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Copper deficiency in the preterm infant of very low birthweight

Four cases and a reference range for plasma copper

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SUMMARY Four preterm infants of very low birthweight (less than 1500 g) developed signs of copper deficiency between age 8 and 10 weeks. All had required prolonged ventilatory support, parenteral nutrition, and nasojejunal feeding. The clinical features, which included osteoporosis, oedema, anaemia, neutropenia, and late apnoea improved when the oral copper intake was increased.

Diagnosis was made more difficult because a suitable reference range for plasma copper was not available. Serial measurements of plasma copper in 39 preterm infants who had no important medical problems were used to produce a reference range for plasma copper from 30 weeks' gestation to term plus seven weeks. This information will aid recognition of hypocupraemia in the very low birthweight infant who is particularly at risk of copper deficiency.

Although infants with the typical features of copper deficiency have been reported since 1956,[1] it was not until 1971 that Al-Rashid and Spangler described an infant of low birthweight who developed oedema, anaemia, bone disease, and recurrent apnoea associated with a low plasma copper concentration.[2] They were the first to show that these abnormalities could be corrected by giving copper supplements. Since then numerous reports of isolated copper deficiency in infants have been published.[3–9] Despite this knowledge, copper deficiency still occurs and is likely to become more common with the increasing survival of the very low birthweight infant.

We describe the clinical features of four infants who have developed copper deficiency in this unit since 1981. Their investigation and treatment stimulated the search for a suitable reference range for plasma copper. This was provided by serial measurement of plasma copper concentrations in 39 preterm infants (29 to 34 weeks' gestation), who were followed from birth to 90 days of age during a nutritional study evaluating a new formula feed. The aetiology and possible implications of copper deficiency are discussed and some recommendations are made for its prevention.

Case reports

Patient 1. A boy weighing 1100 g was delivered vaginally after spontaneous rupture of membranes at 28 weeks' gestation. He developed severe idiopathic respiratory distress syndrome requiring intermittent positive pressure ventilation for 50 days and oxygen for a further 24 days. Fluids were administered first via an umbilical arterial catheter, followed by peripheral venous lines (44 days dextrose-electrolyte 'cocktail' with added vitamins (Solvito, KabiVitrum) and Vamin-Glucose with Ped-el (KabiVitrum)) with nasojejunal tube feeds of expressed breast milk until day 50, when nasogastric feeds were established. Enteral vitamin D, 800 IU/day, was given from day 72, and iron from day 78 (Sytron, Parke Davis (5 ml/day)).

Bilateral intraventricular haemorrhages were seen on echoencephalogram on day 21 when he was transferred to our care. Clinical signs consistent with the diagnosis of patent ductus arteriosus developed on day 59, but no specific treatment was required. His condition was stable but he failed to gain weight. On day 76 he had a prolonged apnoeic attack. He was grossly oedematous with noticeable cranio-

tabes. Wrist and chest radiographs showed fraying and cupping of the metaphyses and generalised bone demineralisation. Plasma calcium (2·4 mmol/l), phosphorus (1·3 mmol/l), and magnesium (1·24 mmol/l) concentrations were normal, but alkaline phosphatase activity (234 IU/l (33 KA/dl)) was slightly raised. Plasma 25-hydroxycholecalciferol was high/normal at 67 nmol/l (27 ng/ml). A total plasma protein value of 48 g/l and a haemoglobin concentration of 10 g/dl prompted the administration of salt-poor albumin (1 g/kg) and a transfusion of packed cells. He was also given gentamicin and penicillin parenterally, although the cultures of blood and cerebrospinal fluid were negative.

He did not improve. The oedema and apnoea persisted. Plasma copper and caeruloplasmin concentrations were found to be low on day 81 (copper 5·2 μmol/l, caeruloplasmin 0·07 g/l) and he was therefore given a 21 day course of oral copper sulphate, 4 μmol (254 mg) copper/kg per day (0·2 ml of 0·5% solution of copper sulphate as the pentahydrate), and changed to a milk with a greater copper content (from OCF, Farley Health Products to SMA Wyeth Laboratories). Forty eight hours later the apnoeic attacks had stopped and by the time he was transferred to his hospital of origin on day 92 his oedema had resolved. The alkaline phosphatase activity had risen to 1390 IU/l (BCL methodology using paranitrophenol as substrate) on day 102 and remained high, at 1056 IU/l one month later and 1240 IU/l two months later. Plasma calcium and phosphorus concentrations remained within normal limits throughout. Vitamin D supplements of 600 IU/day were being given at this time. Hepatic and bone isoenzymes were not differentiated. Repeat radiographs 12 weeks after copper sulphate treatment showed resolution of the bony changes and normal bone mineralisation. At 15 months of age, the only clinical abnormality was a left sided convergent squint secondary to a mild refractive error. His development was appropriate for his corrected gestational age. His weight and head circumference were increasing along the 10th and 25th centiles respectively.

