

Asfotase alfa has a limited effect in improving the bowed limbs in perinatal benign hypophosphatasia: A case report

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Abstract. Hypophosphatasia (HPP) is a rare skeletal dysplasia characterized by impaired bone mineralization, caused by loss-of-function mutations in the tissue-nonspecific alkaline phosphatase (*TNSALP*) gene. Enzyme replacement therapy (ERT) by administration of asfotase alfa was reported to improve the survival rate, bone mineralization, and short stature in the severe form of HPP. However, the effect of asfotase alfa in improving the skeletal phenotypes for the mild form of HPP has not been elucidated. We report a case with perinatal benign HPP who had compound heterozygous mutations of p.F327L and p.R30X in the *TNSALP* gene. No hypomineralization was seen in the radiographs from the neonatal period, but bowing of the femurs and ulnae bilaterally was persistent. ERT was administered during the age of 7.8 to 10.8 yr, although there was an interruption in the treatment for one year. The bowed femurs and ulnae were not improved by the treatment with asfotase alfa at the age of 10.8 yr. Bone mineral density of the lumbar spine was between -0.5 and -1.0 of the z-score, and the patient's height was about -2.0 SD during the treatment. Asfotase alfa might have a limited effect in improving the bowed limbs in perinatal benign hypophosphatasia.

Key words: hypophosphatasia, enzyme replacement therapy, asfotase alfa, perinatal benign hypophosphatasia, bowing

Introduction

Hypophosphatasia (HPP) is a rare inherited disorder caused by loss-of-function mutations of the tissue non-specific isoenzyme of alkaline phosphatase (*TNSALP*) gene (1). HPP has been classified as perinatal severe, perinatal benign, infantile, childhood, adult, and odontohypophosphatasia according to the age of onset and severity (2). To date, more than 400 different defects have been identified in *TNSALP*, and these can be autosomal recessive or autosomal dominant inheritance (https://www.sesep.uvsq.fr/03_hypo_mutations.php) as edited by the University of Versailles-Saint Quentin, which explains the extreme range of the severity of the disease. 22.4% of unrelated Japanese patients with HPP were classified into perinatal benign HPP (3). Most of them were found to be compound heterozygous for p.F327L and another mutation. Enzyme replacement therapy (ERT) with recombinant human bone-targeted *TNSALP*, asfotase alfa, improved the rate of survival in patients with perinatal severe and infantile HPP (4,

5). However, the efficacy of asfotase alfa for perinatal benign HPP has not been elucidated. We report a case with perinatal benign HPP who had persistent bowing of the femurs and ulnae, despite treatment with asfotase alfa during childhood.

Case Report

A 7.5-yr-old boy presented with bowed limbs (Figs. 1 and 2). He had a limited range of motion at the elbow due to posterior dislocation of the radial head. We previously reported this case up to the patient's age of two years (6). The boy was delivered through Caesarian section due to breech presentation at 38 wk of gestation, from non-consanguineous healthy parents. His birth length and weight were 43.7 cm (-2.5 SD) and 3,020 g (mean), respectively. Congenital bowing and shortening of the long tubular bones with low serum alkaline phosphatase (ALP) (126 IU/L), which was measured by the Japan Society of Clinical Chemistry (JSCC) method, and elevated urine phosphoethanolamine (900.8 micro-

