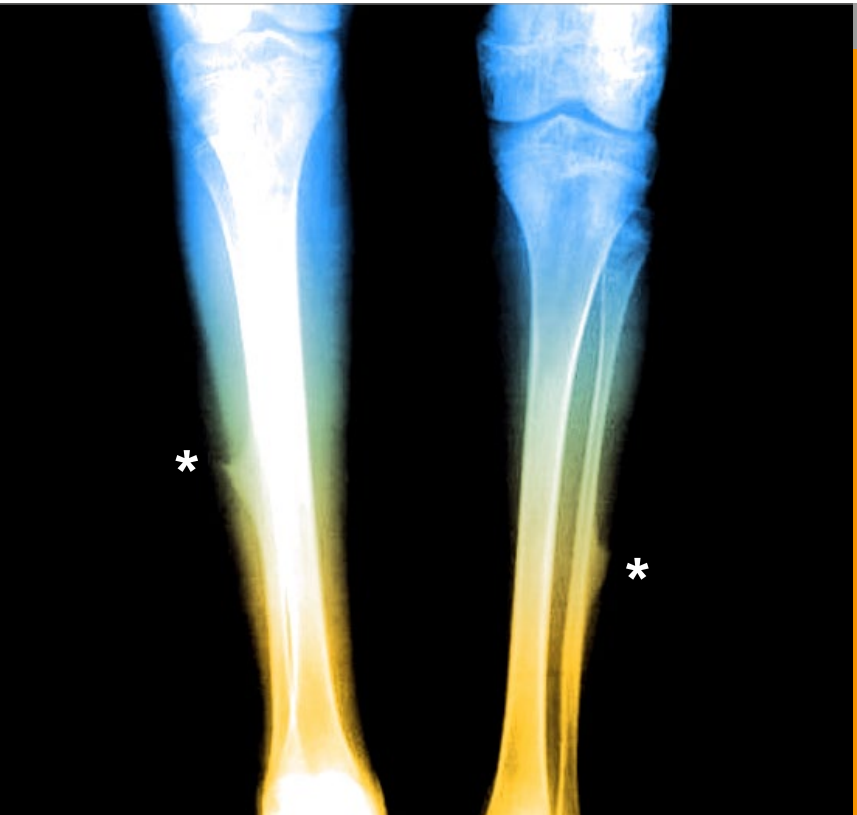
SWISS SOCIETY OF NEONATOLOGY

“Short” long bones: Prenatal diagnosis of hypophosphatasia and immediate postnatal enzyme replacement therapy



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Title figure:
Bowdler spurs (asterisks), named after John Denby Bowdler, MD, pediatric radiologist at the Royal Alexandra Children's Hospital in Camperdown, Australia
(Source: Korean J Radiol 2005;6:52 – 54)

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INTRODUCTION

Hypophosphatasia is a rare inherited (autosomal dominant or recessive) metabolic disorder caused by pathogenic variants in the ALPL gene encoding tissue-nonspecific alkaline phosphatase. The estimated prevalence is 1/500'000 in Europe (1). The clinical presentation of hypophosphatasia ranges from neonatal death with almost no skeletal mineralization in the severe form to dental problems in adults without any osseous symptoms in the mild form (2, 3).

We present the case of a baby girl born to a 27-year-old primigravida, diagnosed prenatally with hypophosphatasia, who was started on enzyme replacement therapy on day one of life.

In the prenatal screening ultrasound performed at 20 weeks of gestation the fetus was noted to have short and bowed long bones (Fig. 1, 2) predominantly affecting the lower extremities as well as right equinovarus deformity. The bone mineralization appeared to be normal (Fig. 3) and there were no signs of thoracic dysplasia or fractures.

Targeted exome analysis on amniocytes showed a homozygous pathogenic variant in the ALPL gene (c.542C > T) suggesting fetal hypophosphatasia. The non-consanguineous parents were both found to be heterozygous for the c.542C > T variant. Based on follow-up ultrasounds and the known missense variant, it was suspected that the child would present with a mild form of hypophosphatasia. An elective Cesarean section was scheduled at 37 weeks of gestation in order to minimize the risks of a traumatic birth.

The baby girl presented with a birth weight of 2900 g (P 40), a length of 46 cm (P 8) and a head circumference of 34.5 cm (P 70). The postnatal course was unremarkable, and the baby was admitted to our neonatal intensive care unit for observation and initiation of treatment.