Patient 2. A boy weighing 1040 g was delivered by caesarian section at 26 weeks' gestation after vaginal bleeding and spontaneous rupture of the membranes. Intermittent positive pressure ventilation was required from the first hour of life for apnoea and severe idiopathic respiratory distress syndrome and was continued for 42 days. Oxygen was given for a further 12 days. Parenteral nutrition was given via an umbilical arterial catheter for 12 days and then by venous lines until day 28, with added breast milk via nasojejunal tube from days 17 to 51, when nasogastric formula feeds were started. Vitamin D, 800 IU/day, and iron (Sytron, Parke Davis (5 ml/day)) were started on day 58.

In the first 24 hours of life he had a right sided pneumothorax and echoencephalogram showed bilateral intraventricular haemorrhage. On day 5 echocardiogram and electrocardiogram confirmed the clinical findings of a significant patent ductus arteriosus (left atrium aortic root ratio greater than 1·2). Surgical ligation was required after an unsuccessful course of oral indomethacin. His chest radiograph showed signs of bronchopulmonary dysplasia. Vitamin E deficiency was suspected on day 64 because of an abnormal in vitro peroxide haemolysis test (35%),[10] pyknocytosis, and peripheral oedema. Vitamin E (DL-tocopherol succinate 25 U/day) was given orally for five weeks.

The oedema persisted despite the return of the peroxide haemolysis test to normal. On day 86 the infant had a prolonged apnoeic attack and developed abdominal distension. The haemoglobin was 7 g/dl with a packed cell volume of 25%. Blood film showed a neutropenia of $0{\cdot}912\times10^9$/l (white blood count=$7{\cdot}6\times10^9$/l) and anisocytosis and polychromasia of the red cells. Plasma proteins (total 44 g/l, albumin 30 g/l), calcium (2·14 mmol/l) phosphorus (1.95 mmol/l), alkaline phosphatase 140 IU/l (20 KA/dl), and urea and electrolytes were normal. Chest radiograph showed persistence of rib fractures dating from thoractomy performed for ligation of patent ductus arteriosus 10 weeks previously, with no evidence of callus formation. Radiographs of wrist and long bones confirmed generalised osteoporosis.

Plasma copper concentration (4·4 μmol/l) and copper oxidase activity were low (0·04 OD; reference range 0·20 to 0·55). He was not gaining weight and head growth had slowed down. A seven day course of oral copper sulphate, 4 μmol (254 mg) copper/kg per day (0·2 ml of 0·5% solution of copper sulphate as the pentahydrate) was given. The oedema gradually diminished, the haemoglobin rose to 9·5 g/dl, the blood film returned to normal with a rise in neutrophils to $1{\cdot}45\times10^9$/l (total white blood count; $8{\cdot}6\times10^9$/l) and the plasma copper concentration increased to 7·2 μmol/l. Thereafter his clinical progress was satisfactory, although when last seen at 9 months of age, his motor development was reported to be slightly delayed.

Patient 3. A boy weighing 940 g, the first of triplets conceived after human chorionic gonadotrophin and clomiphene stimulation, was delivered by low cavity forceps at 27 weeks' gestation. Intermittent positive pressure ventilation was required from birth for apnoea and severe idiopathic respiratory distress

syndrome and was continued until day 56. Oxygen was given for a further 26 days. Parenteral nutrition was administered via an umbilical arterial catheter for 10 days, then venous lines for 26 days, supplementing continuous feeding with breast milk via nasojejunal tube which was given from days 13 to 74, when formula milk (OCF) was started nasogastrically. Vitamin D, 800 U/day was started on day 64, and oral iron (Sytron 5 ml/day) on day 78.

