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Case Report

Asfotase Alfa Treatment in a 2-year-old Girl with Childhood Hypophosphatasia

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ABSTRACT

Childhood hypophosphatasia (HPP) presents with bowing of the limbs, poor mobility, chronic pain, short stature, fractures, and motor impairment. Enzyme replacement therapy (ERT) provides improved pulmonary and physical function in life-threatening perinatal and infantile forms of HPP. However, treatment of those patients without life-threatening HPP is limited. This report describes the results of asfotase alfa (Strensiq®, Alexion Pharmaceuticals, Inc.) treatment in a 6-year-old girl with childhood HPP, who presented with premature loss of primary teeth, low mobility, and chronic pain in the legs. Sequence analysis of the *TNSALP* gene revealed three heterozygous variants; c.526G>A (reported previously), c.1051G>C (novel), c.787T>C (reported previously). After a four-year follow-up under ERT, a marked reduction in leg pain and restlessness was observed and physical therapy assessments showed remarkable improvements in motor function, pain score, and quality of life. The treatment decision in childhood HPP is not as clear as in infantile and perinatal forms and it is mostly based on the clinical and radiological condition of the patient. In patients with childhood HPP without severe skeletal involvement but accompanying motor retardation, ERT may improve quality of life, motor functions, and daily activities.

Keywords: Childhood hypophosphatasia, asfotase alfa, motor function

Introduction

Hypophosphatasia (HPP) is a rare inborn error of metabolism characterized by low serum alkaline phosphatase (ALP) activity (hypophosphatasaemia) due to loss-of-function mutations within the gene for the tissue-non-specific isoenzyme of ALP (*TNSALP*) (1). Inorganic pyrophosphate, pyridoxal 5'-phosphate (PLP), and phosphoethanolamine (PEA), which are natural substrates of *TNSALP*, accumulate and inhibit mineralization. HPP features remarkably broad-ranging manifestations, ranging from neonatal death due and severe skeletal hypomineralization to only dental problems in adults (1). Seven major forms have been defined according to the severity of the disease; perinatal HPP, infantile HPP, childhood HPP, adult HPP, odonto-HPP, pseudohypophosphatasia, and benign prenatal HPP (2). Childhood HPP presents with bowing of the limbs, poor mobility, chronic pain, short stature, fractures, motor impairment, and fatigue (3).

Before enzyme replacement therapy (ERT), HPP treatment was supportive and symptom-oriented (4). Asfotase alfa was first used in perinatal and infantile forms of the disease and was found to improve pulmonary and

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physical functions in these patients (5). However, there is insufficient data regarding indications of ERT in childhood HPP. This report describes the results of a four-year asfotase alfa treatment in a 6-year-old girl with childhood HPP.

Case Description

A 26-month-old girl was admitted due to loss of primary teeth with intact roots, poor mobility, and chronic pain in the legs. She was born at term with a birth weight of 3,500 gr. Her teeth appeared at the age of 9 months, and the loss of teeth without caries started at two years old. She had started walking at 18 months of age and has suffered from gait disturbance and leg pain since then. She was taking non-steroidal anti-inflammatory drugs for leg pain almost every day and had no bone fractures. Her parents were unrelated. Her mother has suffered from severe tooth caries since she was nine years old. She had a history of an ankle fractures but had no skeletal problem. Several family members also had dental problems and fractures (pedigree is shown in Figure 1). At diagnosis; her weight was 9 kg [-2.57 standard deviation score (SDS)], height was 81.5 cm (-1.98 SDS), body mass index (BMI) was (-2.09 SDS), weight-for-height was 81% (-2.46 SDS) and mid-parental target height was 166.5 cm (0.51 SDS). Physical examination revealed scaphocephaly, frontal bossing, low-set ears, blue sclera, an open anterior fontanel, loss of primary teeth, and proximal muscle weakness in the lower limbs. She had difficulty in standing up, climbing stairs, and walking. Other physical examinations were normal. She was prepubertal. Repeated tests for serum ALP activity revealed low values ranging between 15 and 18 U/L (normal reference range for age and sex: 125-320 U/L). Levels of serum calcium, phosphate, thyroid, parathyroid hormones, and 25-hydroxyvitamin D were normal. Radiological examination showed tongue-like lucencies in the metaphyses of the distal femur and proximal fibula (Figure 2). Her bone age was compatible with chronological age (according to Greulich & Pyle). Bone mineral density was normal. Renal ultrasound showed no nephrocalcinosis. Ophthalmologic examination revealed normal findings. In cranial computed tomography, sagittal synostosis not requiring surgery was determined.