The initial physical exam showed a large open anterior fontanel, short femurs (Fig. 4), right pes equinovarus and a skin dimple on the right anterolateral peroneal

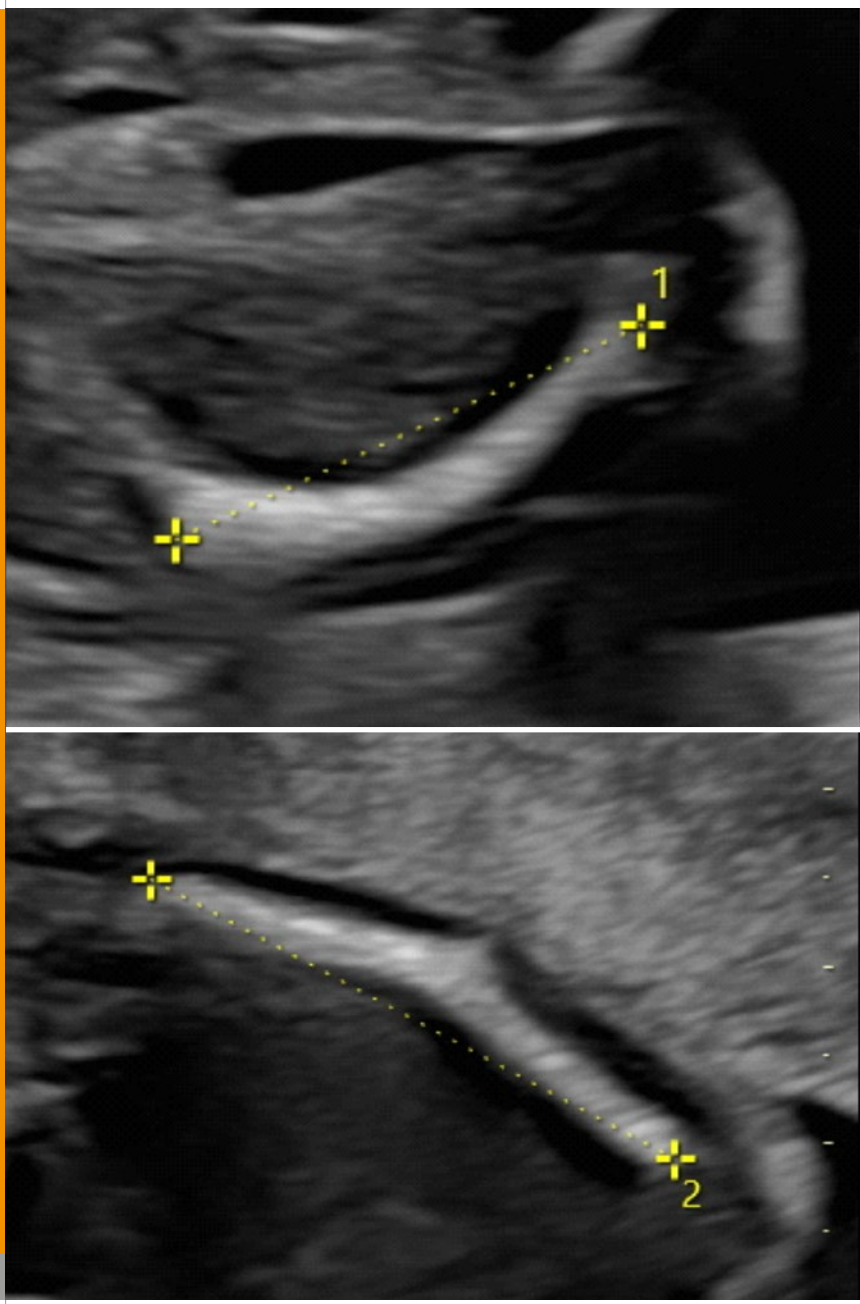

Fig. 1

Prenatal ultrasound examination: short femurs.

