

INFANTILE HYPOPHOSPHATASIA

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Hypophosphatasia (HP) is a rare (1/100,000), inherited disorder,¹ characterized by defective mineralization of the skeletal² and dental structures³ and deficient alkaline phosphatase activity. Clinically, there are four types of HP: perinatal, infantile, childhood and adult.⁴ We report a case of infantile HP, which presented with evidence of florid rickets and very low alkaline phosphatase.

Case Report

A 7½-month-old Saudi male child was admitted with a history of poor general health, and bulging anterior fontanelle, noticed by his mother. There was no fever or vomiting. The baby was born at term by cesarean section, with a birth weight of 2.5 kg, and no neonatal problems. He had been having both breast and formula milk, and some weaning food had started two months previously.

The patient had one sister aged nine years, and one brother aged three, both of whom were normal. There was no family history of rickets, but there was a history of first-degree consanguineous marriage.

On examination, the baby's weight was 5 kg with a length of 62 cm (both were just below the 3rd percentile), and a head circumference of 40.5 cm (on the third percentile). He had normal color. His pulse, respiration, temperature and blood pressure were normal. The anterior fontanelle was significantly bulging, with a size of 2x2 cm, and the sutures were not wide. There was definite clinical evidence of rickets with wide wrists, wide ankles, bowing of both legs, rachitic rosary, Harrison's sulcus and mild frontal and parietal bossing.

There was mild general hypotonia, but reflexes were normal. The abdomen was lax, with liver palpable 3 cm below the right costal margin on the midclavicular line. The spleen tip was palpable. Other systemic examinations were within normal limits.

Investigations showed hemoglobin of 11.3 g/dL, total white cell count of $15.13 \times 10^9/L$ with 25% polymorphs, 70% lymphocytes, 2% eosinophils and 3% monocytes.

Serum calcium was 2.52 mmol/L (2.02-2.60 mmol/L), phosphate 2.6 mmol/L (1.4-4.81 mmol/L), alkaline phosphatase 65 U/L (198-625 U/L), urea 3.7 mmol/L, creatinine 35 mmol/L, sodium 137 mmol/L, potassium 4.54 mmol/L, pH 7.373, bicarbonate 16.2 mmol/L, and chloride 105.2 mmol/L. Radiologic examination of wrists, ankles, hips and knees showed evidence of florid rickets, with widening, cupping and fraying of both ends of the femur, tibia and fibula (Figure 1), and the skull showed beaten silver appearance (Figure 2). Plain x-ray of the abdomen and abdomen ultrasound did not show any calcinosis. The baby's sister and brother had alkaline phosphatase levels of 279 U/L and 319 U/L, respectively, with normal serum calcium and phosphate levels.

Discussion

Hypophosphatasia is an autosomal recessive disorder (although two families are reported to have autosomal dominant transmission^{5,6}) that resembles rickets both clinically and radiologically, and is defined by low tissue nonspecific serum alkaline phosphatase.

The most severely affected perinatal lethal cases die in the neonatal period.^{2,7} They can be detected prenatally by x-ray, which shows dystrophic bones and almost invisible skull. At birth, the skull is soft and may appear like a bag of fluid.²

The infantile form of HP usually presents between one and 12 months. The anterior fontanelle is usually open and bulging. The affected patients show evidence of rickets in the form of broad, wide ankles and wrists, bowing of legs, rachitic rosary and Harrison's sulcus. Constitutional symptoms such as failure to thrive, hypotonia, vomiting and constipation may be present, and are due to hypercalcemia.

Radiologic examinations of bones show changes similar to rickets, with demineralization, and ends of metaphyses becoming irregular and ill-defined, being more patchy and moth-eaten than rickets. Skull shows osteoporosis and beaten silver appearance, which is associated with the delayed bone growth and thus bulging anterior fontanelle.

In severe cases, the alkaline phosphatase may be virtually absent, but in mild cases, it is very low. Hypercalcemia is frequent, and may be life-threatening. Phosphoethanolamine, which is a substrate for normal

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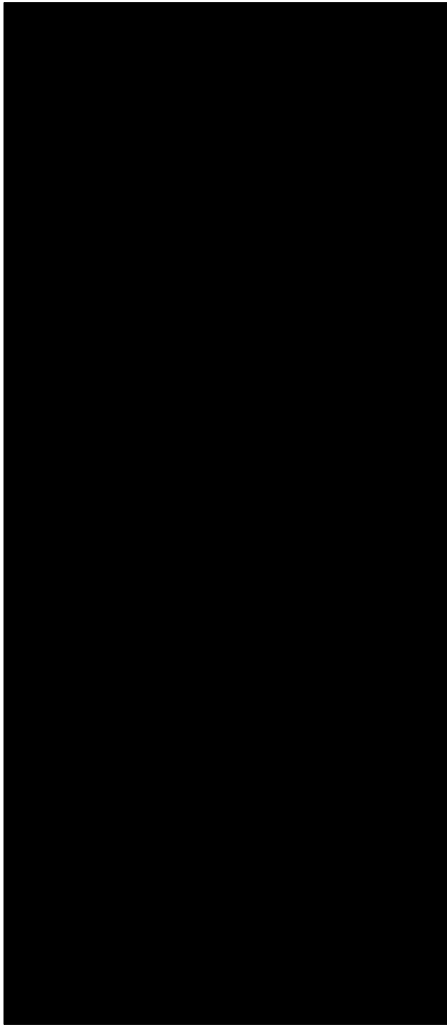


FIGURE 1. X-ray of lower limbs showing evidence of florid rickets with widening, cupping and fraying of both ends of femur, tibia and fibula.

phosphate function, is increased in both urine and blood, but unfortunately we could not estimate this in our case.

Childhood forms of HP present with evidence of rickets, fracture and abnormalities in dentition.³ The adult type may present with osteoporosis and frequent fractures. In our case, the alkaline phosphatase was persistently low but the serum calcium was upper normal, and there was clinical and radiological evidence of florid rickets, so our case fits into the milder form of infantile type HP.

Prenatal diagnosis of HP has been attempted successfully in Japan,⁸ with Southern Blot analysis of restriction fragment-length polymorphisms as a guide, cDNA for the human liver-type alkaline phosphatase as a probe, and BclI as a restriction enzyme. At present, there is no consistent treatment for HP. Enzyme replacement therapy has been attempted by repeated intravenous infusions of alkaline phosphatase-rich plasma, obtained by plasmapheresis from men with Paget bone disease.⁹ The clinical course of the disease often improves spontaneously as the child matures,



FIGURE 2. Skull x-ray showing beaten silver appearance.

although early death due to renal failure or pneumonia may also occur in the severe infantile form.

Our patient was not given any specific treatment. The course and prognosis of the disease were explained to the parents, and the baby was discharged from the hospital with further follow-up arrangements in our outpatient clinic. Unfortunately, the parents failed to turn up for the outpatient follow-up.

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