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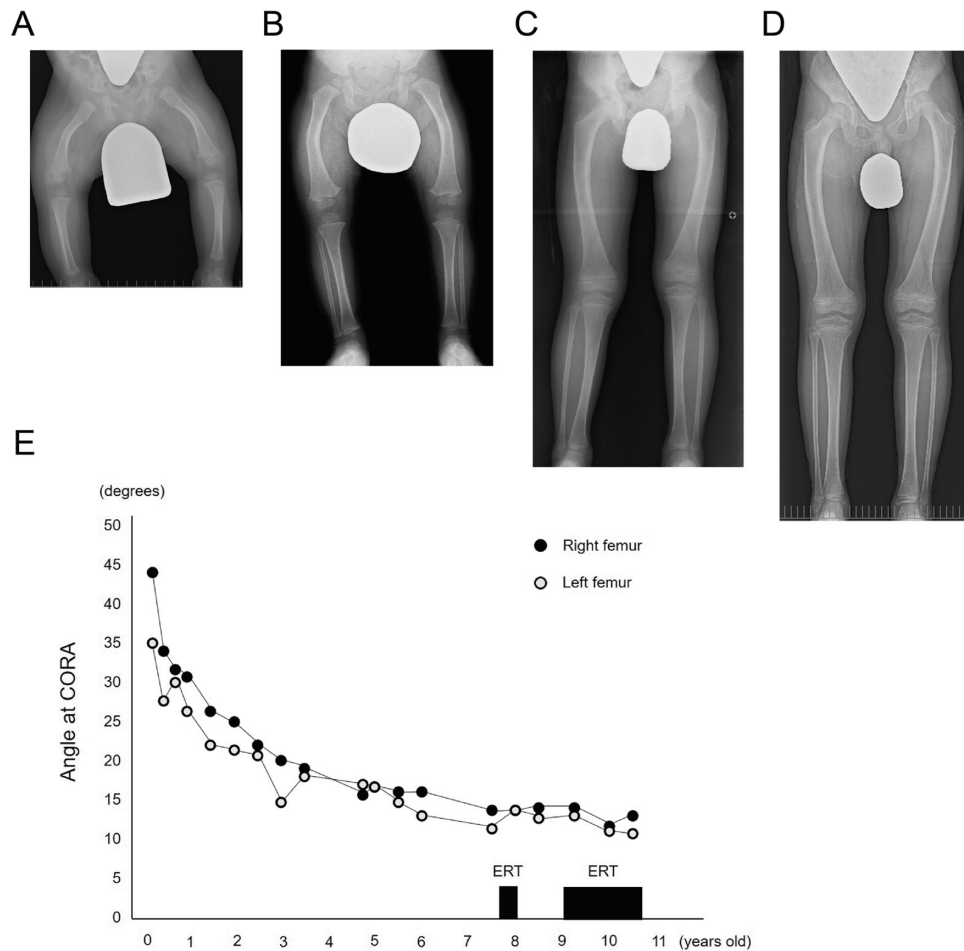


Fig. 1. Radiographs of the lower limbs. A: Anteroposterior radiograph indicated bowing of both femurs at the age of 0.4 yr. B: Bowed femurs persisted at the age of 1.7 yr. C: In addition to the bowed femurs, pelvic inclination was observed due to the leg length discrepancy at the age of 7.5 yr. D: Bowed femurs and pelvic inclination remained persistent at the age of 10.5 yr. The angles of center of rotation of angulation (CORA) (7) in both femurs were spontaneously decreased by the age of seven years, but the deformity persisted even after ERT.

mol/mg) was found. Ossification of the skull, vertebrae, and thorax was normal. He had been diagnosed with benign prenatal HPP (also called perinatal benign HPP) confirmed by genetic testing, which revealed compound heterozygous mutations (c.88C>T; p.R30X and c.979T>C; p.F327L) in the *TNSALP* gene. The angles of center of rotation of angulation (CORA) (7) of the femur spontaneously improved, but the bowing was persistent at the age of 7.5 yr (**Fig. 1**). The patient and his parents were desirous of improvement in the bone deformities, although they understood that there was adequate evidence about the efficacy of ERT for prenatal benign HPP. Asfotase alfa was initiated at a dose of 2 mg/kg/d for 3 d/wk at the age of 7.8 yr. Serum ALP increased during the treatment with asfotase alfa. He showed good adherence to ERT, but discontinued the treatment after four months due to fear of needles and injections.

