European Journal of Medical Genetics 68 (2024) 104915

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: www.elsevier.com/locate/ejmg

Impressive clinical improvement and disappearance of neuropathic pain in an adult patient with hypophosphatasia treated with asfotase alfa

Zografia Zervou [a], Roel Plooij [b], Evert F.S. van Velsen [a], Remco G.M. Timmermans [b], Serwet Demirdas [c], M. Carola Zillikens [a,*]

[a] Erasmus MC Bone Center, Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands
[b] Erasmus MC, Department of Rehabilitation Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands
[c] Department of Clinical Genetics, Sophia Children's Hospital, Erasmus Medical Centre, Erasmus University, Rotterdam, the Netherlands

ARTICLE INFO

Handling Editor: A. Verloes

Keywords:
Asfotase alfa
Tissue-nonspecific alkaline phosphatase
Hypophosphatasia
Neuropathic pain
Femur fracture

ABSTRACT

Hypophosphatasia (HPP) is a rare disorder, resulting from loss-of-function variants of the ALPL gene encoding non-tissue specific alkaline phosphatase (TNSALP). Presentation varies largely, with increased severity usually occurring with earlier disease onset. Here we describe the clinical improvement of a 57-year-old woman with childhood onset HPP, after initiating treatment with asfotase alfa (Strensiq®). This was started because of the rapid and progressive radiological deterioration of bone structure after placement of nails in both upper legs for spontaneous atypical femur fracture (AFF) - like fractures. Initiation of treatment, not only resulted in stabilization of bone structure on X-rays, but within a few weeks there was a dramatic reduction of burning pain sensations in the lower legs, attributed in retrospect to neuropathic pain, and also almost complete disappearance of headaches. Additionally, unhealed metatarsal fractures finally healed after almost 10 years. Drug efficacy was further evaluated through -quality of life questionnaires and multiple tests conducted by the physiotherapist, and showed clear improvements. Within 3 months after starting asfotase alfa, the patient was able to carry out her daily tasks indoors without relying on a walker and even started electric bike rides for 20 km/day. In conclusion, treatment with asfotase alfa, halted rapid radiological bone deterioration after bilateral intramedullary femoral pen placement and strongly increased quality of life, marked by rapid disappearance of neuropathic pain, reduction in headaches and musculoskeletal pains, and enhanced muscle strength and mobility. The quick and almost complete disappearance of neuropathic pain and headache suggests a relation with disturbed levels of metabolites in HPP.

1. Introduction

Hypophosphatasia (HPP, OMIM: 146300) is a rare, genetic disease caused by loss-of-function variants in *ALPL* (MIM: 171760), which encodes tissue nonspecific alkaline phosphatase (TNSALP) (Whyte, 2016, 2017a). Deficient TNSALP activity results in accumulation of its substrates, including inorganic pyrophosphate (PPi), pyridoxal 5′-phosphate (PLP) and phosphoethanolamine (PEA) (Caswell et al., 1991). PPi acts as an inhibitor of skeletal and dental mineralization, through the inhibition of hydroxyapatite crystal formation within the bone matrix (Whyte, 2016).

There are six different forms of HPP, defined according to the age of onset of clinical manifestations: perinatal lethal, perinatal benign, infantile, childhood, adult, and odontohypophosphatasia (Hofmann et al., 2013). The severity of HPP varies from mild to severe, with increased severity usually occurring with earlier disease onset (Whyte et al., 2015). Clinical manifestations can vary largely and may include fatigue, chronic muscle and bone pain, muscle weakness, dental abnormalities, as well as fractures or pseudofractures and neurological symptoms. (Bianchi, 2015).