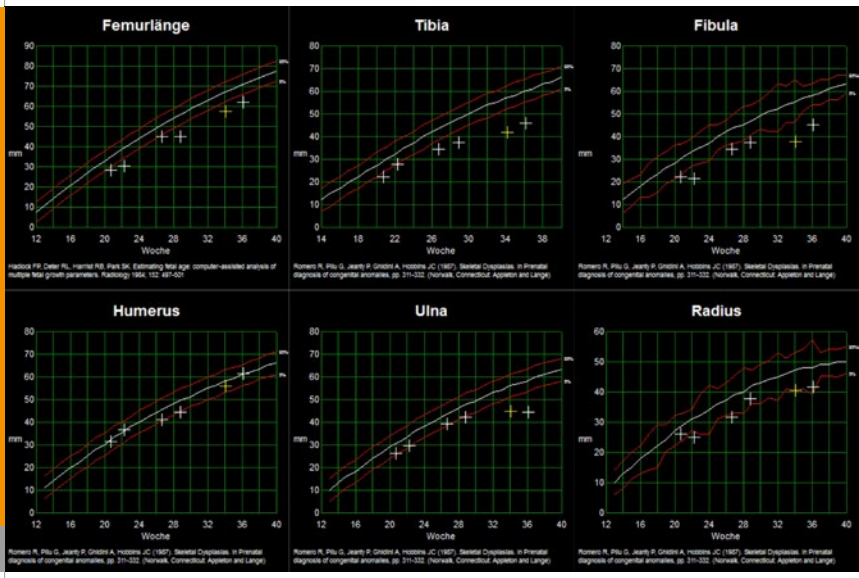

Fig. 2

Prenatal ultrasound examination:
bone length measurements.

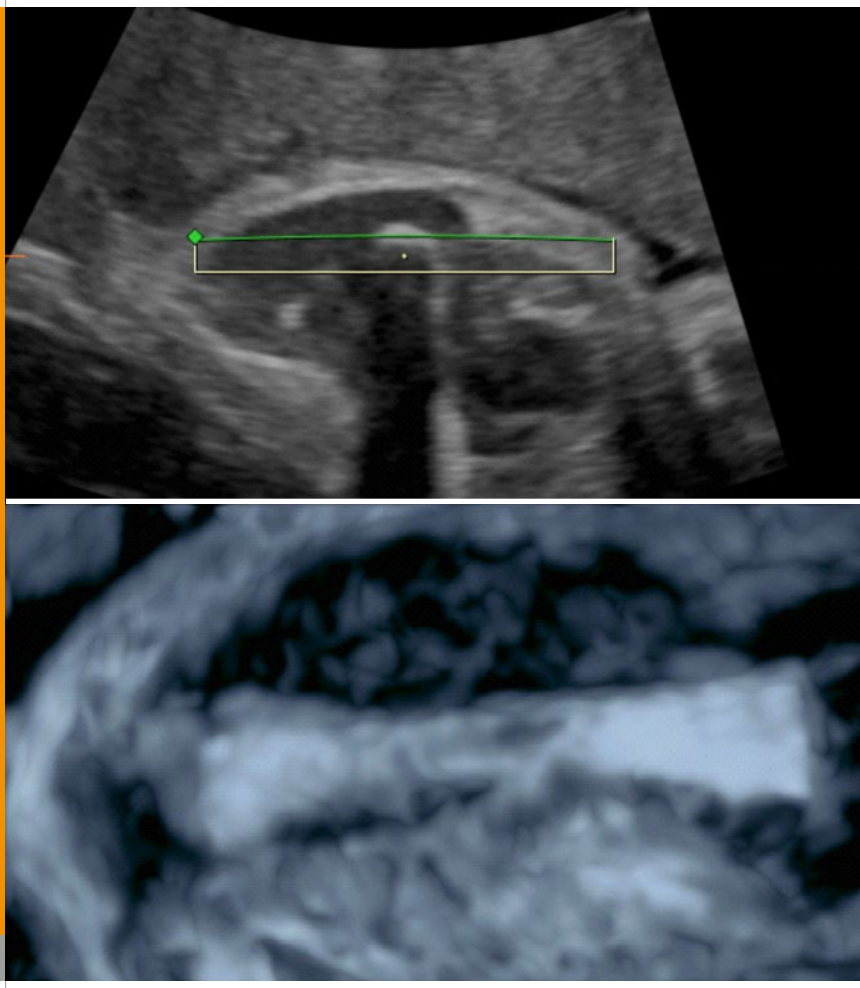

Fig. 3

Prenatal ultrasound examination:
normal bone mineralization.