Results

The entire coding region of the *TNSALP* gene was sequenced using genomic DNA. Sequence analysis revealed a heterozygous variant (c.526G>A) in exon 6, a heterozygous variant (c.1051G>C) in exon 10, and a heterozygous variant (c.787T>C) in exon 7. Her asymptomatic father carried the first heterozygous variant. The mother carried both the second and third variants. The serum ALP, serum pyridoxal 5'-phosphate and urine PEA levels of the family are presented in Table I.

Physical therapy was applied; however, it did not achieve the desired benefit. In order to improve functional mobility, asfotase alfa (Strensiq®, 6 mg/kg/week) was initiated at the age of 31 months through a compassionate use program. The gross and fine motor functional assessments carried out by an expert physiatrist are presented in Table II. Enhancement in motor dexterity was observed. Complaints were markedly reduced, and analgesic medication was no longer required. No side effects were observed except for mild injection site reactions (erythema, pain, lipohypotrophy, and lipohypertrophy).

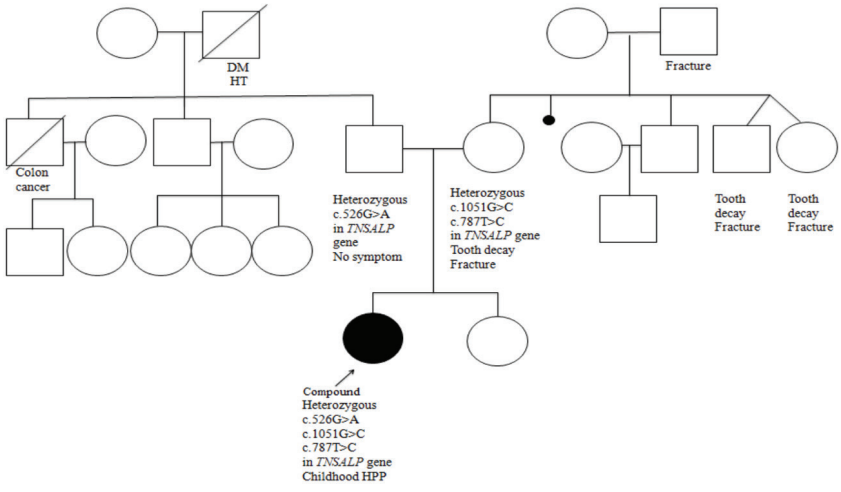

Figure 1. Pedigree of the patient

DM: Diabetes mellitus: HT: Hypertension TNSALP: Tissue-non-specific isoenzyme of alkaline phosphatase HPP: Hypophosphatasia

Pediatric dentistry treatment was given to the patient. The lower incisors were lost in the intraoral inspection (Figure 3). Preventive strategies were performed depending on the condition of the other teeth. The panoramic X-ray at the 4th year follow-up showed that the permanent teeth germs were present (Figure 3). On her last examination at six years old, her weight was 16.6 kg (-1.9 SDS), height was 108.6 cm (-1.82 SDS), BMI was (-1.07 SDS), and growth velocity was 6.3 cm/year. Similar to her peers, she could perform all physical activities such as climbing the stairs both up and down, rolling and playing games with friends.

