another month and oral zinc sulphate 30 mg twice a day (210 μmol (13.5 mg) elemental zinc daily) was instituted. Within 6 days there was a more responsive behaviour pattern and a complete resolution of the dermatitis and diarrhoea (Fig. 2). The plasma zinc and copper rose to 22 $\mu\text{mol/l}$ (144 $\mu\text{g}/100$ ml) and 12.6 $\mu\text{mol/l}$ (80 $\mu\text{g}/100$ ml) respectively and the plasma alkaline phosphatase activity to 305 IU/l.



Fig. 2 Patient 10 days after starting oral zinc supplements.

Table Daily oral intake, faecal output, and net absorption of metals ($\mu\text{mol}/\text{kg}$) and nitrogen (g/kg) in metabolic balance studies performed at 4 and 11 months of age

	At age 4 months			At age 11 months		
	Oral intake	Faecal output	Net absorption	Oral intake	Faecal output	Net absorption
Zinc	1.24	9.64	-8.40	10.60	8.31	2.29
Copper	0.74	2.54	-1.80	0.88	0.69	0.19
Iron	0.80	0.57	0.23	11.03	7.17	3.86
Manganese	0.12	0.11	0.01	4.24	3.66	0.58
Calcium	1180	500	680	2280	1200	1080
Magnesium	230	120	110	800	421	379
Nitrogen	0.73	0.05	0.68	1.89	0.05	1.84

- Net intestinal secretion.

Weaning was started at age 6 months, he continued to thrive, and the zinc supplement was stopped at 10 months.

On readmission, aged 11 months, he weighed 9.25 kg (50th centile), his length was 71 cm (25th centile), and development was commensurate with that of a term infant of the same age. Plasma zinc concentration was 21.5 $\mu\text{mol/l}$ (140 $\mu\text{g}/100\text{ ml}$), that of copper was 14.5 $\mu\text{mol/l}$ (92.1 $\mu\text{g}/100\text{ ml}$), and the plasma alkaline phosphatase activity was 159 IU/l. A repeat metabolic study demonstrated net intestinal absorption of zinc and copper (Table).

When last seen aged 20 months the patient was in excellent health and thriving, having stopped zinc supplements 10 months earlier. Plasma zinc and copper concentrations were normal at 16 $\mu\text{mol/l}$ (105 $\mu\text{g}/100\text{ ml}$) and 30.1 $\mu\text{mol/l}$ (191 $\mu\text{g}/100\text{ ml}$) respectively.

Discussion

The patient had both clinical and biochemical evidence of zinc deficiency which was confirmed by the rapid and complete response to oral zinc supplements.¹

The major excretory route for zinc is via the gastrointestinal tract¹ and the relative rates of excretion and absorption of zinc will determine whether there exists a state of net intestinal absorption or loss. The net intestinal loss of zinc observed in our patient could be explained in at least three ways: inadequate dietary intake of zinc, defective zinc absorption, or excessive loss into the lumen.

The patient's zinc intake during the first balance study was low compared with other reported intakes in infants.²⁻⁴ This could have resulted from a barely adequate daily breast milk consumption (140 g/kg) which, in turn, might have reflected anorexia secondary to zinc deficiency.¹ The concentration of zinc in the milk was also low compared with data on human breast milk collected after a similar period of lactation,¹¹ while the copper, iron, and manganese content approximated to or exceeded the median values from the same studies.¹²⁻¹³ The trace element content of human milk declines during the course of lactation,¹¹⁻¹³ and the zinc deficiency in our patient may reflect a more general unsuitability of mature breast milk for preterm infants.

The high tissue to medium ratio of ⁶⁵Zn which was demonstrated *in vitro* at the time of the first balance exceeded our previously reported ratios in patients with acrodermatitis enteropathica and control subjects.⁹ This suggests that zinc deficiency induces an adaptive mucosal response analogous to the

increased *in vitro* mucosal uptake of iron which occurs in patients with iron deficiency.¹⁴

It has been proposed that human milk contains a ligand which facilitates zinc absorption and that the concentration of this ligand declines during lactation.^{5, 15} Studies in the newborn rat suggest that this ligand no longer enhances zinc absorption after the intestinal mucosa has developed its own intrinsic ligand.⁵ Our *in vitro* study, while indicating that our patient's jejunal mucosa was able to concentrate ⁶⁵Zn, does not exclude the possibility that a quantitative or a qualitative abnormality of such a ligand in the mother's breast milk impaired his *in vivo* absorption of zinc.

Excessive loss of endogenous zinc into the intestinal lumen cannot be excluded as a contributory cause of the zinc deficiency in our patient but it seems an unlikely possibility.

It appears probable that a low intake perhaps associated with impaired absorption of zinc caused the zinc deficiency in our patient.

The cause of the low plasma copper levels and the net intestinal loss of copper during the first balance study is obscure. Impaired net absorption of copper has been noted in preterm infants² and, while there are no data on preterm infants, the plasma copper levels in this patient could be compatible with the low levels usually found in term infants until 2 or 3 months of age.¹⁶ However, the increase in plasma copper concentration after zinc supplementation suggests a causal relationship with the zinc deficiency. The low serum copper concentrations in conjunction with zinc deficiency in the 2 infants who had received intravenous feeding also responded to zinc supplements alone.⁷ In contrast, however, the symptomatic copper deficiency observed in the breast-fed infant diagnosed as having acrodermatitis enteropathica was attributed to the antagonistic effects of her oral zinc supplement on copper absorption.⁶

The diagnosis of acrodermatitis enteropathica in this patient is excluded by the continued good health after stopping zinc supplements, by the positive zinc balance in the second metabolic study while on a normal dietary zinc intake, and by the high mucosal zinc uptake *in vitro*. This emphasises the importance of withdrawing zinc supplementation at some time during the management of patients with suspected acrodermatitis enteropathica, to confirm the diagnosis.

It has been suggested that preterm infants may develop zinc deficiency,^{2, 7} and the absence of symptoms during infancy has been attributed to zinc being released from remodelling bone thereby delaying the onset of any symptomatic zinc deficiency until the second year of life.² This report clearly demonstrates that symptomatic zinc deficiency can

occur during infancy and that it should be considered in the early management as well as in the long-term care of preterm infants.

The early history of this infant was presented at a meeting of the British Association of Dermatologists, and the abstract published in the supplement to the *British Journal of Dermatology*, July 1979.

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