Nutritional rickets in 2 very low birthweight infants with chronic lung disease

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SUMMARY Two very low birthweight infants with rickets are described; one had a low serum 25-hydroxy-vitamin D3 concentration. Similarities in their clinical courses included low birthweights, low calcium intakes, uncertain vitamin D intakes, and chronic administration of frusemide and sodium bicarbonate—all potential aetiological factors in the development of bone undermineralisation. Both infants had a resolution of their chronic lung disease before their treatment for rickets. This experience has led us to the more cautious use of frusemide and sodium bicarbonate in infants at risk for rickets, and shows the need to ensure daily vitamin D supplements.

Very low birthweight infants are known to be at risk of developing vitamin D deficiency rickets.¹⁻³ In this report we describe 2 chronically ill infants of very low birthweights who developed rickets, and discuss the factors in their clinical courses that may be important in the development of their bone disease.

Case reports

Case 1. This 960-g girl was born at 27 weeks'

gestation. The Apgar scores were 4 at one minute and 3 at five minutes. She required mechanical ventilation from days 2 to 18 of life to treat respiratory distress syndrome. She needed increased ambient oxygen until 100 days of age and the diagnosis of bronchopulmonary dysplasia was confirmed on x-rays.

Formula feedings were supplemented with a parenteral amino-acid infusion on days 5 to 12. Routine multivitamin supplement (400 IU/ml

Fig. 1 Relation of sodium intake and frusemide administration to the time of diagnosis of rickets in Cases 1 and 2.

Fig. 2 Comparison of expected in utero calcium accumulation¹⁴ and actual calcium intake in the first 10 weeks of life before the diagnosis of rickets in Cases 1 and 2.

Conversion: SI to traditional units – calcium:
1 mmol/l $\approx$ 4 mg/100ml.

vitamin D) was ordered, but its daily administration was not recorded in her medical record. Feeds were often interrupted during the first 4 weeks of life because of respiratory problems. A mixed acidosis was treated with oral sodium bicarbonate (1–3 mmol per day) for the first 50 days.

From 4 to 10 weeks of age oedema was present. In the absence of any other reason for the oedema, excessive sodium intake was suspected (Fig. 1), and at age 46 days the infant's formula was changed to a low-sodium formula which also contained three-quarters as much calcium as the initial formula

(Fig. 2). Intermittent intramuscular doses of frusemide (1–2 mg/kg) were given for signs of pulmonary and peripheral oedema (Fig. 1). The oedema resolved by day 110 of life and treatment with frusemide was stopped.

Clinical signs of rickets were noted at day 100 and the diagnosis was confirmed by x-rays (Fig. 3). Serum calcium (Ca) was 2.25 mmol/l (9.0 mg/100 ml), inorganic phosphorus (P) 0.94 mmol/l (2.9 mg/100 ml), and alkaline phosphatase 1415 IU/l (normal <480 IU/l). The low-sodium formula was replaced by a formula containing more calcium and sodium, and a daily dose of 5000 IU of vitamin D2 was begun. Three weeks later there was a pronounced x-ray improvement (Fig. 3), serum Ca was 2.42 mmol/l (9.7 mg/100 ml), inorganic P 1.94 mmol/l (6.0 mg/100 ml), and alkaline phosphatase 716 IU/l. The infant was discharged at 5 months on a standard formula plus a vitamin D2 supplement of 400 IU/day. At 6 months she was well, and her serum Ca, P, and alkaline phosphatase concentrations were all normal.

Case 2. This 850-g boy was born at 27 weeks' gestation. Apgar scores were 4 at one minute and 7 at five minutes, and mechanical ventilation was used during the first 55 days of life to treat respiratory distress syndrome. Increased ambient oxygen was required until 90 days of age, and chest x-rays confirmed the diagnosis of bronchopulmonary dysplasia.