A left sided pneumothorax occurred on day 2. The clinical signs of a patent ductus arteriosus were present on day 3. Echocardiogram confirmed an appreciable left to right shunt. Surgical ligation was required on day 25 after failure of two courses of indomethacin. A left sided periventricular haemorrhage was seen on echoencephalogram on day 7. The chest radiograph was consistent with a diagnosis of bronchopulmonary dysplasia, and showed osteoporotic changes in the ribs by day 64. Oedema of face and limbs was noted on day 78. This was attributed to vitamin E deficiency because of an abnormal in vitro peroxide haemolysis test (35%), a plasma tocopherol concentration of 2·8 μmol/l, pyknocytosis on the blood film, and reticulocytosis of 8·4%. A three week course of vitamin E was given (DL tocopherol succinate 25 U/day orally). The in vitro peroxide haemolysis test[10] returned to normal (less than 1%), but the oedema persisted. The haemoglobin concentration was 8·5 g/dl and the packed cell volume 25%. Blood film showed a neutropenia of 0·86 cells $\times 10^9$/l (total white blood count; $8{\cdot}6 \times 10^9$/l) with polychromasia and anisocytosis of the erythrocytes. Plasma calcium (2·45 mmol/l) and phosphorus (1·75 mmol/l) concentrations were within normal limits. Alkaline phosphatase was raised at 371 IU/l (53 KA/dl). Chest and wrist radiographs showed generalised osteoporosis and metaphyseal changes. Plasma copper was considerably reduced (5·3 μmol/l).

Treatment consisted of a change in milk from a low copper formula (OCF) to one with a higher copper concentration (SMA). Three weeks later the blood film had returned to normal (neutrophil count $1{\cdot}96 \times 10^9$/l, total white blood count; $9{\cdot}8 \times 10^9$/l), the haemoglobin had increased to 12·5 g/dl, packed cell volume 39%, and the plasma copper concentration had risen to 10 μmol/l. Plasma alkaline phosphatase activity, although still raised, had fallen to 308 IU/l (44 KA/dl), and plasma calcium and phosphorus concentrations were again normal. Follow up until 16 months of age, has shown his development to be normal and his weight and head circumference are increasing on the 75th centile. Repeat wrist and chest radiographs showed normal ossification and mineralisation at 11 months postnatal age.

Patient 4. A girl weighing 900 g, the first of uniovular twins, was born by spontaneous breech delivery at 28 weeks' gestation. Assisted ventilation was required for 16 days and oxygen for a further five days. Fluids were given via umbilical arterial catheter for one week, supplementing nasojejunal breast milk feeds from day 3. Vitamin E (DL tocopherol succinate 25 U/day) was given from day 1 for 6 weeks. Vitamin D (800 IU/day) was started on day 35 and iron (Sytron, 5 ml/day) on day 45. Mild jaundice, maximum unconjugated bilirubin 222 μmol/l, required treatment with phototherapy for 24 hours on day 3. In the second week of life, clinical signs of patent ductus arteriosus developed. Echocardiogram showed a left atrium aortic root ratio of 1·85, confirming the diagnosis. A four day period of fluid restriction (100 ml/kg per day), diuretics (frusemide), intermittent positive pressure ventilation, and a course of oral indomethacin controlled her congestive cardiac failure.

After a positive Guthrie test (thyroid stimulating hormone) result obtained on day 7, transient hypothyroidism was detected at 16 days of age (thyroid stimulating hormone greater than 270 mU/l; thyroxine, 10 nmol/l; 0·6 triiodothyronine, nmol/l). Maternal thyroid function and that of the other twin were normal. When these tests were repeated two weeks later, normal results were obtained (thyroid stimulating hormone, 2·4 mU/l; thyroxine, 86 nmol/l; triiodothyronine, 1·2 nmol/l). There were no signs of hypothyroidism at any time. Further progress was uneventful until the 9th week of life when she had an apnoeic attack and was feeding poorly with a static weight. Severe oedema was noted accompanied by skin pallor and obvious distension of the veins on the trunk. The haemoglobin was 7·4 g/dl; packed cell volume 28%; and blood film showed polychromasia, anisocytosis, and poikilocytosis of the erythrocytes. The leucocyte count was normal ($9{\cdot}3 \times 10^9$/l, neutrophils $1{\cdot}9 \times 10^9$/l). In vitro peroxide haemolysis test[10] was normal (less than 1%) and plasma tocopherol concentration was also adequate (71 μmol/l). Plasma protein (total protein 45 g/l, albumin 33 g/l), calcium (2·33 mmol/l), phosphorus (2·05 mmol/l), 25-hydroxy vitamin D 31 nmol/l (12·4 ng/l), urea and electrolytes were within the normal ranges. Alkaline phosphatase activity 266 IU/l (38 KA/dl) was slightly raised. Radiographs of the long bones showed changes typical of copper deficiency with subperiosteal new bone formation in the femur, tibia, and humerus, and metaphyseal irregularity and widening at the knee and wrist, with generalised osteoporosis.

