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NEONATAL FORM OF HYPOPHOSPHATASIA*

A Case Report

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Hypophosphatasia is a rare (1/100,000), inherited inborn error of metabolism characterized by low serum and tissue alkaline phosphatase activities resulting in skeletal abnormalities. Four clinical forms are recognized depending on the age of diagnosis. Since treatment is not available and the prognosis is always lethal, detection of index cases and prenatal diagnosis in subsequent pregnancies is very important. Here we report a case with the most severe form of hypophosphatasia associated with lung hypoplasia. *Key words: neonatal, hypophosphatasia.*

Hypophosphatasia is an inherited disorder of bone mineralization characterized by decreased alkaline phosphatase (ALP) enzyme activity. A wide range of presentations has been described, however the disorder can be classified into four forms according to the age of onset of clinical manifestations. This classification as neonatal, infantile, childhood and adult forms of the disease, also has prognostic implications. Infants affected with the severe congenital form cannot survive beyond the neonatal period[1].

Here we report a case with neonatal hypophosphatasia who died from early respiratory insufficiency.

Case Report

The patient was the third child of consanguineous parents who were first cousins. Their first child had been healthy and the second child had been delivered stillborn with multiple anomalies. There was no definite information about the existence of hypophosphatasia in that fetus. The family history revealed no other cases with skeletal abnormalities.

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A female infant was delivered at 35 weeks gestation by cesarean section because of fetal distress. Birth weight was 1900 g, length 32 cm and head circumference 30 cm. Abnormalities apparent at birth included short and bowed extremities, dimples on the extensor surfaces, generalized hypotonia, small chest, very manifest craniotabes, and a large anterior fontanel (Fig. 1). The serum alkaline phosphatase activity was measured at birth and six hours later. Both measurements revealed very low levels of 7 and 10 IU/L, respectively (normal 185-340). The serum calcium and phosphorus concentrations were 10.9 mg/dl and 11 mg/dl, respectively. Radiographs showed hypomineralization of all bones, especially the long bones and ribs, consistent with hypophosphatasia (Fig. 2).

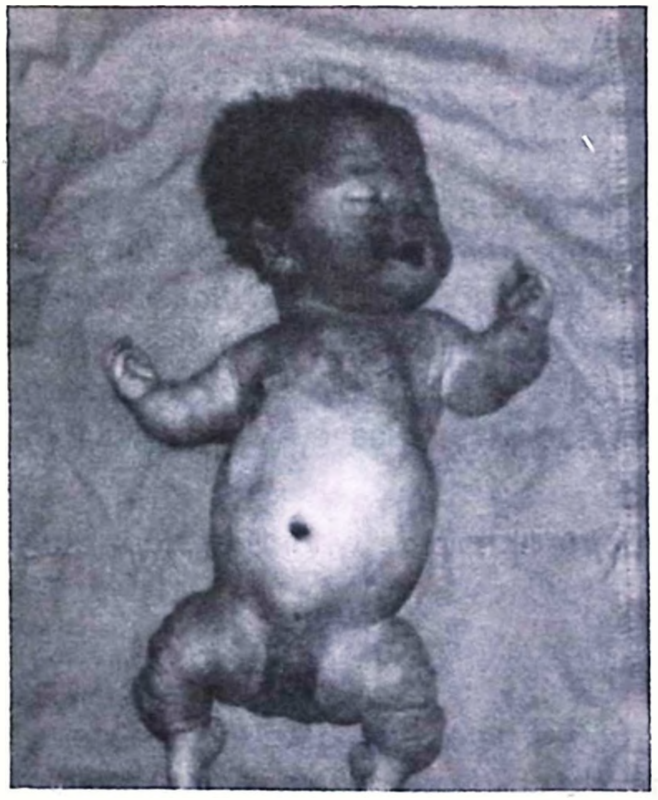

Fig. 1: Lethal neonatal form of hypophosphatasia. Note the curved and shortened limbs.