One year later, he reinitiated ERT with subcutaneous injection of asfotase alfa at the same dose per body weight. Although serum ALP increased

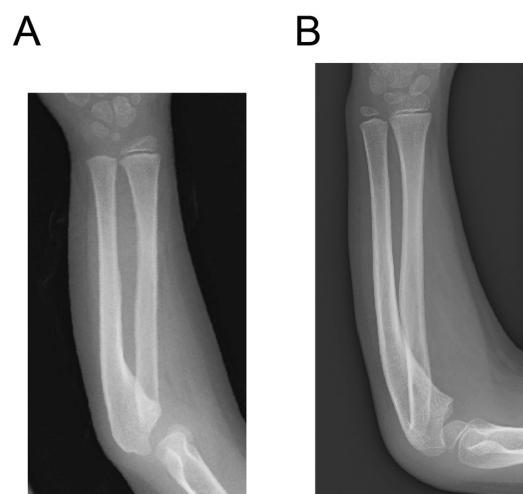


Fig. 2. Radiographs of the left forearms. A: Left ulna was bowed with posterior dislocation of the radial head at the age of 7.5 yr. B: Bowed ulna and dislocation of the radial head were persistent at the age of 10.5 yr.

during the second treatment (Fig. 3A), his femurs and ulnae remained bowed (Figs. 1 and 2). Insole lift was prescribed for leg length discrepancy. Z-score of the lumbar spine in the bone mineral density (BMD) test did not show any change after the treatment with asfotase alpha (Fig. 3B). The growth velocity of height was constant during the ERT (Fig. 3C). He decided to discontinue the injection at the age of 10.8 years, since there was no improvement in the bowing of the limbs.

Discussion

ERT has been reported to contribute to the improvement of fracture, shortening and bowing of limbs, and metaphyseal flare, in addition to improvement in the rate of survival for perinatal severe and infantile HPP (5). Patients with mild forms of HPP are often desirous of improvement in the skeletal abnormalities. Mild forms of HPP usually result from heterozygosity for dominant severe alleles or from compound heterozygosity for severe and moderate alleles (8). The p.F327L mutant has been shown to retain less than 70% of the enzymatic activity compared to the wild-type protein (3, 8), while the mutated protein of p.R30X in *TNSALP* seemed to be too short to show enzymatic activity.

The combination of p.L520Rfs86X and p.F327L are the most common pathogenic alleles for perinatal benign HPP in the Japanese population. ERT was initiated at the age of four months in a patient of perinatal HPP with these compound heterozygous mutations, and the bowing of femurs improved (9). In another case with the same combination of mutations, bowing of the long bone spontaneously improved without ERT (6). The spontaneous correction of the bowed femurs was noted before ERT in the current case. The effect of asfotase alpha in improving bowed limbs in cases of perinatal benign HPP is controversial.

BMD did not change after the treatment with asfotase alpha in the current case. *Io et al.* (9) also showed that BMD of the lumbar spine remained below -2 SD despite early ERT in a patient of perinatal HPP with compound heterozygous mutations. Asfotase alpha might not have the potential to enhance the BMD in perinatal benign HPP. Moreover, the BMD z-score has limited utility in assessing deficient bone mineralization in patients with HPP, although dual X-ray absorptiometry (DXA) has been commonly used in the assessment of children with HPP (10).

Asfotase alpha has been reported to increase the height z-score in children with severe HPP with onset