In 2015, the Federal Drug Administration (FDA) and the European Medicines Agency (EMA), approved enzyme replacement therapy (ERT) with recombinant human TNSALP, asfotase alfa (Alexion Pharmaceuticals, Inc., Boston, MA, USA) (Whyte, 2017b). Treatment with asfotase alfa resulted in improvement in the clinical and radiological features of children with perinatal and infantile hypofosfatasia (Whyte et al., 2016a). To date, there is limited data regarding the effectiveness of asfotase alfa in adult individuals with infantile and childhood-onset HPP

* Corresponding author. Rg-5, Erasmus University Medical Center, Dr. Molewaterplein 40, 3015, GD, Rotterdam, the Netherlands.
E-mail address: m.c.zillikens@erasmusmc.nl (M.C. Zillikens).

https://doi.org/10.1016/j.ejmg.2024.104915
Received 30 August 2023; Received in revised form 16 January 2024; Accepted 28 January 2024
Available online 5 February 2024

(Nishizawa et al., 2020; Freitas et al., 2018; Klidaras et al., 2018; Kishnani et al., 2019; Rolvien et al., 2019; Genest et al., 2020; Magdaleno et al., 2019). Here, we describe the substantial clinical improvement of an adult patient with childhood onset HPP after starting asfotase alfa.

2. Material and methods

2.1. Case description

The patient is a 57-year-old woman, born to non-consanguineous Dutch parents. She has been experiencing symptoms consistent with HPP since her early childhood, although she received a formal diagnosis only at 34 years of age. At the age of 3-years she underwent surgery for craniosynostosis. Over the years she complained of progressive musculoskeletal pains, headache and deformities of the legs. From the age of 23 she needed dental frames, plates and crowns due to caries and periodontal disease, and at the age of 25 she underwent a supracondylar corrective osteotomy of the left femur. Upon presentation at our department, at the age of 34, she had severe pain throughout her body, mainly in the head, shoulders, knees, lower legs and feet. In retrospect her mother also had symptoms that could be attributed to HPP and a maternal cousin turned out to be diagnosed with HPP in another country. Clinical examination revealed a height of 165.5 cm, a pelvic tilt (due to a shorter left leg), varus deformity of the knees and a lumbar lordosis. On palpation of the skull there was prominence with bony irregularities at the site of the cranial sutures. Lab results showed a decreased serum alkaline phosphatase (ALP) level of 13U/L (upper limit of normal 98U/L) and increased levels of PLP and PEA in urine. Genetic analysis revealed a heterozygous likely pathogenic variant of the ALPL gene (c.202_204delACG, p.Thr68del). The same variant was later also reported in the maternal cousin with HPP. The patient's symptoms worsened over the years and, in addition to severe headaches, joint and bone pain in hips, knees and legs, she suffered from muscle weakness and increasing sensations of burning pain at the anterior side of both lower legs. The latter is suggestive for neuropathic pain. Furthermore, she experienced several spontaneous insufficiency fractures e.g., of the feet. Feet fracture did not heal or only partially over 10 years despite wearing orthopedic shoes, with some of them recurring (Fig. 1). Following the feet fractures, the patient experienced a gradual decline in motor abilities, leading to loss of independent walking and reliance on a walker. Pain in the right upper leg, that was present for nearly two years, had been attributed to subcutaneous calcifications in the hips. On a routine out-patient visit in 2019, she mentioned severe increase of the pain, possibly after a fall. CT-scan showed a transverse incomplete AFF - like fracture in the right femur below the minor trochanter and a transverse lucent line at the lateral cortex above the knee in the left femur (Fig. 2). Subsequently, she underwent surgical intervention with nail placement which was followed by rapid and progressive deterioration of the bone structure and mineralization on X-rays (Fig. 3). Because of fear that the surgical material might fail due to persisting non-union, treatment with asfotase alfa was initiated in March 2021 (Fig. 3).

2.2. Methods

To evaluate the biochemical status, the effectiveness and possible side effects of the drug, biochemical serum (creatinine, eGFR, calcium, phosphate, (ALP), vitamin B6, PTH, 25-OH-vitamin, plasma PEA (P-PEA)) and urine PEA (U-PEA) samples were obtained at different timepoints during the treatment (baseline, 6 weeks, 3, 6, 9, 12, 15, 18, 21 and 24 months after initiation of ERT). Our laboratory, as in many hospitals, does not indicate a lower limit for ALP, only an upper limit (98 U/L). ALP level below 40U/L requires further investigation to rule out hypophosphatasia (Vieira et al., 2021). Furthermore, bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry (GE Healthcare Lunar Prodigy Advance, H8950AN encore, v.17 SP4) at baseline, 12 and 24 months. A renal ultrasound was performed at baseline, 12 and 18 months to evaluate the presence of calcifications. Radiographs of the feet, left knee, upper and lower legs were performed frequently to assess the bone structure and mineralization. A pulmonary function test was conducted at baseline and at 12 months after initiation of asfotase alfa.

