Case Reports

Osteopenia of Prematurity

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Osteopenia of prematurity and neonatal metabolic bone disease are terms used to describe the reduced skeletal mineralization seen in preterm babies at term as compared with those who have remained *in utero.* During the last trimester of pregnancy there is a rapid accretion of calcium and phosphorus due to active transport across the placenta(l). The osteopenia makes the preterm newborn more susceptible to fractures during minimally invasive procedures and even with routine handling while in the Neonatal Intensive Care Unit (NICU)(2,3).

Poor mineralization of the rib cage and muscular weakness due to hypophosphatemic myopathy in babies with respiratory distress are important factors causing difficulty in weaning off ventilation(4). We report on two preterm infants with osteopenia of prematurity resulting in fracture of the long bones.

Case Reports

Case 1: A baby boy weighing 950 g was born at 27 weeks gestation. He developed severe hyaline membrane disease requiring prolonged assisted ventilation starting from day 1 of life. After receiving surfactant therapy and being weaned off the ventilator at the age of 32 days, he was oxygen-dependent for a duration of 58 days. During this period, clinical and radiological evidence of bronchopulmonary dysplasia was observed and he received a 14 day course of dexamethasone. His other problems included septicemia, grade II intraventricular hemorrhage and patent ductus arteriosus. As he was going into right-sided heart failure, he also received several injections of frusemide during the first few weeks of life.

During the sixth week of life, it was noticed by the nursing staff that he had slight swelling of the left mid arm region which was tender to touch. He cried due to pain while attempting to move the left upper limb. X-ray of the arm revealed an oblique fracture of the shaft of the left humerus, of recent origin *(Fig.* 1). He had undergone no active procedure prior to this event. One week earlier, the serum alkaline phosphatase level was 573 IU/L, serum phosphate was 1.38 mmol/L and the serum calcium was within normal limits. The fracture was treated with immobilization of the limb. Satisfactory healing occurred without sequelae.

Case 2: A baby girl weighing 965 g was born at 27 weeks of gestation. She had moderate respiratory distress syndrome for which she received ventilatory support and surfactant therapy. She did not have any other major complications, although necrotizing enterocolitis was suspected and treated on clinical grounds. She had re-

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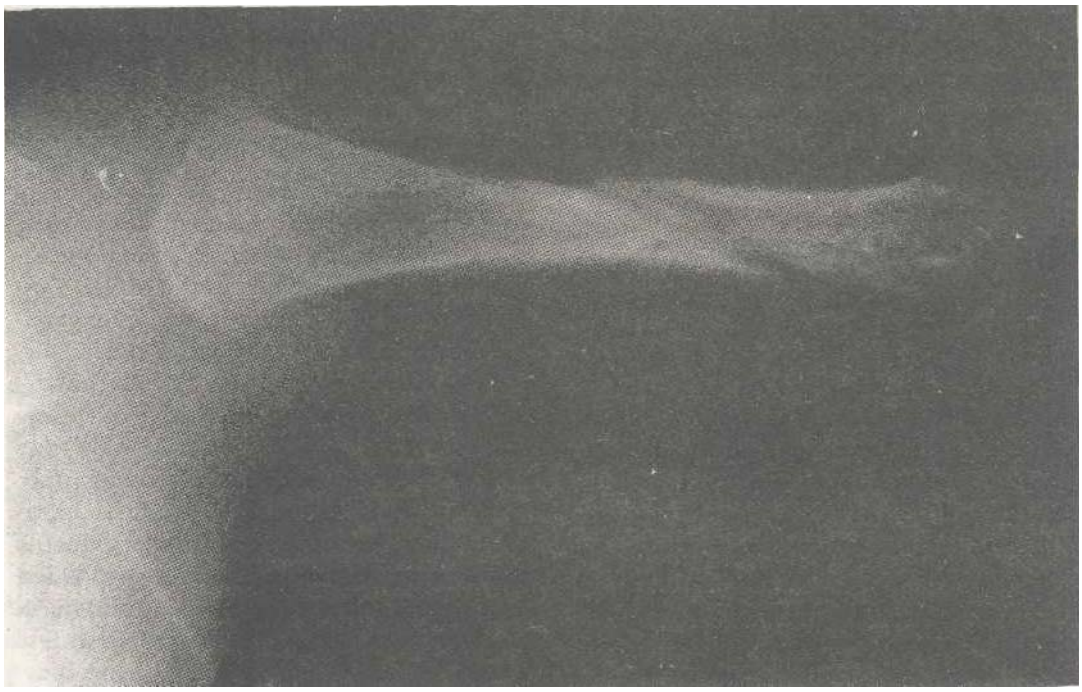

Fig. 1. X-ray showing oblique fracture of the shaft of left humerus.

ceived a total of four boluses of frusemide injections: two along with packed red cell transfusions, the other two for edema and impending heart failure which was thought to be due to prematurity and bronchopulmonary dysplasia. During the fifth week of life, she was noticed to have reduced movement of her left lower limb. There was no obvious swelling, tenderness of any other sign of local inflammation. X-ray of the limb showed a fine hairline fracture of the lower one-third of the femur. Four days prior to the diagnosis, the alkaline phosphatase was 1227 IU/L, calcium level was 1.57 mmol/L and phosphate level was 1.22 mmol/L. She required four weeks of parenteral nutritional due to her feed intolerance and necrotising enterocolitis. This was followed by a combination of parenteral and nasogastric feeding. Her fracture healed well by immobilization of the affect ed limb.