Plasma copper and caeruloplasmin could not be detected on repeat assays. A transfusion of packed

cells was given with a seven day course of oral copper sulphate, 4 μmol (254 mg) copper/kg per day (0·2 ml of 0·5% solution of copper sulphate as the pentahydrate). The infant's condition improved generally with these measures. She gained weight and the oedema subsided over the next five days. Plasma copper and caeruloplasmin values at the end of treatment were 4·7 μmol/l and 0·11 g/l respectively.

Since then until the infant was last seen at 10 months of age, her weight and head circumference have increased steadily on the 3rd centile and her development has been appropriate for her corrected gestational age.

Methods

The methods used for biochemical analyses at the Royal Hospital for Sick Children, Yorkhill are those described previously.[11]

The somewhat arbitrary limit for alkaline phosphatase activity of 212 IU/l (30 KA/dl) was selected to separate normal from abnormal results. The major advantage of employing a method based on King Armstrong units is the wealth of information in the published reports on reference ranges in normal and abnormal populations. In patient 1, serum alkaline phosphatase activity was not determined here but elsewhere, using a BCL method employing paranitrophenol as substrate with an adult reference range of 98 to 279 IU/l.

Reference range for plasma copper

All preterm infants of birthweight 1200 to 2000 g who were appropriate for gestational age with regard to birthweight and length for sex were included in the study. Gestational age was assessed using prenatal ultrasound and postnatal Dubowitz assessment,[12] range 29 to 34 weeks. Infants were randomly allocated to one of three formula milks which were being evaluated for infant feeding (Lijempf, Holland) or to expressed breast milk from the breast milk bank. The same method of feeding was continued throughout the study. Those infants who developed appreciable medical or surgical problems such as patent ductus arteriosus, severe idiopathic respiratory distress syndrome, intraventricular haemorrhage or who could not tolerate milk feeds were excluded from the study.

Plasma copper was measured by atomic absorption spectrophotometry using a Perkin-Elmer 306 atomic absorption spectrophotometer in conjunction with a heated graphite analyser (HGA-72). Analyses were performed on days 1, 6, 28, and 90 and when the infants reached 2500 g in weight. Plasma samples were diluted fivefold in Triton X-100 itself diluted to a concentration of 0·1% (v/v) with double distilled water, and 20 μl aliquots were analysed by injection into standard grooved graphite tubes. At a plasma concentration of 3·4 μmol/l intrabatch and interbatch coefficients of variation were 8·6% and 10% respectively. At a concentration of 13·4 μmol/l the corresponding figures were 2·9% and 3·5%. The sensitivity of the method for 95% confidence limits was 0·3 μmol/l. Accuracy was ensured by employing specimens from the Guilford quality control scheme in each batch of assays. No analysis was accepted where the results for control sera were outside 1 SD of the method mean.

Copper and zinc concentrations in the three formulas and pooled breast milk from the bank were measured by atomic absorption spectrophotometry and are shown in Table 1. Although the copper content and copper:zinc ratio in the milks varied, the mean plasma copper concentrations in each group were not significantly different. (Student's paired *t* test, P=>0·1. The results were therefore combined for analysis (Fig. 1, Table 2).

Table 1 *Copper and zinc concentrations of milk feeds and pooled expressed breast milk*

Milk used	*No*	*Copper (μmol/l)*	*Zinc (μmol/l)*	*Copper: zinc ratio*
Expressed breast milk	15	5·4	24	0·23
Formula 1	7	4·2	70	0·06
Formula 2	10	4·4	71	0·06
Formula 3	7	4·0	56	0·07