Motor function was evaluated through five test batteries every six months. The 6-min walking test (6 MWT), timed-up-and-go test (TUG), timed chair-stand-test (TCST) were used to evaluate overall motor function. Biodex isokinetic dynamometer was used to measure the extension and flexion strength of the knee and Mecmesin AFTI ® hand-grip strength dynamometer to measure the hand-grip strength. For the assessment of the knee strength the patient sat on a chair, which is part of the dynamometer. The rotational axis of the dynamometer was aligned with the transversal knee-joint axis and connected to the point of force application at the distal end of the tibia. Range of motion was set from a knee joint angle of 90°–160°, with a fully extended leg corresponding to a knee angle of 180°. For the assessment of the hand-grip strength, the patient sat straight on an armless chair, with the elbows flexed to a 90° angle and the forearms in a neutral position. To measure the maximum effort, the patient was asked to grip a dynamometer in five different positions for each hand. An experienced physiotherapist conducted all the measurements.

In addition, quality of life questionnaires (BPI (Cleeland, 2009), GARS-4 (Kempen and Suurmeijer, 1990; Gijm et al., 2012), EQ-5D-5L (Rabin and Charro, 2001; Dolan, 1997; Versteegh et al., 2016), RAND-36 (23–25)) were used to assess the drug efficacy. The BPI was used to evaluate pain, with the severity score being calculated as the average of four pain items ("worst," "least," "average," and "now"), and

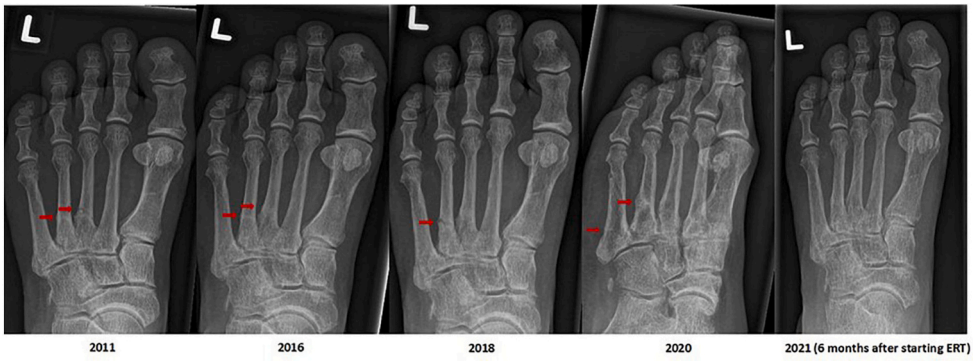

Fig. 1. Left foot fractures
2011: fracture of MT III-IV; 2016: partial consolidation of MT III-IV; 2018: re-fracture of MT-IV; 2020: fracture of MT-V, partial consolidation of MT-IV; 2021: complete consolidation of fractures.

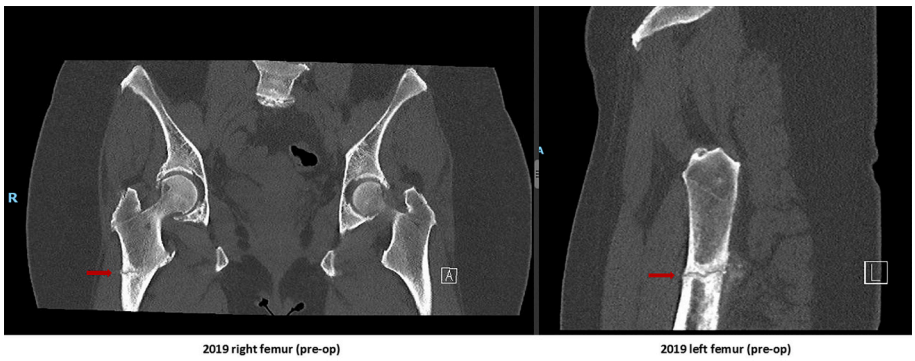

Fig. 2. Right and left femur pre-operation
CT-scan of the femora showed a transverse incomplete AFF - like fracture in the right femur below the minor trochanter and a transverse lucent line at the lateral cortex above the knee in the left femur.

