

Sophie is an ex-preterm infant recently discharged from the neonatal unit. Her parents took her to the general practitioner (GP) because of a rash that had been present for about 10 days. She had been born at 27 weeks gestation with a birth weight of 1055 g and was discharged receiving supplemental oxygen via a nasal cannula. She was otherwise well and was being breast fed. The GP found a rash that was localised to her scalp (fig 1) and the underside of her chin. The rash on her scalp was red and scaly, and was well circumscribed and slightly raised. The rash on her chin consisted of a few pale pink macules. There were no papules or vesicles, and it was not angry looking. On further enquiry the GP elicited a history of a nappy rash the previous week. This had largely resolved with the use of proprietary creams.

The GP thought the chin rash was probably caused by mild irritation secondary to dribbling milk after feeds. He made a presumptive diagnosis of cradle cap and advised the use of simple emollients on the scalp.

The GP then reviewed the discharge letter from the neonatal unit.

The pregnancy was complicated by spontaneous rupture of the membranes at 18 weeks gestation and two doses of antenatal dexamethasone had been given. Sophie required three days of ventilation and was in air by the end of the first week, but had required supplemental oxygen since 2 weeks of age. She did not require parenteral nutrition and was on full feeds of expressed breast milk by the end of the first week of life. She received a combination of breast milk and preterm milk formula until 8 weeks of age (35 weeks postmenstrual age), and thereafter she was fully breast fed. On the neonatal unit she had received multivitamin drops containing vitamin D (280 iu/day), A, and C and these were continued after discharge. Her neonatal course otherwise appeared relatively uneventful with no evidence of retinopathy of prematurity or neurological compromise, with normal cranial ultrasound scans. She was discharged at 37 weeks postmenstrual age, 2–3 weeks before she presented to the GP with the rash.

COMMENT

- ▶ The requirement for supplementary oxygen is secondary to chronic lung disease (CLD) of prematurity. This is the result of a number of processes that are usually triggered by surfactant deficient hyaline membrane disease (HMD). HMD is primarily caused by immature lung development but may be complicated by co-existing infection (group B streptococcal infection can cause an identical radiological and histological picture). Preterm prolonged rupture of the membranes increases the risk of infection in utero. If this is associated with oligohydramnios before 20 weeks gestation there is a high chance of significant pulmonary hypoplasia.
- ▶ Over half of all infants born at less than 28 weeks develop CLD, which is the clinical correlate of the pathological diagnosis of bronchopulmonary dysplasia (BPD). The classic definition of BPD requires an abnormal chest x ray and the need for supplementary oxygen at 28 postnatal days; however, the more common and useful definition now used is that of CLD, which is defined as the continuing need for supplementary oxygen at 36 postmenstrual weeks. The aetiology is almost always multifactorial (table 1).

Sophie's mother requested a repeat appointment a few days later. The rash on her scalp showed no signs of improvement, the rash on her chin was much worse, and she had now developed a rash on her wrist (figs 2 and 3). She nevertheless remained generally well. Her oxygen requirement was unchanged (100 ml/min) and she was still breast feeding well every 3–4 hours. On examination she appeared otherwise healthy and her weight was following the centiles appropriately. The rash was still present on her scalp but there was no additional evidence of cradle cap.

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Figure 1 Rash on the scalp. Reproduced with permission of the child's parents.

The GP considered the possibility that the rash on the wrist was secondary to scabies infestation. He knew that infants may develop a widespread rash with scabies, and he also knew that Sophie had been home for a sufficient period of time to develop the condition (incubation period at least two weeks).¹ However, he felt that the rash on the chin was not consistent with such an explanation and he therefore made a tentative diagnosis of infantile seborrhoeic dermatitis. There appeared to be a few satellite lesions, but the mucous membranes showed no evidence of thrush. He asked that the emollients be continued and he also prescribed 0.5% hydrocortisone.

COMMENT

- ▶ Infantile seborrhoeic dermatitis is an eczematous condition of unknown aetiology that generally occurs in the first few weeks of life.¹ It most commonly affects the scalp manifesting as cradle cap, a yellowish or whitish, greasy and scaly rash. The face is also frequently involved, as are the skin folds and the napkin area. The differential diagnosis consists mainly of atopic dermatitis, psoriasis, and, if in the typical distribution, napkin ammoniacal dermatitis.
- ▶ Scabies might present as a widespread rash affecting the face, scalp, and wrists, especially in infancy. Vesiculopapular rashes on the palms and soles are characteristic but not universal, and scratching in older infants may create widespread eczematous changes.¹

A few days later the rash on Sophie's chin appeared worse and her mother sought a further opinion from the GP.