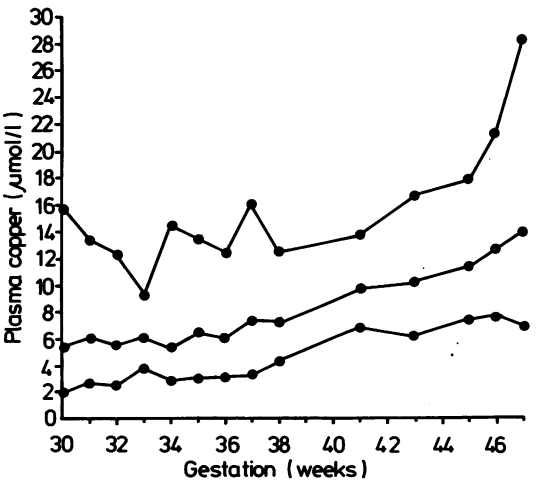

Fig. 1 *Serial measurements of plasma copper (μmol/l) in 39 preterm infants (values, geometric mean of 95% confidence limit).*

Table 2 *Serial measurements of plasma copper (μmol/l) in 39 preterm infants*

Gestational age (weeks)	*No*	*Plasma copper (μmol/l)*		*Range*
		Geometric mean	*95% confidence limits*	
30	7	5·5	1·9–15·8	2·5–13·2
31	16	6·1	2·8–13·6	3·2–14·7
32	19	5·6	2·5–12·4	2·5–12·3
33	14	6·1	3·9–9·5	4·4–8·6
34	17	5·5	2·1–14·6	1·7–12·0
35	16	6·5	3·1–13·6	3·5–12·7
36	12	6·1	3·0–12·4	3·2–9·0
37	12	7·3	3·4–16·1	4·5–14·1
38	9	7·3	4·3–12·4	5·0–11·6
41	3	9·8	6·9–13·9	8·0–11·1
43	7	10·2	6·2–16·7	7·7–15·9
45	6	11·5	7·4–17·9	9·0–15·1
46	2	12·8	7·7–21·2	10·7–15·3
47	5	13·9	6·9–28·1	8·0–20·2

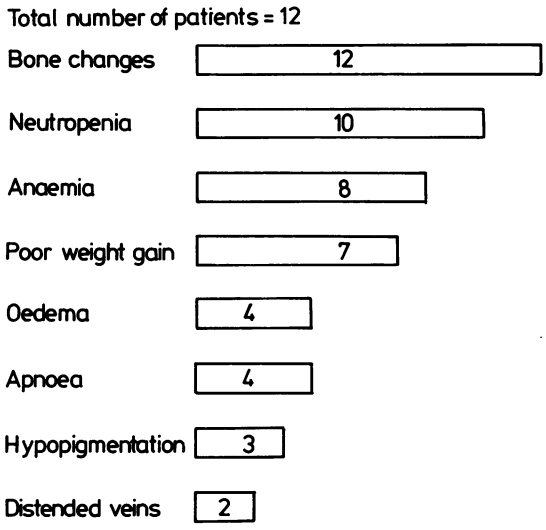

Fig. 2 *Clinical features of copper deficiency in the preterm infant ([3–9] and this report).*

Discussion

Infants of very low birthweight are at risk of developing multiple nutritional deficiencies as a result of their extreme prematurity and the unique problems of maintaining their growth postnatally. Poor bone mineralisation leading to generalised osteoporosis is almost universally seen in this very low birthweight group and those with chronic lung disease are especially prone to metaphyseal changes and fractures. Many authors have suggested that despite normal plasma concentrations, these changes are due to deficiencies of vitamin D, calcium, and phosphorus, singly or in combination.[13–15] Copper deficiency can cause similar bone changes which probably resolve gradually as nutrition improves with increasing postnatal age. The diagnosis is less likely to be missed if other more specific features of copper deficiency such as neutropenia and subperiosteal new bone formation, are present. In these patients, however, a low plasma copper was only detected after time consuming investigations had been completed to exclude infection, vitamin E deficiency, and vitamin D deficiency.

The most useful early features which were seen in all the infants were poor growth, oedema, and osteoporosis, which were present up to four weeks before the other signs of copper deficiency were seen. It is surprising that oedema, a striking clinical feature in our patients, was not seen in the eight previously reported cases of copper deficiency in preterm infants[2–9] (Fig. 2). Unexplained apnoeic attacks were a presenting feature in three of our patients, but are only mentioned in Rashid's original case report associated with infection, whereas no infection was proved in our patients. Three reports mentioned decreased pigmentation of the skin. In our patients skin pallor was considered consistent with the degree of anaemia.