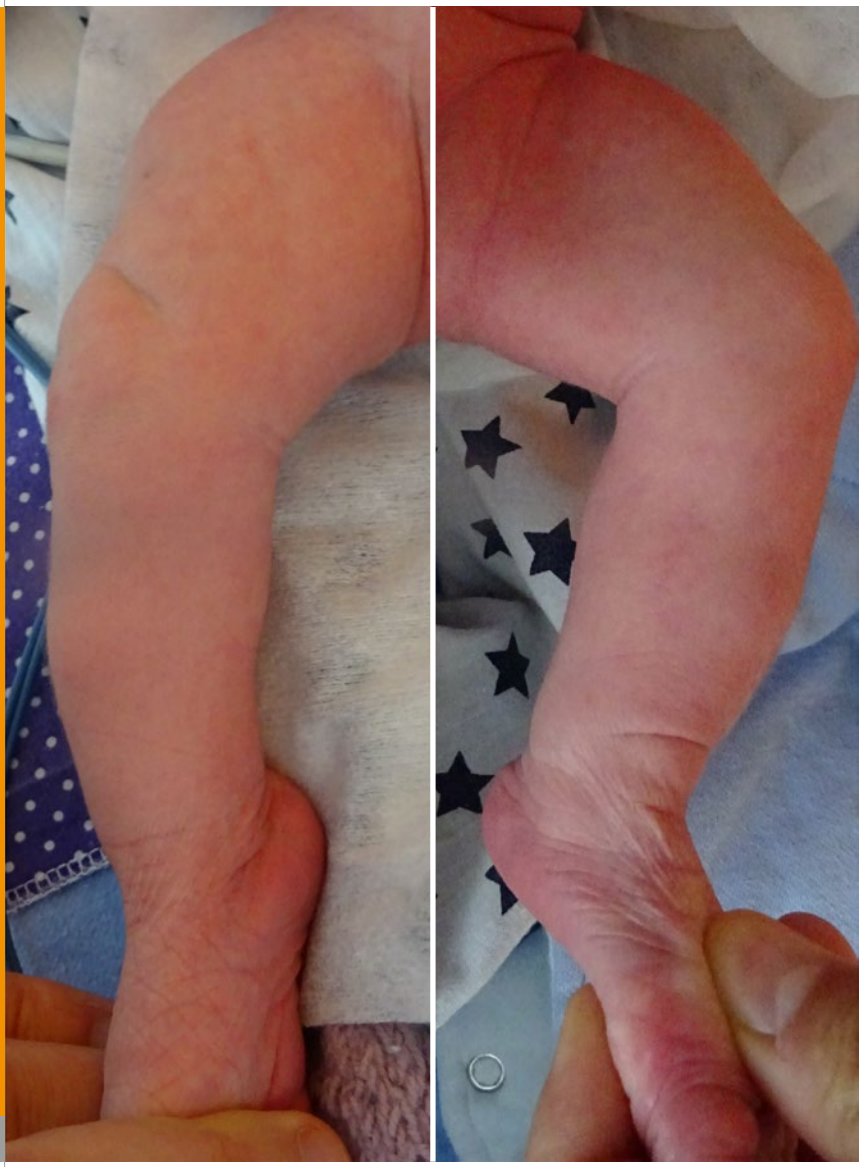

Fig. 4

Short femur length.

region (Fig. 5), representing a healed Bowdler spur (with normal X-rays findings).

X-rays of limbs and thorax were obtained to assess bone deformities, bone mineralization and potential fractures. Characteristic tongue-like lucencies with features of rickets, most marked at the proximal end of the humerus, distal ends of radius and ulna (Fig. 6) and both ends of the tibia were detected (Fig. 7). The left femur had a mild deformity, possibly from an antenatal fracture. The ribs were formed but slightly thinner than normal (Fig. 8). These findings are compatible with a benign infantile form of hypophosphatasia.

Laboratory values on day 1 of life were as follows: parathyroid hormone (PTH) 3.8 pg / ml (normal range, 10 – 70 pg / ml), 25-hydroxy-vitamin D 41 nmol / l (normal range, 50 – 135 nmol/l), total calcium 2.71 mmol/l (normal range, 1.75 – 2.7 mmol/l), inorganic phosphate 1.79 mmol/l (normal range, 1.6 – 2.6 mmol/l), alkaline phosphatase 23 U/l (normal, up to 650U/l), normal renal function tests and normal liver enzymes.