Table 1 Chronic lung disease: aetiological factors

- ▶ Prenatal factors
 - cytokine release (in utero infection)
 - genetic predisposition (including race, sex, etc)
 - gestation (degree of prematurity)
- ▶ Postnatal factors
 - mechanical ventilation (baro- and volutrauma)
 - air leak syndromes (including pulmonary interstitial emphysema)
 - oxygen toxicity (poor antioxidant capacity)
 - malnutrition (macro- and micronutrient deficiencies)
 - pulmonary oedema (excess fluid, patent ductus arteriosus)
 - infection



Figure 2 Rash on the wrist. Reproduced with permission of the child's parents.

The GP considered that the rash had shown no improvement despite the use of emollients and topical hydrocortisone. The rash on the chin caused him particular concern. He wondered about the possibility of a candida infection. Even though there were no abnormal signs in the mouth and no perineal rash he was concerned that the use of a steroid medication might have made Sophie more susceptible to thrush. He prescribed a topical antifungal cream (1% clotrimazole combined with 1% hydrocortisone) for the chin and arranged to review Sophie two days later with a colleague.

Despite the use of a topical antifungal cream there was no appreciable improvement and Sophie attended for review with the GP and his partner. The rash on her lower chin now appeared even more inflamed.

The GPs together considered the list of possible causes, and the various factors that supported the putative diagnoses (table 2). They also reviewed the relevant background history. They noted that Sophie was breast fed and that current evidence suggests an associated decreased incidence of atopy.¹ They also noted that Sophie's neonatal course had been relatively uneventful, and they were not aware of any associations between her two main medical problems: CLD and the unexplained rash. She was otherwise well, gaining weight, and her developmental progress was satisfactory. She was feeding every 3–4 hours and was on no additional



Figure 3 Rash on the chin. Reproduced with permission of the child's parents.

Table 2 Differential diagnosis of the rash

Differential diagnosis	Factors supporting this diagnosis	Factors not supporting this diagnosis
▶ Infantile seborrhoeic dermatitis (ISD)	Infant age group (<4–6 months old at onset) Widespread rash	Rash on chin not typical No classic cradle cap Unusual distribution No response to emollients or steroid
▶ Atopic dermatitis	May be difficult to distinguish from ISD ¹	No family history Breast fed (evidence equivocal) No response to emollients or steroid
▶ Irritant or contact dermatitis	Localised rash on chin	Unusual distribution with no clear precipitating factors or history No response to emollients or steroid
▶ Candidal dermatitis	Sore looking rash Satellite lesions May have been exacerbated by steroid cream	No oral or perineal thrush No response to antifungal cream Rash on wrist and scalp not typical
▶ Impetigo	Rash on chin looks typical May have been exacerbated by steroid cream	Rash on wrist and scalp not typical
▶ Scabies	Widespread lesions including wrist	No family history Rash on chin not compatible No lesions on palms or soles
▶ Nutritional deficiency	Preterm infant (poor stores) Chronic disease (increased requirements)	Rare presentation No growth failure or other signs Hospital course seems uncomplicated

medications. She was passing yellow seedy stools (2–3 times a day) typical of a breast fed infant. She had no siblings. Both parents were well and her mother was vegetarian.

The rash on her lower chin now appeared more sore and angry and they considered the possibility of impetigo. The antifungal cream was discontinued, as were the emollients, and a proprietary antimicrobial cream containing hydrocortisone, nystatin, and oxytetracycline was prescribed. They decided to refer Sophie for a further opinion if no improvement occurred during the next 2–3 days.

COMMENT

▶ Impetigo occurs mainly in children and is usually caused by *Staphylococcus aureus* infection, although it may also be caused by streptococci. Unless widespread or associated with systemic illness, topical antibiotic treatment usually suffices.¹ Bullous impetigo occurs in the newborn period with flaccid fluid or pus filled blisters that readily burst. Parenteral antibiotic treatment is necessary. Impetigo secondary to super-added infection of pre-existing eczema or scabies, etc, is the most common presentation.

Despite three days of treatment with an antimicrobial cream (also containing an antifungal and steroid) there was no improvement and therefore Sophie was

referred to a dermatologist for a further opinion. The dermatologist confirmed the findings of the GP and specifically noted the lack of any perineal rash. He also found that her weight gain was good and general examination normal (aside from the need for oxygen). The following investigations were organised: full blood count, urea and electrolytes, liver function tests, bone chemistry, serum zinc, serum vitamin B12, and red cell folate concentrations.