Copper is present in many intracellular enzymes and reduced function of these in the copper deficient state is presumed to account for the variety of clinical features which are seen. The bone changes are thought to be secondary to deficiency of lysyl oxidase activity which is involved in cross linkages of peptidyl-lysine residues in collagen. This enzyme also plays a part in desmosine formation in elastic tissues. Poor quality elastin and collagen could account for the oedema seen in these infants by altering vascular permeability and soft tissue characteristics. Cardiac decompensation, in part due to dysfunction of cytochrome oxidase also a cuproenzyme, may be another contributory factor. The venous distension which has been reported and was seen in one of our patients might be caused by abnormal elastin, producing effects similar to those seen in copper deficient swine which developed vascular aneurysms.[16] It is possible that these factors may also affect spontaneous closure of the ductus arteriosus.

The function of the superoxidase group of enzymes is of particular interest in the preterm infant. This group of enzymes is found in all cells capable of aerobic metabolism, and many are copper dependent.[17] Their function is to protect the cell from the superoxide radical which may be implicated in retrolental fibroplasia and bronchopulmonary dys-

plasia. It has been suggested that failure of antioxidant mechanisms dependent on vitamin E may predispose this group of infants to ventricular haemorrhage.[18] The combined effects of copper deficiency on vascular structure and the antioxidant mechanisms of the cells could well have a similar but additive effect, and may have been important factors in the occurrence of intraventricular haemorrhage in three of the infants described.

Anaemia is a prominent feature of copper deficiency (Fig. 2) and contributed to the anaemia of prematurity in three of our patients. Two were probably also vitamin E deficient and this may have contributed to their oedema and anaemia. The precise mechanism for the development of anaemia in copper deficiency is not known. It is well known, however, that caeruloplasmin, a cuproenzyme, plays an important role in iron mobilisation and transport from the site of absorption in the duodenal mucosa via the liver to transferrin. Decreased concentrations of erythropoietin have also been reported in copper deficiency.[19] Neutropenia, one of the most characteristic findings (Fig. 2), is thought to predispose these infants to infection, although infection was not a particular problem in our patients. Again, the mechanism of neutropenia is not known, although it is possible that deficiency of cytochrome oxidase inhibits synthetic processes within the marrow cells leading to delayed cell maturation. This could account for changes that have been seen in the bone marrow in copper deficiency which include vacuolisation of many cellular elements and granulocyte maturation arrest.[2]

Three infants presented with late, unexplained apnoea which may have been caused by seizure activity. The precise effects of copper deficiency on the developing central nervous system of the human are not known, but failure of myelination and later striking demyelination occur in sheep and rats which are rendered copper deficient.[20] These effects are though to result from reduced activity of cytochrome oxidase.

The diagnostic problems presented by these infants stimulated the search for a reference range for plasma copper in the preterm. Previous studies have presented serial measurements in term infants up to 2 years of age,[21] and up to 6 weeks of age in preterms, although not related to gestational age.[22] Two studies have reported data for preterm infants related to gestational age, but over a shorter period of time. In one, over half of the patients were light for dates,[23] and in the other infants with appreciable medical problems were included.[24] The 39 infants in our study had been preselected on the basis of a relatively uncomplicated neonatal course and satisfactory prenatal and postnatal growth. They therefore represented as nearly 'normal' a population as possible for the preterm. Serial measurements of plasma copper gave us a reference range for infants from 30 weeks' gestation to term plus seven weeks (Table 2 and Fig. 1). Although there was a wide variation with very low concentrations in some infants in the first few weeks of life, there was a consistent rise in plasma copper from 38 to 40 weeks, to concentrations that are found in term infants. The copper deficient infants had low copper concentrations which failed to rise in this way. Using this information we have recently been able to diagnose copper deficiency in three other infants at a much earlier stage.

Although we have found the serial measurement of plasma copper useful, various criteria for the investigation of copper status in neonates have been proposed. Plasma copper represents a small fraction of total body copper and therefore is not necessarily a reliable indicator of tissue copper status. The concentration may be raised in times of stress or infection,[25] and possibly when excretion through the biliary tract is impaired. Measurements of hair copper content have not proved useful. Bradfield found normal copper concentrations in the hair of infants with gross copper deficiency and no increase in hair copper concentrations when copper was replaced.[26] More promising methods involve the measurement of specific cuproenzyme activity. The most useful enzymes seem to be erythrocyte superoxide dismutase, and the oxidase activity of caeruloplasmin. There is a variety of reasons why these infants became copper deficient. Prolonged parenteral nutrition and a low enteral copper intake were important factors (Table 3). They were also deprived of the fourfold increase that occurs in fetal liver copper in the last trimester of pregnancy.[27]