The infant was started on enzyme replacement therapy with subcutaneously administered Asfotase alfa (Strensiq®, Alexion Pharma GmbH, Zurich, Switzerland) on day 1 of life (2 mg / kg 3 times / week) according to current recommendations (4). The injections were well-tolerated, follow-up laboratory

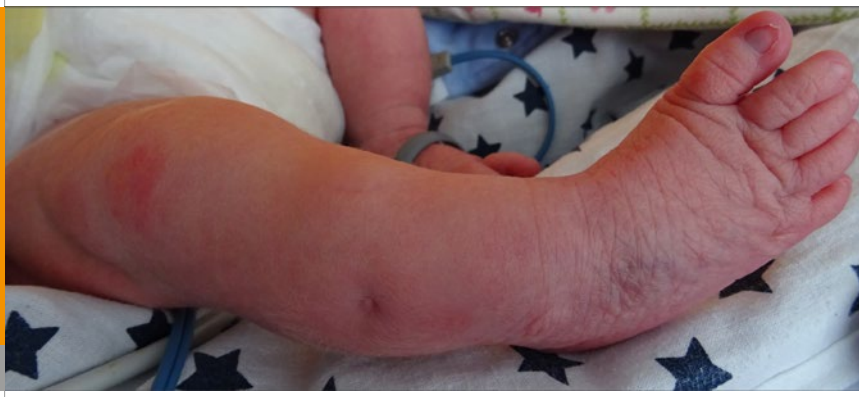

Fig. 5

Dimple in the anterolateral peroneal region.

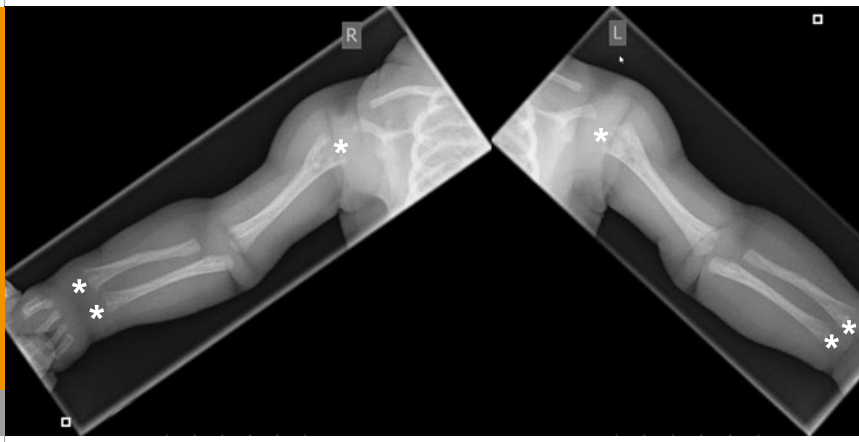

Fig. 6

X-ray of upper limbs with tongue-like lucencies (asterisks).