The dermatologist reviewed the presentation and the background history, and noted the lack of response to the various topical medications. He felt the rash would be compatible with a diagnosis of zinc deficiency and referred to the paediatric team for further investigation. The stools had been more frequent over the preceding few days but there was no diarrhoea.

A working diagnosis of zinc deficiency was made and Sophie was commenced on oral zinc (1 mg/kg a day) using effervescent zinc sulfate tablets.² All the topical preparations were discontinued. Three days later Sophie's mother was contacted by telephone and reported a dramatic improvement in Sophie's rash. At this stage the blood results were available (table 3).

Table 3 Results of the initial blood tests

Haemoglobin	8.9 g/dl (5.5 mmol/l)	Urea	1.1 mmol/l
Haematocrit	26%	Creatinine	34 µmol/l
MCV	85.1 fl	Calcium	2.65 mmol/l
Platelets	436 × 10 ⁹ /l	Phosphate	1.52 mmol/l
Neutrophils	2.4 × 10 ⁹ /l	Protein	53 g/l
Lymphocytes	4.2 × 10 ⁹ /l	Albumin	38 g/l
Vitamin B12	191 ng/l (180–1150)	Bilirubin	42 µmol/l
Red cell folate	352 µg/l (175–650)	Alkaline phosphatase	152 U/l (150–375)
Serum zinc	0.1 µmol/l (5–15)	Alanine transaminase	20 U/l (3–50)

MCV, mean cell volume.



Figure 4 Resolution of the rash on the wrists following zinc supplementation. Reproduced with permission of the child's parents.



Figure 5 The rash under the chin also resolved. Note the absence of the nasal cannula evident in fig 3. Reproduced with permission of the child's parents.

The investigations, combined with the response to zinc supplementation, confirmed the diagnosis of zinc deficiency and also revealed a mild anaemia. The zinc was continued and a review appointment was planned for the following week.

COMMENT

► Mild anaemia is common in preterm babies at a few weeks or months of age; it rarely requires a blood transfusion unless haemoglobin is very low or if there is also growth failure and/or significant ongoing chronic disease. Many preterm infants receive blood transfusions which will provide a large amount of iron, and all low birth weight formulas contain sufficient iron without the need for additional supplementation. Iron stores are therefore usually sufficient. Breast fed preterm babies may not have adequate stores during rapid periods of growth and those born weighing < 1800 g may benefit from supplemental iron until a good weaning diet has commenced.²

Two weeks after starting zinc supplementation the rash had completely resolved (figs 4 and 5). Sophie's oxygen requirements had decreased and she no longer needed supplementary oxygen during the day to maintain an oxygen saturation > 95% (note the absence of a nasal cannula in fig 5).

The biochemical and haematological investigations were repeated (table 4). Serum copper concentration was also measured as this has a similar pattern of absorption and storage to zinc, and although copper deficiency is excessively rare it has been reported in an infant receiving high dose zinc supplementation.³ The raised alkaline phosphatase concentration was also noted. Serum calcium was at the upper limits of normal and serum phosphate at the lower limits of normal. The biochemical picture was consistent with a

degree mineral deficiency. Sophie's mother asked whether breast feeding should be discontinued, but she was encouraged to continue in view of the long term health benefits associated with breast feeding.

COMMENT

- Mineral bone disease (osteopenia of prematurity) is common in preterm infants. Mineral deficiencies are similar to other micronutrient deficiencies in that they are usually caused by a combination of poor stores (for example, secondary to preterm delivery) and inadequate intake and often precipitated by a period of rapid growth. Because of solubility problems, mineral intake during parenteral nutrition is particularly poor. Specialised low birth weight formulas and breast milk fortifiers contain added calcium and phosphate. Breast milk contains inadequate mineral concentrations for most preterm babies, and overt clinical deficiency, particularly phosphate deficiency, is not uncommon.²
- Breast milk is also a poor source of vitamin D. Preterm infants are at specific risk since they do not get the 1–2 hours a day of sunlight exposure necessary for endogenous production. Infants need 200–400 iu vitamin D each day and supplements may be necessary where dietary intake and/or sunlight exposure is inadequate.
- There is some evidence that mineral bone disease may impair long term linear growth in preterm infants, but the data are conflicting and most controlled trials have simply focused on short term biochemical outcomes.

