To the Editors:

A case of hypophosphatasia

An 8-week old girl was admitted for the management of multiple limb deformities. She was born vaginally at term. There was intrauterine growth retardation (IUGR). Although she had limb deformities (short and curved limbs) there were no perinatal complications. Birth weight was 2.2 kg, head circumference (9th centile), and length 44 cm (< -3 SD). A provisional diagnosis of metaphysial chondrodysplasia was made. She was the third product of non-consanguineous parents. The first pregnancy ended as a first trimester abortion and the second in a 6-year old healthy child.

She was an active, alert baby weighing 3.1 kg (< -3 SD). Head circumference was 36 cm (2nd centile) and the length was 49 cm (< -3 SD). The anterior fontanelle was widely open, upper and lower limbs were short and curved (Figures 1 and 2). The cardiovascular system and abdomen were clinically normal. Serum calcium was 2.25 mmol/l (normal: 2.2 - 2.7 mmol/l). Xrays of the upper limbs, lower limbs and skull showed generalized osteopenia with curved femur and humerus. There were no fractures. Radiologically a differential diagnosis of osteogenesis imperfecta and hypophosphatasia were considered. To differentiate between the two, serum alkaline phosphatase was done. The levels were low, 86 U/l (normal range for infants 150-420 U/l). This confirmed the diagnosis of hypophosphatasia. Biochemical evaluation showed serum calcium of 2.3 mmol/l, serum phosphate 2.58 mmol/l (1.25 - 2.1 mmol/l) and serum alkaline phosphatase activity 41.5 U/l.

Hypophosphatasia is now recognised as an inborn metabolic disorder characterised by abnormally low levels of tissue non-specific alkaline phosphatase (TNSALP) activity. It results in defective skeletal and dental mineralisation (rickets, fractures and dental anomalies), and accumulation of enzyme substrates (phosphoethanolamine (PAE), pyridoxal-5'phosphate (PLP) and inorganic pyrophosphate) (1). The intestinal and placental ALP activity is normal (2).

Figure 1. *Xray of a lower limb.*

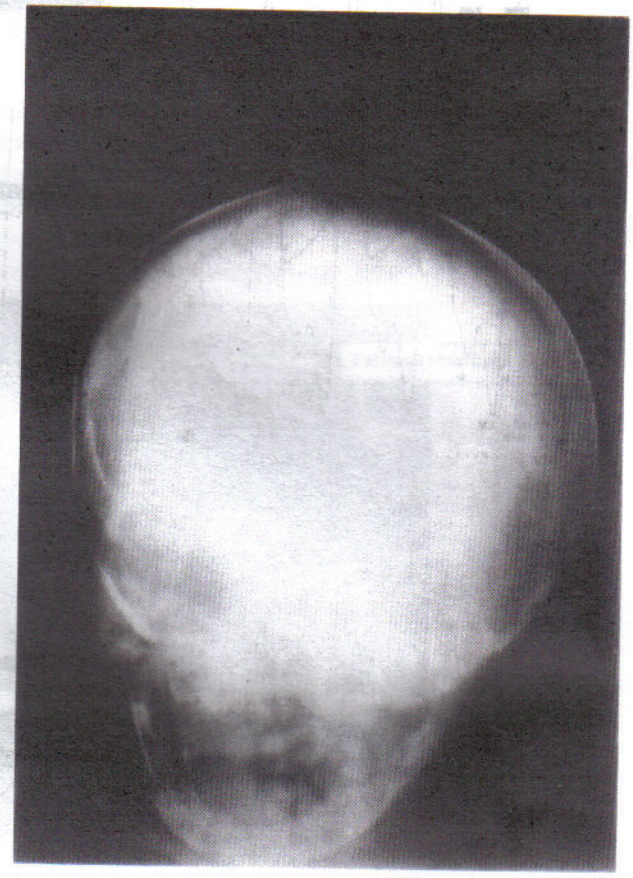

Figure 2. *Xray of the skull*

Clinically there are four forms of hypophosphatasia, perinatal, infantile, childhood and adult (3). The perinatal and infantile forms are inherited as autosomal recessive traits and childhood and adult forms show an autosomal dominant inheritance (2,3). The lethal forms (perinatal and infantile) are characterised by moth-eaten appearance at the ends of long bones, deficiency of ossification throughout the skeleton and marked shortening of long bones. Milder forms will present with bowing of legs and variable degrees of short stature (2). Less common features are wormian bones, poor calcification of skull bones, delayed closure of fontanelles, dental hypoplasia, delayed eruption and premature loss of teeth. Hypercalcaemia may lead to nephrocalcinosis. In the childhood form frequent fractures, bone pain and milder skeletal deformities will be seen (2). There is defective metabolism of PLP resulting in reduced levels of gamma-aminobutyric acid (GABA) in the brain which may cause seizures (3).

Diagnosis is by confirming low serum total alkaline phosphatase activity, irregular and incomplete ossification of bones and an increase in urine PEA and PLP (4). Neutrophil alkaline phosphatase (NAP) score has been reported to be low in isolated cases and may be diagno-

stically helpful (4). Bone xrays in hypophosphatasia resemble rickets and osteogenesis imperfecta. Fetal ultrasound scan shows markedly defective mineralisation of bone (4).

No satisfactory therapy has been found, but infusion of plasma rich in ALP has been helpful in healing bone. The clinical condition often improves spontaneously as the child matures, although early death from respiratory failure due to flail chest or renal failure due to nephrocalcinosis may occur with infantile forms (2). Analgesics should be considered in children with hypophosphatasia to relieve pain and improve quality of life (5). Seizure activity can be reduced by administration of pyridoxal (3). Patients having an identical clinical presentation and xray changes with normal ALP activity are referred to as having pseudohypophosphatasia.

References

1. Wendling D, Jeannin LL, Kremer P, Fellmann F, Toussirot E, Mornet E. Adult hypophosphatasia: Current aspects. *Joint Bone Spine* 2001; **68**: 120-4.
2. Chesney RW. Metabolic bone diseases. In: Behrman RE, Kliegman RM, Arvin AM eds. Nelson Text Book of Pediatrics. 15th ed. Bangalore: Prism books 1988-89.
3. Kanis JA. Disorders of calcium metabolism. In: Weatherall DJ, Ledingham JGG, Warrel DA eds. Oxford text book of medicine. 3rd ed. Oxford: Oxford University Press 1186.
4. Fredric NS. The limb: metabolic abnormalities of the skeleton. In: Fredric NS, Kuhn JP, eds; Essentials of caffey's pediatric xray diagnosis. Chicago: Year Book Medical Publishers,1990; 897-997.
5. Girschick HJ, Seyberth HW, Huppertz HI. Treatment of childhood hypophosphatasia with nonsteroidal anti-inflammatory drugs. *Bone* 1999; **25**: 603-7.

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