Several attempts have been made to assess copper requirements in the preterm. From balance studies, two authors have recommended a minimum intake

Table 3 *Mean copper intake (μmol/kg per day) during parenteral and enteral feeding*

Patient	*Parenteral feeding*			*Enteral feeding*	
	Mean intake	*Duration (days)*		*Mean intake*	
		Parenteral	*N/J*	*N/J*	*N/G*
1	*	44	41	0·4	0·5
2	0·2	28	34	0·8	1·0
3	0·1	26	61	0·6	0·4
4	0·3	7	34	0·6	0·4

N/J=Nasojejunal feeding.
N/G=Nasogastric feeding.
* Not estimated because given at another unit.

of approximately 1 μmol/kg per day.[27 28] On the basis of these data the mean copper intakes of the infants described here were inadequate during parenteral feeding and only reached acceptable concentrations in one during enteral feeding (Table 3). Fluid restriction is inevitable in these patients because of early fluid retention, patent ductus arteriosus, and consequent cardiac decompensation. This limits the volume of Vamin-Glucose with Ped-el which can be given parenterally and since this is the only source of copper in standard parenteral nutrition regimens (0·9 μmol/l copper/100 ml of standard solution), copper intake is low. When milk feeds are started the choice between breast milk or formula milk is important since the copper concentrations vary considerably from one to another. Several of the standard infant formulas and one of the preterm infant formulas which are available in the United Kingdom have a considerably lower copper concentration than breast milk (Table 4). Breast milk itself is not considered to be nutritionally ideal for the very low birthweight infant, but Widdowson *et al* showed that the retention of copper from breast milk is greater than from formula milk.[27] The bioavailability of copper is dependent to some extent on the relative concentrations of other elements such as zinc and cadmium in the diet. Alteration of the copper: zinc ratio during treatment of copper deficiency has been reported to precipitate clinical zinc deficiency[29] and the reverse could occur. Another important consideration is the obligatory phytate content of soya based milks, and the casein content of the feed. These organophosphate compounds can precipitate copper and other metals in synergism with calcium in vitro.

This wide variation in the content of infant feeds is probably a consequence of the report on infant feeding published by the Department of Health and Social Security of 1980, which failed to recommend a minimum copper concentration for infant formulas.[30]

Table 4 *Copper concentration and copper:zinc ratio of mature human milk compared with the standard and preterm infant formulas available in the UK in 1984*

	Copper (μmol/100 ml)	*Copper:zinc ratio*
Mature human milk	0·6	0·14
Standard formulas		
SMA/Wysoy*	0·79	0·14
OCF	0·61	0·12
Premium	0·6	0·1
Ostermilk 2	0·25	0·08
Plus	0·25	0·05
Milumil	0·2	0·06
Preterm formulas		
Osterprem	1·89	0·12
Nenatal	1·26	0·1
SMA LBW	1·10	0·14
Prematalac	0·79	0·13
Preaptamil	0·16	0·1
Vamin Glucose with Ped-el	0·9	

Sources of information

Mature human milk	—	DHSS Reports on Health and Social Subjects Nos 12 (1977) and 18 (1980)
SMA/Wysoy SMA LBW	—	John Wyeth & Brother Ltd (American Home Products, USA)
OCF Ostermilk 2 Osterprem	—	Farley Health Products Ltd (Glaxo Group Ltd, UK)
Premium Plus Nenatal Prematalac	—	Cow & Gate Ltd (NV Nutricia, Holland)
Milumil Preaptamil	—	Milupa Ltd (Altana AG, West Germany)
Vamin Glucose Ped-el	—	KabiVitrum Ltd

* Contains phytate.

Conclusion

The infant of very low birthweight is at risk of many important nutritional deficiencies, one of which is copper. In view of the widespread implications of this condition, we would like to make the following recommendations:

(1) That these infants are given at least 1 μmol/kg per day of copper during parenteral and enteral feeding;
(2) That facilities for measurement of plasma copper and caerulplasmin are available to all neonatal units, and that these should be considered as routine investigations in infants with osteoporosis or oedema;
(3) That the diagnosis is considered early and treatment given before major clinical features occur.

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