A few weeks later Sophie developed typical cradle cap followed by mild eczema. These were treated successfully with simple emollients. She continued to be breast fed and was commenced on solids. Zinc supplements were discontinued at 3 months of age (6 months postmenstrual age) and serum zinc

Urea	1.3 mmol/l	Protein	52 g/l
Creatinine	39 µmol/l	Albumin	41 g/l
Calcium	2.82 mmol/l	Bilirubin	47 µmol/l
Phosphate	1.63 mmol/l	Alkaline phosphatase	752 U/l (150–375)
Serum zinc	9.4 µmol/l (5–15)	Alanine transaminase	32 U/l (3–50)
Serum copper	7.1 µmol/l (3–11)		

concentrations two months later were normal. She was discharged from further follow up at 2 years of age with normal growth and developmental parameters.

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ZINC AND ZINC DEFICIENCY

Zinc is an essential nutrient and is the most important oligometal in humans. It is a constituent of several hundred metallo-enzymes including the DNA and RNA polymerases.³ Deficiency affects a huge range of homeostatic functions including carbohydrate metabolism, and protein and nucleic acid synthesis (and therefore cell replication and growth). Regulation of gene transcription may also be affected because of the so called "zinc finger" elements (sites on transcription proteins that bind with DNA to initiate transcription). It also has an important role in antioxidant enzyme systems (for example, superoxide dismutase) by stabilising cell membranes and preventing lipid peroxidation. Zinc is therefore vital in the continuity of growth from embryonic to fetal and neonatal life.

Dietary zinc is absorbed from the small intestine, secreted into the portal circulation, and primarily bound to albumin or α 2-macroglobulin.³ Exactly how much zinc is absorbed is uncertain but stable isotope studies suggest that over 50% is absorbed in preterm infants.⁴ Tighter binding to casein rather than whey proteins may explain the higher absorption rates of infants receiving breast milk. Absorption is also decreased by phytates and calcium which may form insoluble complexes with zinc. Zinc is stored in the skeleton and there are also large stores bound to metallothioneine in the liver.³ Zinc is lost in the stool, but can also be lost in large quantities when urinary losses are excessive, especially if induced by a thiazide diuretic.

Overt zinc deficiency is rare in preterm infants but the clinical effects may include growth failure, poor feeding, skin lesions, poor wound repair, anaemia, and diarrhoea, along with depressed immune and antioxidant capacity.³ Symptomatic zinc deficiency has been documented in several case reports, but it is likely that subclinical deficiency is more common than currently recognised.⁵ Unfortunately, as with many micronutrients, measurement of serum concentrations is not likely to determine clinical deficiency accurately, but nevertheless might serve as a useful screening test. Consideration should be given to checking serum values where a relevant history exists and when any of the above problems are noted, but the diagnosis is usually made following a therapeutic trial of zinc supplementation.²

In this case the relatively low alkaline phosphatase at presentation was probably a reflection of zinc deficiency, and the rapid rise after supplementation illustrates that metabolic bone disease is often only clinically apparent when linear growth is taking place. Alkaline phosphatase concentrations are frequently normal despite low mineral intake in the first few weeks in preterm babies because either ongoing disease and/or dietary macronutrient deficiency prevents growth.

It is also possible that the pathogenesis of CLD was partly nutritional in origin,⁶ as adequate protein synthesis for alveolar growth may have been compromised by zinc deficiency. Impaired antioxidant systems (also secondary to zinc deficiency) may have exacerbated the problem of oxygen free radical damage that is also thought to be important in the pathogenesis of CLD.

Dietary intake

Recommended dietary intakes for zinc are approximately 0.4–1 mg/kg/day depending on route, ongoing losses, and accumulated deficit³ and would ordinarily be met if a preterm low birth weight formula was used and full enteral feeds (150 ml/kg per day) tolerated. Trace elements are usually added to parenteral nutrition, but the amount in solution may not be sufficient when prolonged parenteral nutrition is necessary, or in the face of excess losses (for example, via an ileostomy). Additional supplemental zinc (plus other trace elements) can be provided intravenously in this situation.

Breast milk

The zinc concentration of colostrum is high. Concentrations in breast milk fall over the first few weeks, but it usually contains sufficient zinc to meet the needs of term infants. Concentrations at 6 months are lower still but by this stage most babies have good stores and many will be receiving zinc from weaning foods. In many of the case reports, low breast milk zinc concentrations have been documented that are more likely to explain the deficiency rather than a defect of absorption.⁷

In this case the mother still had stored frozen aliquots of breast milk that could be analysed for zinc values. These showed concentrations of 34.8 μ mol/l and 4.6 μ mol/l at 4 and 10 postnatal weeks, respectively. A range of breast milk zinc concentrations have been published⁸ with approximate mean (SD) values of 50 (10) μ mol/l and 25 (13) μ mol/l at 4 and 10 weeks postpartum, respectively. In this case it seems likely that breast milk concentrations were below normal. It is uncertain whether the mother herself also had low stores as she had already started to take what was left of the zinc preparation after administering the infant's daily dose (tablets contained 45 mg zinc of which only 5 mg was given to the infant), so her serum values were not measured. Concentrations of zinc in breast milk do not seem to be affected by the type of milk (fore or hind) and there is no apparent diurnal variation.⁹ In well nourished women concentrations are probably not affected by zinc intake, and it seems unlikely that maternal dietary habit (for example, vegetarianism) has much of an effect either.