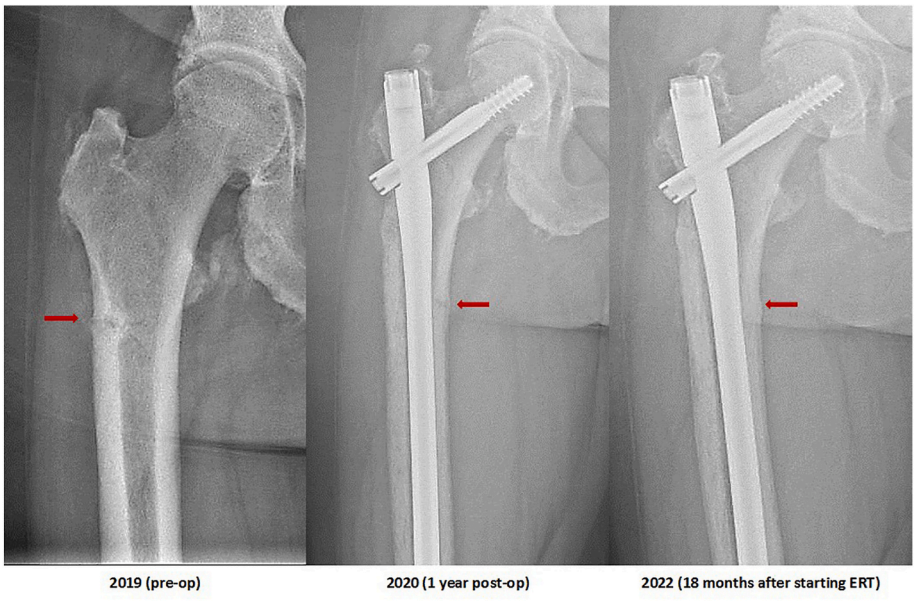

Fig. 3. Right femur pre-/post-operation and after treatment with asfotase alfa
Deterioration of the bone structure and mineralization of left femur after nail placement, halted after start of asfotase alfa.

the interference score as the average of seven interference items (general activity, walking, work, mood, enjoyment of life, relations with others, and sleep). The scale ranges from 0 to 10, where higher scores indicate greater pain levels (Cleeland, 2009). The GARS-4 was used to evaluate the daily activities. ADL, which stands for activities of daily life, was measured using 11 items with a score range of 11–44. HDL, which refers to household activities of daily life, was assessed using 7 items with a score range of 7–28. The scale ranged from 0 to 4, where higher scores indicated greater limitations in daily activities (Kempen and Suurmeijer, 1990; Gijm et al., 2012). The EQ-5D-5L assesses five dimensions, each describing a different aspect of health: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. A scale ranging from 0 to 5 was utilized, where higher scores represent more problems for each dimension (Rabin and Charro, 2001; Dolan, 1997; Versteegh et al., 2016). The RAND-36 questionnaire consists of 36 items that are categorized into 9 groups: physical functioning (10 items), role limitations due to physical problems (4 items), role limitations due to emotional problems (3 items), vitality (4 items), mental health (5 items), social functioning (2 items), pain (2 items), general health perception (5 items), and health change (1 item). Each category is scored on a scale of 0–100, where a higher score indicates a more favorable state of health (van der Zee and Sanderman, 1993; Ware and Sherbourne, 1992; Hays et al., 1993).

The study was approved by the Ethics Committee of Erasmus Medical Center and written consent was obtained from the patient (MEC-2020-0737).

