

Enzyme Replacement Therapy in Hypophosphatasia

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ABSTRACT

Hypophosphatasia (HPP) is associated with significant morbidity and mortality in pediatric patients. The disease also imposes a high disease-burden in adult-onset HPP. Asfotase alfa (AA) is the first-in-class, bone-targeted, enzyme-replacement therapy designated to reverse the skeletal mineralisation defects in HPP. A male newborn presented with extreme fontanel gap and respiratory distress. He was diagnosed with perinatal lethal HPP thus AA treatment was started. Serum alkaline phosphatase (ALP) levels increased as high as 12,700 U/L during treatment. Any side effect related to AA was not observed. AA may be a valuable emerging therapy for the treatment of HPP.

Key Words: *Hypophosphatasia. Asfotase alfa.*

INTRODUCTION

Hypophosphatasia (HPP) results from mutations in the gene for the tissue-nonspecific isozyme of alkaline phosphatase (TNSALP). Markedly reduced serum alkaline phosphatase (ALP) activity may lead to increased serum/urine phosphoethanolamine (PEA), inorganic pyrophosphate (PPI) and pyridoxal-5'-phosphate (PLP) levels. Excessive PPI accumulation inhibits the formation of hydroxyapatite crystals in the bone.¹

Herein, we present the use of asfotase alfa (AA) in a male infant with perinatal lethal HPP.

CASE REPORT

A male newborn with a birth weight of 3000 g was referred to our department due to extreme fontanel gap. He was born at gestational age of 39 weeks to a 26-year mother through cesarean section. He was the second alive baby from the fifth pregnancy of the mother. Immediately after birth, he was promptly intubated and ventilated due to respiratory distress. The parents were third-degree relatives. During pregnancy, bone deformities were noticed. On physical examination, his weight was 3000 g; height, 45 cm and head circumference, 33 cm. Hypotonia and coarse facial appearance were remarkable. His skull bones were not well-formed. Skeletal radiographs demonstrated thin ribs, thoracic cage deformities, and poor ossification of the skull and epiphysis of the long bones (Figure 1). Laboratory examinations revealed serum phosphate, 7.3 mg/dl

(range 2.5-4.5), serum calcium, 9.8 mg/dl (range 9-11); serum ALP, 0 U/l and parathyroid hormone, 40 pg/ml (range 12-72). Serum total 25-hydroxy vitamin D level was within normal range. Perinatal lethal HPP diagnosis was made, based on the physical findings, laboratory investigations, and radiographic skeletal abnormalities. Plasma PLP and urine PEA levels were markedly elevated [3942 µg/L (normal range 0-50) and 1081 µmol/L (normal range 15-341), respectively]. AA (Strensiq) therapy (2 mg/kg/d subcutaneously three times per week, a total of 6 mg/kg/week) was started when the infant was 40 days old. A mild hypercalcemia was detected once before the initiation of the treatment and calcium level increased to 11.7 mg/dl. Hypercalcemia did not recur. Serum calcium and phosphate levels were normal. However, increased ALP levels as high as 12,700 U/L were noted during the treatment (Figure 2). During the treatment period of 8 weeks, the drug was tolerated well with no documented side effects such as nephrocalcinosis. Minimal increase in bone mineralisation during the follow-up was observed radiologically. There was no significant improvement in respiratory functions. He died when he was 97 days old due to ventilator-associated pneumonia and sepsis. The chest X-rays at

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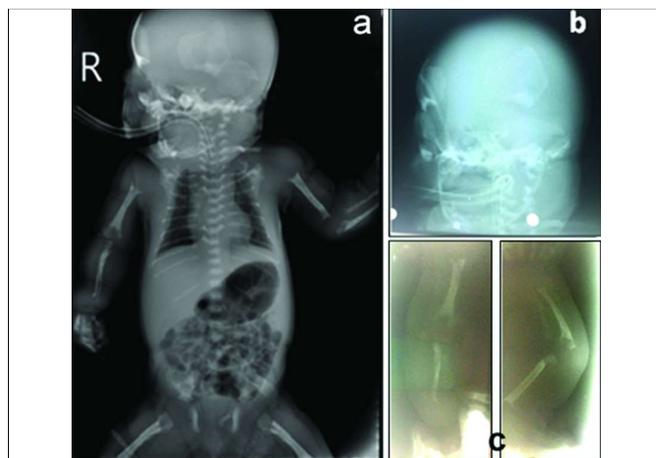


Figure 1: Body x-ray just after birth (a), head (b), upper extremities (c).