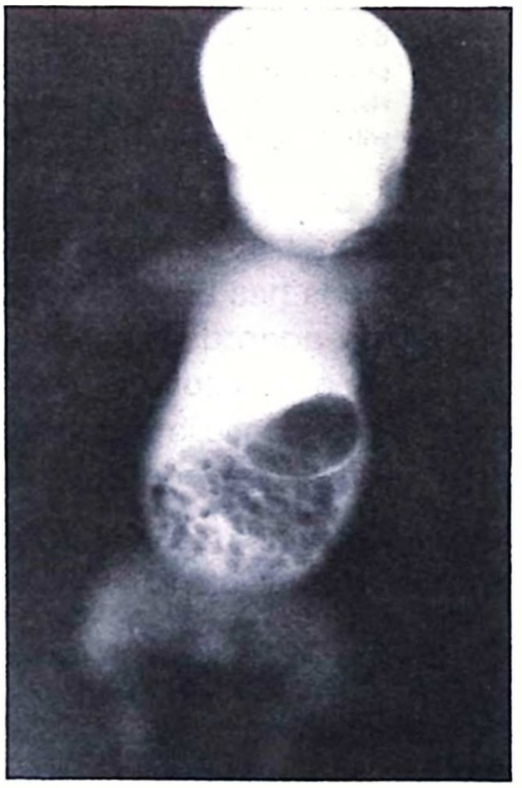

Fig. 2: Radiograph of the case. Note severe hypomineralization.

The infant was in respiratory distress. She was ventilated mechanically, but unfortunately lived only nine hours. The postmortem examination revealed pulmonary hypoplasia. A widened and flattened endochondral zone with pronounced disorganization of the chondrocytes was noted.

Discussion

Human ALPs are glycoproteins, and four isoenzyme forms have been identified. The placental, intestinal and placental-like isoenzymes are expressed in the

placenta, intestinal mucosa and neoplastic tissue, respectively. The liver/bone/kidney isoenzyme, however, is expressed in all tissues and localized particularly in hepatic, skeletal and renal tissue[2]. Only the latter form, which is also called tissue nonspecific (TNS) ALP, has a known biological function. The studies concerning hypophosphatasia indicate that TNS-ALP is necessary for normal bone mineralization, and its deficiency causes well-known deformities of the skeleton[2, 3]. The blood or urine levels of substrates for ALP including, phosphoetanolamine (PEA), inorganic pyrophosphate (PPi), and pyridoxal-5' phosphate (PLP), are found to be increased in subjects with hypophosphatasia.

Hypophosphatasia varies widely in its clinical expression and has four main forms. Cases with the infantile form have early failure to thrive, hypotonia, renal compromise from hypercalcemia and severe skeletal deformities. This form presents in the first six months and is lethal in approximately 50 percent of cases. The childhood and adult forms are milder conditions, causing premature loss of deciduous teeth. Pathologic fractures in adulthood may be the first findings[1, 4].

Neonatal hypophosphatasia can be diagnosed easily at birth with its characteristic appearance. The short and deformed extremities, cutaneous dimples, small thorax with short ribs, shortness of stature and manifest craniotabes are the prominent findings. In our case, similar findings including abnormally soft cranial bones, severely shortened limbs and respiratory distress strongly suggested hypophosphatasia (Fig. 1).

Radiographs of these infants reveal small, sclerotic bones at the base of the skull and a membranous calvaria. The ribs are small, thin and deformed. Sclerotic patches are also observed in the ribs and other tubular bones. In accordance with these findings, long bones and ribs were not visible in the radiographs of our case due to generalized hypomineralization (Fig. 2). In addition to the clinical and radiographic findings, the diagnosis was confirmed by deficient levels of ALP. Unfortunately, we had no urine sample from which to make a PEA analysis.

Infants with this form of disease die within a few days from respiratory insufficiency due to reduced thoracic volume. In fact, the respiratory distress of our case deteriorated in spite of mechanic ventilation, and the lungs were found to be hypoplastic on autopsy.

The frequency of consanguinity and the recurrence rates indicate an autosomal recessive transmission mode in the neonatal and infantile forms. Since no effective treatment is currently available and the prognosis is always lethal, prenatal diagnosis is very important in these forms. Measurement of the ALP activities in amniotic fluid, cultured amniotic fluid cells or chorionic villi has been reported as a diagnostic method[5, 6]. However, the reliability of these tests is not yet fully established. More reliable results have been noted with DNA analysis[7, 8].

Since impaired mineralization occurs in utero, ultrasonographic diagnosis is possible in neonatal hypophosphatasia. The diagnosis may be considered in the presence of polyhydramnios, very low echogenicity of all bones and the sign of the prominent falx cerebri, skeletal deformities, abnormal measurements of the bones and small thorax[9]. Currently, ultrasound scanning seems informative and more available than enzymatic and molecular studies in our country.

In conclusion, this fatal disorder, although very rare, is one that should be taken into consideration in the newborn when manifest craniotabes, respiratory distress, or short and bowed limbs are present. Radiographic changes and low ALP levels confirm the diagnosis. The presence of an index case indicates the need for more careful prenatal diagnostic evaluation of subsequent pregnancies.

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