3. Results

3.1. Clinical picture

Within 3–4 weeks after starting asfotase alfa, the patient mentioned that the burning pain in the lower legs had decreased dramatically and also the headache was less severe. Accordingly, paracetamol dose could be reduced from daily 6000 mg to 3000 mg, and she reported better sleep. By 3 months, she was able to perform her household activities without relying on a walker indoors. After 6 months, she achieved milestones such as cycling and climbing stairs independently after 6 years. Possibly because of this increased mobility she experienced more pain in her left knee, were she was already known to have osteoarthritis, severe deformities, and chondrocalcinosis. After 9 months, the burning pains in the legs, as well as the headache, had completely disappeared. At the 12-month evaluation, she was able to cycle up to 20 km per day. Her physical condition kept improving and 18 months after starting

asfotase alfa she was able to travel abroad, which she was unable to do for many years. At the 24-month evaluation, the main complain which persisted was the knee discomfort. During treatment, patient experienced local injection site reactions but no other side-effects.

3.2. Laboratory and radiology results

At the baseline examination, before start of asfotase alfa, at age 55 years, laboratory results showed low ALP (21 U/L), raised U-PEA levels (19 mmol/mmol creat), and significantly raised levels of vitamin B6 (410 nmol/L). BMD T-score was high at the lumbar spine (LS T-score + 2.7) and normal at total body (TB T-score + 0.7) and remained stable at the 12-month evaluation (LS T-score + 2.6, TB + 1.0), whereas T-score of total body increased at 24-month evaluation (LS T-score 3.1, TB 1.8). Pulmonary function test including flow/volume-loop, forced vital capacity (FVC), forced expiratory volume in the first second (FEV1) and FEV1/FVC ratio, was normal at baseline and after 12 months. A CT scan of skeleton showed an osteopenic aspect of the bones, particularly in the upper legs and tibiae, along with degenerative spine changes, such as narrowing of the thoracic discs and the presence of multiple anterior spondylophytes. Additionally, there were signs of older consolidated rib fractures, bilateral coxarthrosis at the hip and gonarthrosis at the knee, with joint space narrowing and presence of osteophytes. Furthermore, chondrocalcinosis was present in both knees and shoulders. A renal ultrasound showed no signs of nephrolithiasis or nephrocalcinosis at baseline, nor at 12 and 18 month's evaluation.

Asfotase alfa treatment was started at 2 mg/kg given subcutaneously 3 times per week. Regarding the laboratory results, vitamin B6 normalized, ALP levels rose to >10.000U/L (Supplementary Fig. 1) and U-PEA decreased but fluctuated after 15 months. Serum levels of calcium, phosphate, 25-OH-vitamin D, PTH did not change (Supplementary Fig. 1). Radiographs of upper legs during treatment showed a stabilization of bone loss (Fig. 3) and healing of metatarsal fractures at the left foot (Fig. 1).

3.3. Quality of life assessment

Regarding quality of life, self-reported pain scores on the BPI showed an improvement in the severity and interference score 3 months after initiation of ERT (Supplementary Fig. 1). Specifically, the severity score was 68.2% reduced and interference score 91.2%. Pain, physical function and activities of daily life, assessed by the GARS-4, EQ-5D-5L and RAND-36 questionnaires, were also positively affected (Supplementary Fig. 2). Particularly, she experienced less pain and restrictions in the performing of daily activities (ADL) and household daily activities (HDL) with an enhancement of 45.8% and 42.1%, respectively (Supplementary Fig. 2). Within a span of 3 months, all items examined using RAND-36 and EQ-5D-5L demonstrated enhancement and a positive trend persisted throughout the 24-month evaluation period (Supplementary Fig. 2). Specifically, each of the five domains comprising EQ-5D-5L (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) exhibited a decrease in scores compared to baseline, with mobility and the ability to carry out usual activities showing the most notable improvements (50% and 75%, respectively). Furthermore, all nine groups evaluated by RAND-36 exhibited higher scores in comparison to the baseline assessment, with the most pronounced improvement observed in physical functioning (900%, 5 to 50), role limitations due to physical restrictions (0–100) and bodily pain (300%, 22.5 to 90).