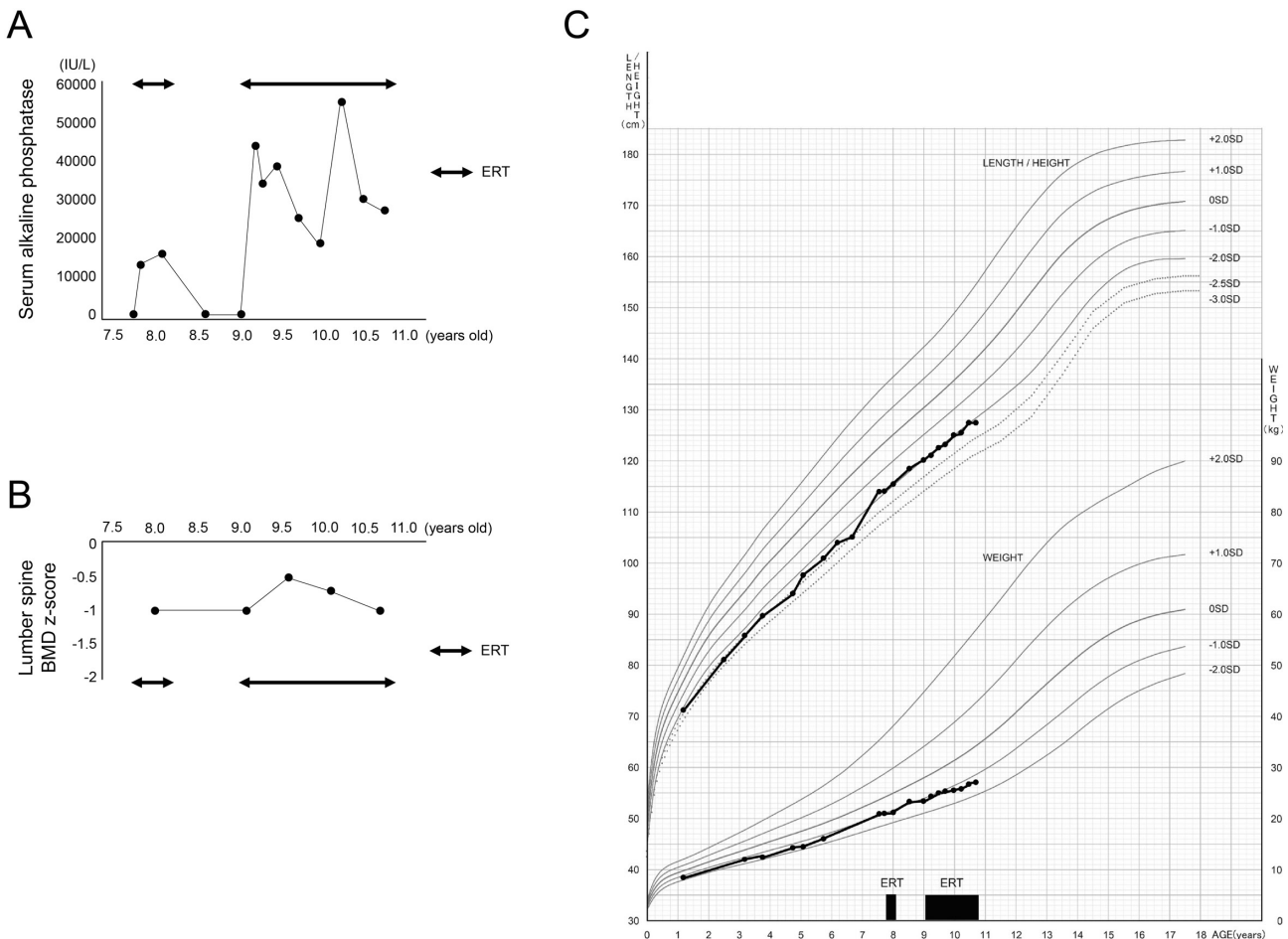


Fig. 3. Clinical course during enzyme replacement therapy (ERT). A: Serum alkaline phosphatase (measured by JSSC method). B: Bone mineral density of the lumbar spine (BMD). C: Growth chart.

before six months of age (11). However, the height z-scores remained below normal after seven years of ERT in children with life-threatening perinatal or infantile HPP (12). Despite improvement in the severe short stature, asfotase alfa might not increase the height in

cases with mild HPP.

Bowed limbs were not improved by the treatment with asfotase alfa in the current case. Asfotase alfa had a limited effect on skeletal phenotypes associated with perinatal benign HPP.

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