Discussion

411 *TNSALP* mutations have been identified in HPP (http://alplmutationdatabase.hypophosphatasie.com/). Broad-ranging clinical heterogeneity is associated with the great variety of missense mutations and some mutations' dominant-negative effect. In severe forms of this disease (perinatal and infantile HPP), mutations are mostly homozygous (5) or compound heterozygous (2). Childhood HPP can either be inherited autosomal recessively or autosomal dominantly (1,6). Our patient had three

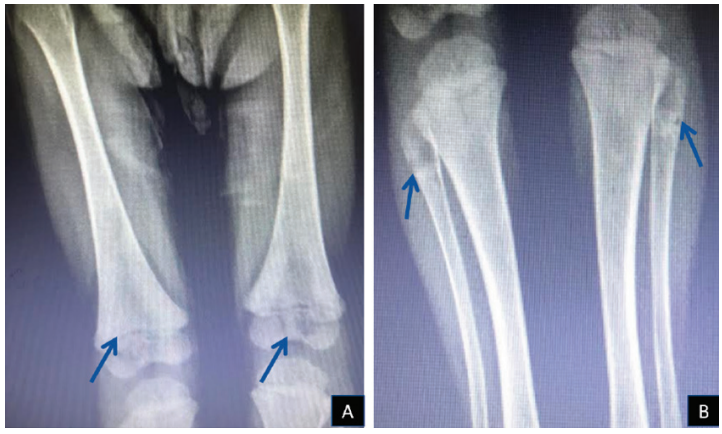

Figure 2. X-ray images of lower extremities (A, B). A. Characteristic "tongue" sign of metaphyseal radiolucencies are present in the femoral metaphysis (arrows). B. Oval radiolucent lesions and apparent physeal widening are present in the proximal fibula (arrows)

Table I. Biochemical test results

Biochemical tests	Proband	Mother	Father
Serum alkaline phosphatase (U/L)	15 U/L (N: 125-320)	12 U/L (N: 33-107)	34 U/L (N: 33-107)
Serum pyridoxal 5'-phosphate (µg/L)	740.1 µg/L (N: 5-50)	37 ug/L (N: 5-50)	66.5 ug/L (N: 5-50)
Urine phosphoethanolamine (µmol/g creatinine)	927.5 µmol/g kre (N: 33-342)	132 µmol/g kre (N: 0-48)	10.30 µmol/g kre (N: 0-48)

N: Normal range

Table II. Gross and fine motor functional assessment

Tests	Before treatment	At the six months of treatment
2-minute walk test	Uncooperative	Uncooperative
10-meter walk test	13 seconds	9.59 seconds
9-step stair climb test	With one hand support 10.44 seconds	Without support 5.07 seconds
Timed floor to stand-natural test	4.46 seconds	1.69 seconds
Nine-hole peg test **Insertion and removal times**	Right hand: 47.4/24.5 seconds Left hand: 40.3/26.3 seconds	Right hand: 23.69/26.3 seconds Left hand: 25.3/23.1 seconds
Child health assessment questionnaire	Pain score: 8.5 Disability index: 2.6	Pain score: 2.5 Disability index: 0.55
Toddler quality of life questionnaire **(Best possible score 180)**	27.7	73.6
Jumping	Absent	Present

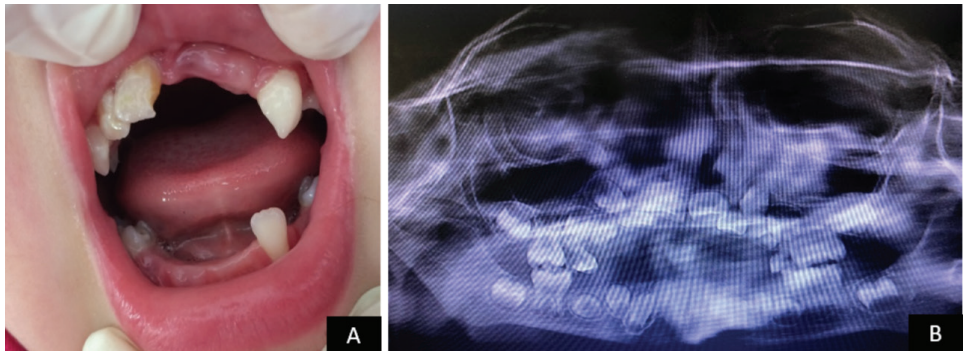

Figure 3. Intraoral appearance at diagnosis (A) and panoramic X-ray image at the 4th year of treatment (B)