3.4. Motor function evaluation

During treatment, functional improvement was evident in the results of the 6 MWT, TUG, TCST (Supplementary Fig. 3), knee and hand-grip-strength assessment. Particularly, 6 MWT, TUG and TCST test demonstrated an improvement of 146% (160–395 m), 66% (24.76–8.41 s) and 71% (29.36–8.53 s), respectively, in comparison with the baseline measurement. Three months after initiation of treatment, she was able to carry out the TUG test without using a walker. Similarly, after 12 months, the patient was able to perform the TCST test without requiring assistance from her upper extremities.

During the 24-month assessment, there was a consistent enhancement observed in both knee flexion and flexion strength. The peak torque during left knee extension at speeds of 60 and 180° per second showed improvements of 116% and 79%, respectively. Similarly, during left knee flexion, there were remarkable enhancements of 797% and 370%, respectively, in peak torque (Supplementary Fig. 4). An improvement, although less impressive, was also observed at the right knee. In particular, there was a 47% and 49% enhancement in right knee extension at both speeds, while flexion showed improvements of 60% and 83%, respectively (Supplementary Fig. 4). However, the progress in the left knee became less noticeable after the initial 3-month evaluation (Supplementary Fig. 4). This was attributed, as mentioned above, to increased physical activity, along with severe deformities, chondrocalcinosis and presence of severe osteoarthritis. Similar to knee strength, hand-grip strength (HS) exhibited an improvement through the 24-month evaluation (Supplementary Fig. 4). In particular, there was a noticeable improvement in all five positions of the right hand, with percentages of 48%, 40%, 70%, 67%, and 65%. Similarly, the left hand showed improvements of 65%, 33%, 69%, 96%, and 80% in its respective positions (Supplementary Fig. 4).

4. Discussion

We report the case of a 57-year old patient who was operated for craniosynostosis as a child and diagnosed with HPP at the age of 34. Treatment with asfotase alfa was started at the age of 55 because of severe deterioration of bone structure on X-rays of the upper legs, following nail placement for incomplete transverse femur fractures with AFF like aspect. Here, we report not only that the bone deterioration was halted, but also describe a dramatic decrease of burning pains in both lower legs within 3–4 weeks after starting therapy, which was in retrospect attributed to neuropathic pain. Moreover, at evaluation after 3 months she demonstrated an improvement on her quality of life, motor skills and muscle strength and a decrease of musculoskeletal pain as evidenced by ongoing improvements of multiple QoL questionnaire and physical function tests. After 24-months the 6 MWT, TUG and TCST test showed a 146%, 66% and 71% improvement, respectively. Impressive improvement was also observed at the knee and hand-grip strength measurements.

Asfotase alfa (Strensiq®), a recombinant human TNSALP, was approved for the treatment of HPP by the Federal Drug Administration (FDA) and the European Medicines Agency (EMA) in 2015 (Whyte, 2017b). Previous studies reported favorable outcomes on skeletal health and ventilatory status and improved survival in perinatal, infantile, and childhood HPP (Whyte et al., 2016a, 2016b, 2019). However, there is a scarcity of data available regarding the efficacy of asfotase alfa in treating adult patients (Nishizawa et al., 2020; Freitas et al., 2018; Klidaras et al., 2018; Kishnani et al., 2019; Rolvien et al., 2019; Genest et al., 2020; Magdaleno et al., 2019). Similar results as in our case were reported in a 32-years old woman with childhood-onset HPP (Nishizawa et al., 2020), where also within 3 months after starting asfotase alfa, notable improvements were reported in knee strength, 6 MWT and TCST test (Nishizawa et al., 2020). Another study, evaluated the physical performance of 14 adult patients with childhood-onset HPP, receiving asfotase alfa. Within 12 months of starting therapy, 6 MWT, TUG and TCST showed a 20%, 22% and 41% improvement, respectively (Rolvien et al., 2019). On the other hand, hand-grip strength exhibited a modest enhancement of 1% after 6 months of treatment (Rolvien et al., 2019). Furthermore, in a study examining the effectiveness and safety of asfotase alfa over a period of 5 years, involving 13 patients ranging in age from 13 to 66 years, similar outcomes were observed (Kishnani et al.,

2019). The results indicated a notable improvement in the distance covered during the 6 MW T within 6 months of starting asfotase alfa (Kishnani et al., 2019).