Breast milk is best for all infants regardless of whether they are born preterm or not. However, it is unlikely to satisfy the nutrient requirements of most preterm infants and some form of supplementation (either as supplemental milk formula or breast milk fortifier) is almost always necessary in the pre-discharge setting. However, the best method of supplementation and the precise requirements are uncertain, and consideration should be given as to how supplementation may adversely affect the known benefits of breast milk. If mothers are to be encouraged to breast feed, then careful explanation of the rationale for "multi-supplementation" (for example, of vitamins, iron, zinc, etc) must be given, if cessation of breast feeding is to be avoided.

Deficiency

Zinc deficiency in preterm infants is probably much more common than acrodermatitis enteropathica which presents with a similar constellation of symptoms and signs after a latent period when fetal stores are exhausted. As it is more likely to be seen at a later stage of infancy than that associated with preterm delivery, behavioural and cognitive effects may be apparent and children may be miserable or depressed.¹⁰

There are now numerous controlled trials in both developed and developing countries that demonstrate zinc deficiency to be a major worldwide cause of growth retardation that may be prevented by zinc supplementation,¹¹ even in infants born preterm.¹²⁻¹³ Studies of maternal supplementation are conflicting but some have shown beneficial effects on fetal growth and a lower incidence of preterm delivery.¹⁴ Further confirmatory data are needed before widespread zinc supplementation can be recommended.

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ARCHIVIST.....

Inappropriate treatment of status epilepticus

A review of admissions to the intensive care unit (ICU) of the Great Ormond Street Hospital for Children in London (RFM Chin and colleagues. *Journal of Neurology, Neurosurgery, and Psychiatry* 2004; **jn 32797**) has led to the conclusion that only one in six children admitted to the ICU with status epilepticus (SE) was treated appropriately before arrival in the emergency department.

During a 3-year period, 1 April 1998 to 31 March 2001, there were 2285 admissions to the ICU, 98 (4.3%) with SE. The 98 episodes occurred in 91 children aged between 1 month and 12 years (median 2.2 years) and there was an equal number of girls and boys. Seventy-eight children (86%) were under 5 years old and 70 (77%) had had no previous episode of SE. All of the children were intubated and ventilated, in 55 episodes because of respiratory insufficiency after seizures had stopped and in the remaining 43 in order to give treatment (thiopentone) to stop the SE.

The main diagnoses were prolonged febrile convulsion (31%), acute symptomatic SE (24%), and SE in idiopathic epilepsy (21%). The main cause of acute symptomatic SE was CNS infection (18 of 24 cases). Pre-ICU treatment was with diazepam or lorazepam in almost all episodes. The dose was unknown in 12 episodes and was considered to have been too high in three and too low in 29. It was considered appropriate (within the range of 80-120% of the ideal dose defined as 0.1 mg/kg for lorazepam and 0.45 mg/kg for diazepam) in 54 episodes (55%). Respiratory insufficiency was more frequent among the 53 children who had more than two doses of benzodiazepine (64% vs 45%). Rectal paraldehyde and intravenous phenytoin were used almost equally as second line drugs. The dose of phenytoin was usually appropriate (92% of cases) but the dose of paraldehyde was often considered high (30%) or low (16%). The median duration of ventilatory support was 15 hours and median stay on ICU one day (range 1-13 days). Five children died of acute bacterial meningitis (2), acute liver failure (1), brain tumour (1), and neurodegenerative disease (1).

The main messages of this paper appear to be: 1) get the dose right (consult guidelines) and 2) don't give too many doses of benzodiazepine before moving to a second line drug and then, if necessary, to thiopentone anaesthesia with intubation and ventilation on ICU. (Two doses of benzodiazepine is probably enough (be aware of doses already given by someone else) and thiopentone anaesthesia is recommended when the seizure has lasted for 40 minutes or more after the start of treatment.) The authors state that appropriate audit and modifications of standard guidelines are required.