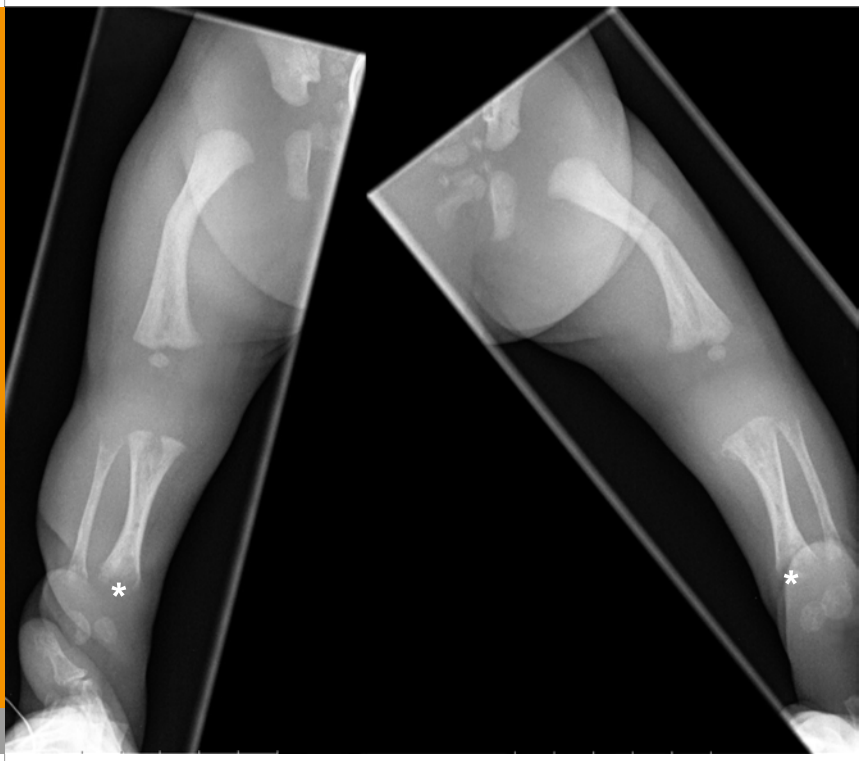

Fig. 7

X-ray of lower limbs with tongue-like lucencies (asterisks).

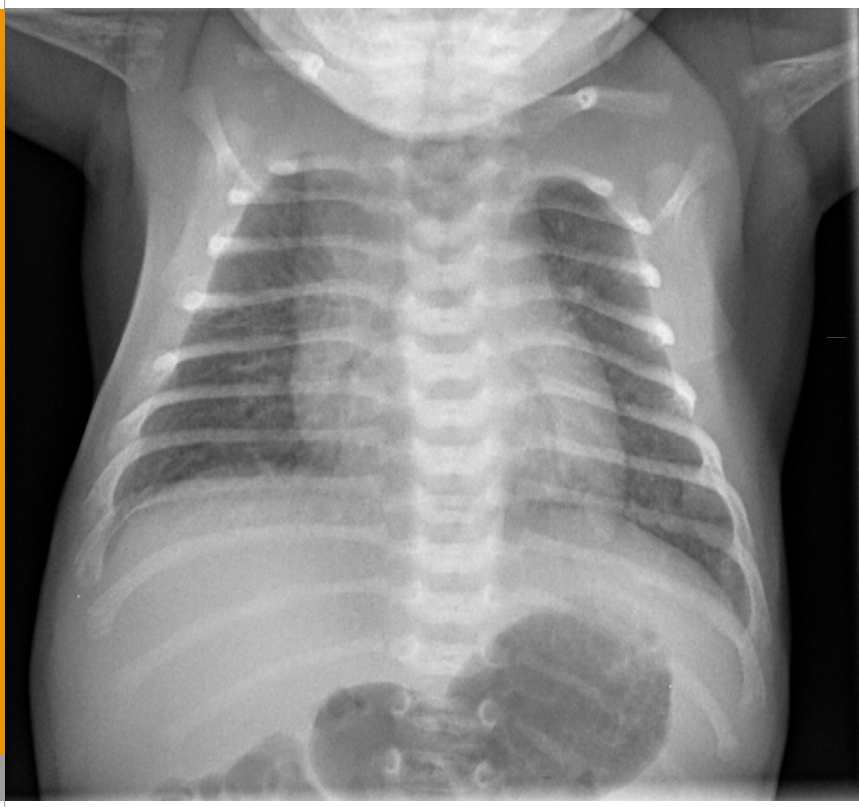

Fig. 8

Chest X-ray with thin ribs.

investigations showed normal calcium and phosphate values, as well as normalization of the PTH level (12.1 pg / ml) and an increase of the alkaline phosphatase to 4877 U/L. The child was discharged on day 8 of life with ongoing enzyme replacement therapy 3 times / week and regular follow-up appointments (5).

DISCUSSION

Hypophosphatasia is caused by a decrease in the activity of the "tissue non-specific" isoenzyme of alkaline phosphatase, leading to an accumulation of substrates such as inorganic pyrophosphate (an inhibitor of mineralization) and pyridoxal-5'-phosphate, the major circulating form of vitamin B6 (2,6,7). The high inorganic pyrophosphate levels block hydroxyapatite crystal growth, causing rickets or osteomalacia. Deficiency of the enzyme also leads to disrupted vitamin B6 metabolism, which in severe cases can lead to pyridoxine-responsive seizures (2).

The traditional classification of clinical forms of hypophosphatasia is based on the age at presentation (Table 1).