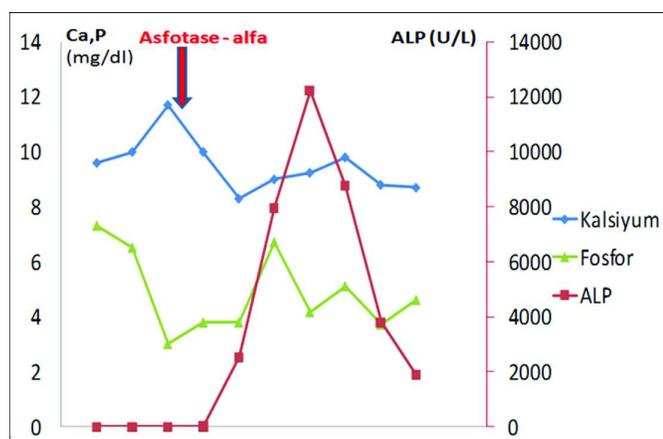


Figure 2: Calcium, phosphate and ALP levels of the patient, before and after treatment with asfotase alfa.



Figure 3: Chest X-ray just after birth and at various time points.

presentation and various time points during the follow-up are shown in Figure 3.

DISCUSSION

The severity and clinical presentation of HPP are highly variable. The main clinical manifestations of the disease are hypomineralisation of bones and teeth, rickets, respiratory insufficiency, growth retardation, hypotonia, pyridoxine-dependent convulsions, hypercalcemia/hypercalciuria and craniosynostoses. HPP is classified into six different forms according to its severity and clinical presentation: perinatal lethal, prenatal benign, infantile (starts before the first six months of life), childhood (6 months-18 years of age), adult and odontogenic HPP (there are no bone, joint or muscle findings).^{2,3}

Respiratory problems occur in perinatal HPP in association with the deformity of the thorax and pulmonary hypoplasia.⁴ Skeletal findings and muscle weakness in perinatal and infantile HPP and their impact on pulmonary functions and thorax stability are the main prognostic factors.^{4,5} In the present case, respiratory distress necessitating mechanical ventilation appeared immediately after the birth and subsequently sepsis developed due to pulmonary infection.

The recommended dose in all forms of the disease is 6 mg/kg/week.² In the present case, AA was started subcutaneously at the postnatal day 40 with a dose of 2 mg/kg/d three days a week.

Whyte *et al.* evaluated the efficacy of AA in patients with life-threatening HPP. Patients (five perinatal and six infantile HPP) below the age 3 years whose symptoms had been identified within the initial six months of life were included in the study. A patient with infantile HPP was excluded from the study due to convulsion, irritability, a decrease in oxygen saturation and fever which developed after the first dose of AA. A case with prenatal HPP died at the age of 7.5 months due to pulmonary sepsis. A significant improvement was observed in rickets and respiratory functions after 24 weeks of treatment and this improvement continued through week 48.⁴ In another study, the efficacy of AA replacement in patients with perinatal/infantile HPP was compared with untreated controls (historical controls) with a similar age distribution and clinical situation. The median duration of follow-up was 2.7 years. The survival rate was 95% in AA group and 42% in untreated controls at the end of the first year of life. These rates were 82% versus 27% when the patients reached five years of age.⁵

The present case remained under AA treatment for about 8 weeks. Before the initiation of AA therapy, hypercalcemia was observed. Apart from this mildly elevated serum calcium level, post-treatment calcium and phosphorus levels were within normal limits. Hypercalcemia and hypercalciuria occur frequently in infantile HPP. The disturbed calcium homeostasis is poorly understood but appears to reflect a combination of defective uptake of mineral by a poorly growing skeleton as well as progressive skeletal demineralisation.⁶ Hypercalcaemia seems to be related to impaired bone mineralisation in conjunction with normal bone resorption.⁷ Increased ALP levels were also detected after AA treatment, which is consistent with a previous report (14200 U/L).⁴

During the treatment period of 8 weeks, no side effects related to AA were observed. Injection area reactions (63%), lipodystrophy (28%), ectopic calcification of cornea, conjunctivae, and kidney (14%), and hypersensitivity reactions (12%) are the main side effects of AA treatment.⁸ There is a tendency towards ectopic calcification in patients with HPP. Ophthalmologic evaluation should be performed for possible foci of calcification. AA treatment may also increase the preexisting craniosynostoses. Antibodies against AA were detected in 78% of the treated patients. Of these antibodies, 45% are neutralizing antibodies. Antibody formation may cause a decrease in the circulating AA levels.⁸

In this case, we could start the treatment only at the postnatal day 40 due to customs problems. The prognosis could have been better if the treatment has started earlier. Respiratory functions may worsen in the early stages of AA treatment, which probably reflects the natural course of the disease.^{4,5} Besides, improvement in respiratory functions in some patients is slower than

the others. This indicates poor respiratory function at baseline or long-standing pulmonary impairment.⁵ In the present case, it is difficult to comment on the treatment success as the treatment period is not long enough. However, a minimal increase in bone mineralisation on skeletal graphs was reported by radiologists at the fourth week of treatment. Significant improvements in skeletal abnormalities were observed in patients with infantile/perinatal HPP-treated with AA at 24 weeks of treatment.⁴

Perinatal lethal and infantile HPP are the most severe forms of the HPP. Early initiation of enzyme replacement therapy and appropriate supportive care is important for prognosis.

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