heterozygous variants in the *TNSALP* gene; c.526G>A in exon 6, c.1051G>C in exon 10, c.787T>C in exon 7. The first variant, c.526G>A (p.A176T) in exon 6 was previously identified in infantile, mild, and severe childhood as well as adult and odonto-HPP, and it was shown by *in vitro* studies to possess a dominant-negative effect (7). In segregation analysis, the father of the patient carried the same heterozygous variant. This phenotypic difference could be explained by intra-familial variability in gene expression and incomplete penetrance of the variant as previously reported in HPP (8). The second variant (c.1051G>C, p.E351Q) is a novel variant and *in silico* analysis predicted it to be disease-causing (Mutation taster, http://www.mutationtaster.org) or likely pathogenic (Varsome, https://varsome.com/). The third variant (c.787T>C, p.Y263H) is a disease-associated polymorphism (9). The patient's mother was heterozygous for the second and third variants. She had suffered from multiple tooth decay and had undergone dental treatments; however, no skeletal disease was present. Based on *in silico* analyses and the mother's clinical findings, we suggest that c.1051G>C in exon 10 may be associated with odonto-HPP.

In a study evaluating 173 pediatric patients with HPP, researchers expanded the HPP classification; childhood HPP was divided into two subgroups, "mild" and "severe" according to radiological findings (2). Severe childhood HPP is characterized radiologically by diffuse osteopenia, calcification and osteosclerosis zones and clinically by muscle weakness, delayed walking, and waddling gait (2). Furthermore, lower height and weight z-scores, autosomal recessive inheritance, and the presence of two mutations in the *TNSALP* are more prominent in severe childhood HPP (2). According to this classification, our patient had severe childhood HPP due to gait disturbance, muscle weakness, low height and weight Z-scores, and compound heterozygous mutations, despite the absence of severe radiological findings.

The bone-targeted ERT, asfotase alfa (Strensiq®), was approved for pediatric-onset HPP in 2015. In life-threatening HPP (infantile and perinatal), ERT has shown improvements in skeletal findings as well as pulmonary and physical functions (5). In life-threatening HPP, it is relatively easy to make a treatment decision given the poor prognosis of the disease and the benefits of ERT. On the other hand, childhood HPP is usually not a life-threatening condition. The literature data regarding the decision on ERT in childhood HPP is not precise (3), despite significant improvements in growth, muscle strength, motor function, agility, and quality of life with five years of treatment (10). According to the clinical experience of Rush (3), ERT should be considered in the following conditions: No significant improvement in motor function with rehabilitation, pain resistant to conservative treatment, severe rickets, bone fractures, significant functional limitations without bone fracture, and short stature with insufficient growth velocity. ERT was initiated in our patient at 31 months of age owing to gross motor delay and the lack of adequate response to physical therapy. Six months after treatment had commenced, a marked reduction was observed in complaints and physical therapy assessments showed remarkable improvement in motor function, pain scores, and quality of life. She was able to participate in age-appropriate activities and keep up with her peers in the school environment. Considering the diagnosis and treatment process, we concluded that the patient benefited from this treatment.

Due to inadequately mineralized cementum anchoring the teeth to the periodontal ligament, early and painless tooth loss with intact root is one of the important findings in HPP (2). The primary dentition can be affected more than the permanent teeth. Therefore, dental problems should be followed up. There is insufficient data on the effectiveness of ERT on dental problems. Our patient had regular dental

examinations, and the permanent tooth roots were healthy in the last panoramic X-ray.

In conclusion, although HPP nosology is useful for classifying patients and using a common language, considering the disease's wide clinical presentation, individual evaluation may be better for treatment decision. Since impaired growth and developmental delay will result in a decreased quality of life and an inability to perform daily activities effectively, ERT should also be considered in patients without significant radiological findings, such as in our case.

Ethics

Informed Consent: Informed consent was obtained from the patient's parent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.Ç., B.E.F., H.Ç., Ö.E., B.D., Design: G.Ç., B.E.F., H.Ç., Ö.E., B.D., Data Collection and/or Processing: G.Ç., B.E.F., H.Ç., Ö.E., B.D., Analysis and/or Interpretation: G.Ç., B.E.F., H.Ç., Ö.E., B.D., Literature Search: G.Ç., B.E.F., H.Ç., Ö.E., B.D., Writing: G.Ç., B.E.F., H.Ç., Ö.E., B.D.

Conflict of Interest: The authors declared that there were no conflicts of interest.

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