For the first time, we report a case of HPP with severe burning pains in both lower legs, consistent with neuropathic pain, that profoundly decreased after 3–4 weeks and completely disappeared after 9 months. The rapid improvement in these pains after starting ERT suggests a relation with metabolic changes induced by the treatment. For example, vitamin B6 levels normalized rapidly after treatment initiation. We hypothesize that neuropathic pain in HPP may be related to a disturbed vitamin B6 metabolism. TNSALP is necessary for the conversion of PLP, the active form of vitamin B6, to pyridoxal in order to cross the cell membrane and the blood–brain barrier. Thus, through the deficient production of TNSALP, HPP could lead to vitamin B6 excess extracellularly or deficiency intracellularly and result in neuropathic pain, as neuropathic pain has been associated with both vitamin B6 deficiency (Brown et al., 2023) and excess (Vrolijk et al., 2017). Up to date, there has been limited information available on the neurological symptoms reported in HPP, such as neuropathic pain (Colazo et al., 2019), found that among 82 patients with childhood and adult onset HPP, there was a 35% prevalence of neuropathy, which is higher compared to the general US population (Prevalence ratio: 2.39). However, the specific symptoms of neuropathy have not been described. Additionally, Cruz et al. (2017) recently identified changes in the levels of various brain metabolites, apart from GABA, in mouse models of HPP when compared to control wild-mice. These metabolites, including cystathionine, adenosine, methionine, histidine, 3-methylhistidine, N-acetylaspartate, and N-acetyl-aspartyl-glutamate, are involved in neurotransmission, myelin synthesis, the methionine cycle and transsulfuration pathway. These findings offer insights into the neurological characteristics of HPP, and further clinical studies are required to investigate the mechanism leading to those symptoms (Cruz et al., 2017).

Due to the impressive results of asfotase alfa on the patient's clinical course and quality of life, we continued her treatment. A reduction of the dose of asfotase alfa to 1.6 mg/kg, 3 times per week, at the 15-month evaluation, resulted in an increase in neuropathic pain, headache and muscle weakness within 2 months. Therefore, the previous dose was reintroduced and we do not plan a new dose reduction for now. In conclusion, the administration of asfotase alfa demonstrated remarkable efficacy, in a female adult with childhood-onset HPP. Treatment was initiated because of the rapid and progressive deterioration of radiological bone after placement of nails in both upper legs, for spontaneous AFF - like fractures, which was halted after treatment initiation. Moreover, a reduction in musculoskeletal pain and significant enhancements in muscle strength and daily activities were seen. To our knowledge, for the first time, neuropathic pain is being described as a symptom of HPP that remarkably and quickly decreases after the initiation of asfotase alfa. We hypothesised that vitamin B6 metabolism could be related to the mechanism leading to neuropathic pain and potentially also to headaches, but further research is needed to investigate this hypothesis.

Funding source

The study was not funded.

Patient consent statement

The described patient gave written informed consent for publication of this manuscript.

CRediT authorship contribution statement

Zografia Zervou: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Roel Plooij:** Data curation, Methodology, Writing – review & editing. **Evert F.S. van Velsen:** Data curation, Methodology, Writing – review & editing, Supervision. **Remco G.M. Timmermans:** Data curation, Methodology, Writing – review & editing. **Serwet Demirdas:** Data curation, Methodology, Writing – review & editing. **M. Carola Zillikens:** Conceptualization, Data curation, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare no conflicts of interest and no competing financial interests exist.

Data availability

Data will be made available on request.

Acknowledgements

This publication has been supported by ERN BOND - European Reference Network for rare Bone Diseases, which is partly co-funded by the European Union within the framework of the EU4Health Programme 2021–2027.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmg.2024.104915.

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