Form	Manifestations
Perinatal	Infants have very poorly mineralized bones and usually require ventilatory support. Without treatment, mortality in this group is close to 100% in the first year of life and is often associated with pulmonary complications.
Benign prenatal	Infants with bone deformity in utero show an improvement to the "odontohypophosphatasia" phenotype, where skeletal and other manifestations beyond the dentition resolve spontaneously.
Infantile	Diagnosed in the early months of life with failure to thrive and increasing respiratory difficulty and in some cases with seizures. Biochemical abnormalities such as hypercalcemia with calciuria leading to nephrocalcinosis are present in almost all cases at diagnosis. The mortality in this group is more than 50% by the age of 9 months without treatment.
Childhood or juvenile	Typically presents with early loss of primary dentition with intact tooth roots, bone pain, rachitic-like lesions and poorly healing fractures.
Adult	Initially presents with clinical manifestations suggesting osteoporosis, such as recurrent fractures and low bone mass, along with ill-defined musculoskeletal pain.
Odontohypophosphatasia	Early loss of deciduous teeth (before the age of 4 years), not accompanied by other manifestations.

Table 1.
Classification of clinical forms of hypophosphatasia (8, 9, 12).

The clinical manifestations of hypophosphatasia, especially the skeletal complications, vary with the form of the disease and with age. Bone growth may be slowed by disruption of endochondral ossification and softening of bone tissue (8, 9). Craniosynostosis is a frequent finding in the more severe forms (8). Dentition is affected by lack of cementum, contributing to early exfoliation and also by poor enamel formation, which contributes to accelerated carious deterioration. Pyridoxine-dependent convulsions are seen in both perinatal and infantile forms (8, 9). Motor delay can be observed to a variable extent according to clinical forms (8, 9).

The diagnosis of hypophosphatasia is based on the clinical manifestations and an inappropriately low alkaline phosphatase activity (10). More than 330 distinct pathogenic variants in the alkaline phosphatase liver type (ALPL) gene encoding the tissue-nonspecific alkaline phosphatase (TNSALP) enzyme have been identified, making genetic testing helpful as a confirmatory tool in cases of diagnostic uncertainty and to counsel the family on the risk of inheritance for other family members (5, 10).

The differential diagnoses of hypophosphatasia are summarized in Table 2.

Age at diagnosis	
Antenatally	• osteogenesis imperfecta • thanatophoric dysplasia • achondrogenesis • campomelic dysplasia
Perinatally	• neonatal severe hyperparathyroidism • osteogenesis imperfecta type V • mucolipidosis II
In infancy	• nutritional rickets • idiopathic hypercalcemia • other causes of failure to thrive • other causes of nephrocalcinosis
In childhood	• mild osteogenesis imperfecta • nutritional rickets • myopathic disorders • inflammatory arthritis • chronic recurrent multifocal osteomyelitis • fibrous dysplasia
In adulthood	• osteoporosis • osteoarthritis

Table 2.
Age-dependent differential diagnosis of hypophosphatasia (9, 13).

The management of the disease was, until recently, essentially symptomatic. In 2015, an enzyme replacement therapy with Asfotase alfa (Strensiq®) was approved by the European Medicines Agency. The therapy is designed to reverse skeletal hypomineralization and to correct other ensuing manifestations of the severe forms (8). The benefits of therapy have been demonstrated in perinatal and infantile forms, leading to significant improvements of life expectancy (95 % 1-year survival and 80 % 6-year survival) (11), as well as improvements of pulmonary symptoms (10). Common side effects include local reactions at the injection site such as erythema, discoloration, pain, pruritus, edema, and induration (5). Data referring to long-term side effects is still scarce as the therapy has only been recently introduced and the number of patients treated to date is small (5).

A clinical phase 2 study published in 2019, evaluating the outcomes up to 6 years of therapy concluded that, in general, the treatment with Asfotase alfa was well tolerated, with less than 10 % of patients presenting major adverse effects (11). A group of patients presenting with very severe disease was classified as radiographic non-responders, and needed more intense monitoring, dose adjustments and additional therapeutic measures (11).

In conclusion, hypophosphatasia is a rare inherited disorder, characterized by extreme variability in the

clinical presentation, making the diagnosis difficult (12). Enzyme replacement therapy with Asfotase alfa shows promising results in the severe forms of infants and children with improvements in lung function and bone development (12), emphasizing the importance of prompt diagnosis of perinatal and infantile hypophosphatasia in order to avoid delays in the initiation of therapy.

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