In both our cases, Vaminolact (electrolyte free) and Intralipid 10% were the aminoacid and lipid preperations used. Enteral feeding was with expressed breastmilk whenever possible. Supplementation of Similac 24 had to be given at times. While on total parenteral nutrition (TPN), 0.5 mmol/kg of calcium (calcium chloride) and 3 mmol/kg of phosphate (so dium phosphate) was given on alternating days, to avoid possible precipitation if added together. In addition, alpha calcidol 50 nanograms/kg/day was given. When enteral feeding was established, the same dose was continued by oral route.

Discussion

These two cases demonstrate the fragility of the bones of premature infants and the need for extreme caution in handling,

Neither infant had undergone any spe-

cial procedures, but sustained the fractures during the phase of growth which involved routine handling in NICU. Metabolic bone disease of preterm neonates is now being increasingly recognized(l,4). The diagnosis is usually based on either radiological abnormality or increase in plasma alkaline phosphatase levels as in our second case. Radiological diagnosis is likely to be imprecise because the assessment is subjective and a major loss of bone mineral might have to occur before characteristic changes would be apparent(5). Although raised plasma alkaline phosphatase activity is observed in association with frank rickets, growth activity is also a contributing factor. It is difficult to decide which of these plays the major rale(6). Dual energy X-ray absorptiometry is a new method for noninvasive bone mineral assessment. The sensitivity of this method should also permit precise evaluation of the effects of therapeutic agents such as corticosteroids and diuretics(7). Reduced mineral accretion during the last trimester of pregnancy is an important factor in the development of osteopenia of prematurity. Small for dates babies have reduced mineralization^), as do babies of diabetic mothers and those with severe pre-eclampsia(9). Attempts have been'made to establish a "normal" intrauterine mineral accretion curve as an adjunct to the investigation and treatment of infants at risk for development of postnasal osteopenia(10). In the early neonatal period of preterm infants, inadequate calcium and phosphorus availability is the principal etiological factor in the development of osteopenia. Calcium deficiency affects phosphorus balance through phosphaturic action of parathyroid hormone and phosphorus deficiency similarly affects calcium homeostasis. Our first case had low phosphate levels and the second case had suboptimal levels of calcium as well. Following birth, there is a well-recognized physiological fall in plasma calcium. The upper limit of normal plasma phosphorus level is the highest in neonates at 2.0-2.2 mmol/L. Regular measurement of plasma and urine parameters of these minerals should guide the management.

It has been shown that prenatal deficiency of phosphate due to placental insufficiency can be corrected by phosphate sup plementation, thereby preventing rickets of prematurity(l1). Parenteral nutrition fluids should be prepared in such a way as to provide these nutrients in the required dos age with no precipitatory effect in solution. Aluminum is an inhibitor of bone mineral ization and may be present as a contaminant in parenteral nutrition solutions(12). Delay in maturation of the renal enzymes, 1-alpha hydroxylase, with low plasma con centrations of 1,25-dihydroxyvitamin D may also occur(3). Increased parenteral in take of calcium and phosphorus has result ed in greater retention of these minerals during parenteral nutrition therapy and in greater bone mineral content after therapy(14). Immobility is also known to cause loss of bone mass. Prolonged periods of se dation or paralysis during mechanical ventilation increase the possibility of loss of bone mass(l). The prolonged use of ste roids and diuretics in the treatment of chronic lung disease in very low birth weight infants is likely to be deleterious to mineralization(4). Hence, osteopenia of prematurity has a multifactorial etiology. Its pathogenesis consists mainly of decreased bone formation and increased bone resorption, though some studies have put more emphasis on high turnover osteopenia with resorption predominating(15).

The search for a solution to this problem involves several aspects. In view of the reported mineral inadequacy in human milk for preterms(16), early correction of

phosphorus deficiency and subsequent calcium and phosphorus supplementation should be practiced. Preterm baby formulas provide added mineral supplementation, but very low birth weight and very premature infants are unable to tolerate adequate enteral feeds and close supervision should be kept over the prescription of parenteral fluids. Routine supplementation of vitamin D to preterm babies, at least in the early weeks, is successfully practiced in many centers. It is encouraging to know that recent studies have shown a phase of rapid mineral accretion starting at 40 weeks postconception in preterm infants which substantially reduces the perinatal mineralisation deficit(17). The exact mechanism of this is not yet fully understood. However, in preterm infants, efforts to reduce the deficit in the early weeks of life should be pursued with systematic vigour.

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