From day 4 to day 8 of life he received a parenteral amino-acid infusion to supplement his formula feeds (Fig. 2). A daily vitamin preparation (400 IU/ml vitamin D2) was ordered but its regular administration could not be confirmed. Oral sodium bicarbonate (1–3 mmol per day) was given as partial treatment for a mild mixed acidosis during the first

Fig. 3 (Case 1). X-rays of forearm. (a) At age 100 days, showing undermineralisation, metaphyseal flaring, and a pathological fracture of the distal radius. (b) After 3 weeks' treatment of rickets, showing improvement of the rachitic changes.

8 weeks (Fig. 1). Frusemide (2–3 mg/kg per day, intramuscular or oral) was given during the first 10 weeks for signs of pulmonary oedema (Fig. 1).

On day 105 the diagnosis of rickets was made clinically and by x-ray. Serum Ca was 1.85 mmol/l (7.4 mg/100 ml), inorganic P 1.16 mmol/l (3.6 mg/100 ml), and alkaline phosphatase 2128 IU/l. Serum 25-hydroxy-vitamin D₃ (25-OHD₃) was <16.2 mmol/l (<6 ng/ml) (normal 35–216 mmol/l; 13–80 ng/ml). The infant was treated with 5000 IU vitamin D₂ for 3 weeks. Nine weeks later, the x-ray and clinical signs of rickets had resolved and serum Ca was 2.32 mmol/l (9.3 mg/100 ml), inorganic P 2.0 mmol/l (6.2 mg/100 ml), alkaline phosphatase 801 IU/l, and 25-OHD₃ >270 mmol/l (>100 ng/ml).

Discussion

These two patients had rickets diagnosed at 3 to 4 months of age. They each had a birthweight <1000 g, respiratory difficulties that led to feeding difficulties with a resultant decrease in calcium intake, and an uncertain vitamin D intake; both were treated with sodium bicarbonate, frusemide, and a parenteral amino-acid infusion. All these clinical factors can cause or aggravate rickets. Unlike the patients described by Glasgow and Thomas,⁴ our two infants appear to have had classical bronchopulmonary dysplasia,⁵ which antedated the development of rickets. Both patients had a resolution of their oxygen requirement before the diagnosis and successful treatment of their rickets.

Nutritional vitamin D deficiency was probably important in both patients. Serum 25-OHD₃ concentrations were measured only in Case 2 who had a low value at an age when a normal serum concentration should be present.⁶ Additionally, a reduced dietary calcium intake could have played a part in causing rickets. Day *et al.*⁷ demonstrated improved bone mineralisation in infants of very low birthweights when dietary intake of calcium was increased to give the same intake as would have occurred *in utero*. Kooh *et al.*⁸ reported a child with isolated dietary calcium deficiency and normal serum 25-OHD₃ concentration: the patient had clinical, x-ray, and biochemical bone disease indistinguishable from vitamin D deficiency rickets, which healed with dietary calcium supplementation alone.

The drugs given to these patients may also have contributed to the development of rickets. Both frusemide and sodium bicarbonate can cause calciuresis in conjunction with natriuresis. Adults treated for hypercalcaemia with normal saline infusions have a pronounced increase in urinary calcium excretion.⁹ Frusemide has been used in the treatment of hypercalcaemia because it increases

urinary calcium excretion.^{10–11} Chronic administration of frusemide to neonates has resulted in excessive calciuria, as well as nephrolithiasis and nephrocalcinosis.¹² Total parenteral nutrition¹³ has also been associated with systemic bone disease in infants of very low birthweights. However, the short duration of this treatment in our patients probably excludes it as a major factor in the development of their bone disease.

A review of the clinical courses of the two rachitic infants thus suggested a number of potentially important aetiological factors including inadequate dietary vitamin D and calcium intakes, and prolonged treatment with sodium bicarbonate and frusemide. Although the relative contribution of each of these factors cannot be known, this experience stresses the need to guarantee the daily administration of vitamin D supplements and calcium intake to infants of very low birthweights and the need to maintain a high index of suspicion for the occurrence of rickets in such infants receiving prolonged treatment with frusemide or sodium bicarbonate.

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