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CASE REPORT

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Early non-traumatic exfoliation of primary teeth as the first sign of hypophosphatasia: a 6-year pediatric case report

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Abstract

Background: Premature exfoliation of primary teeth without trauma is an unusual finding that raises suspicion of an underlying systemic disorder. Among the possible causes, hypophosphatasia (HPP) is a rare inherited metabolic disease characterized by deficient alkaline phosphatase (ALP) activity, leading to impaired skeletal and dental mineralization. Pediatric dentists are frequently the first professionals to identify the initial signs of this condition. **Case**: This report describes the 6-year follow-up of a male patient who first presented at 22 months of age with premature loss of four anterior primary teeth, short stature, and balance issues. No traumatic events were reported by the parents. Clinical examination revealed further mobility of the primary incisors and confirmed short stature and unstable gait. Laboratory tests revealed persistently low ALP levels, hypercalciuria, and high urinary phosphoethanolamine (PEA) levels. Radiography revealed subtle metaphyseal radiolucency. Genetic analysis confirmed a heterozygous mutation in the *liver/bone/kidney alkaline phosphatase* (*ALPL*) gene, establishing the diagnosis of HPP. Management was performed by a multidisciplinary team, including pediatric endocrinologists, geneticists, orthopedists, orthodontists, and pediatric dentists. Dental care focused on prevention, professional hygiene sessions, topical fluoride applications, and monitoring occlusal development. Orthodontic assessments were performed when the permanent teeth erupted. Over the years, the child lost additional primary teeth with intact roots but maintained masticatory efficiency, vertical dimension, and good oral function. Growth parameters and skeletal phenotype remained stable, and enzyme replacement therapy (ERT) was not considered necessary. **Conclusions**: This case illustrates the key role of early dental signs in timely HPP diagnosis, the potential significance of a rare haplotype, and the effectiveness of interceptive orthodontic management over six years.

Keywords

Case report; Hypophosphatasia; Pediatric dentistry; Premature tooth loss; Primary dentition

1. Introduction

The premature loss of primary teeth is an uncommon finding in pediatric dentistry that should not be underestimated. Although traumatic events are the most frequent cause of early exfoliation, the absence of a clear history of trauma should raise suspicion of an underlying systemic disorder [1, 2].

Systemic diseases associated with premature exfoliation of primary teeth include Papillon-Lefevre syndrome, Chediak-Higashi syndrome, Down syndrome, Langerhans cell histiocytosis, hypophosphatemic rickets, leukocyte adhesion deficiency, and hypophosphatasia (HPP) [3]. HPP is particularly important because it directly affects skeletal and dental mineralization. Early recognition enables timely referral and preventive dental strategies that preserve function and quality of life [4].

HPP is a rare metabolic disease first described by Rathbun in 1948 [5]. It is caused by loss-of-function mutations in the *liver/bone/kidney alkaline phosphatase* (*ALPL*) gene (chromosome 1p36.12; *Mendelian Inheritance in Man* 171760), which encodes tissue-nonspecific alkaline phosphatase (TNSALP) [6–9]. TNSALP hydrolyzes substrates including inorganic pyrophosphate (PPi), pyridoxal-5′-phosphate (PLP), adenosine monophosphate (AMP), and phosphoethanolamine (PEA). Their accumulation leads to defective mineralization. To date, more than 315 mutations in *ALPL* have been reported, with autosomal dominant or recessive inheritance patterns [9, 10].

HPP includes a wide range of clinical manifestations de-

pending on the age of onset. Six main clinical forms have been described: perinatal lethal, benign prenatal, infantile, juvenile, adult, and odonto-HPP [11–14]. Severe forms are associated with life-threatening skeletal abnormalities, whereas milder forms in childhood often present with premature exfoliation of primary teeth, short stature, and subtle skeletal changes [12, 15, 16].

Diagnosis is based on the integration of clinical signs, laboratory investigations, and radiographic findings, and is confirmed through genetic analysis. The key diagnostic markers include low ALP levels, elevated urinary PEA levels, and increased serum PLP [16, 17]. Genetic analysis confirms the diagnosis and contributes to the classification of disease severity.

Despite the early appearance of oral signs, diagnosis is often delayed, as reported in a recent global registry study [18].

Management requires a multidisciplinary approach involving geneticists, pediatric endocrinologists, dentists, and orthopedists. Dental management is particularly challenging, as these individuals are considered patients with special healthcare needs and often require dental treatment in hospital settings [19–21].

This report describes a case of early exfoliation of primary teeth in a 22-month-old male infant, which led to the identification of a genetic form of HPP.

2. Case report

In 2018, a 22-month-old boy was brought to the emergency department of the Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto Giannina Gaslini Children's Hospital with suspected oral trauma. He was the third child of healthy, non-consanguineous parents. His psychomotor development was slightly delayed, as he had begun walking at approximately 18 months, and his growth parameters revealed short stature (10th percentile) with gait instability and a tendency to fall. The parents reported that four anterior primary teeth (71, 72, 81, 61) had exfoliated between 15 and 18 months of age without any traumatic event.

Clinical examination revealed marked mobility and extrusion of tooth 51. The dentition was consistent with the chronological age, although with an incomplete formula. Deep bite, increased overjet, and lower lip interposition were observed. There were no signs of pain, gingival inflammation, or mucosal lesions. The early exfoliation of multiple primary teeth with intact roots in the absence of trauma raised suspicion of systemic disease, and the family was referred to a pediatrician for further evaluation.

Between 2019 and 2020, the child underwent multidisciplinary diagnostic workup. Orthopedic examination revealed flat feet that required only annual monitoring. Laboratory investigations demonstrated persistently low serum ALP activity (20 IU/L; reference range, 142–335 IU/L), hypercalciuria (9.1 mEq/L; reference, 0.5–7.5 mEq/L) with abundant calcium oxalate crystals, and markedly increased urinary PEA (1204 μmol/mmol; reference, 0–20 μmol/mmol). Radiographs of the femur and tibia, performed between 2 years and 8 months and 5 years and 6 months of age, showed subtle but stable metaphyseal radiolucency. These radiographic findings remained stable over time (Figs. 1,2) and were consistent with a mild skeletal form of HPP. Bone density assessment, performed at 5 years and 6 months with a Lunar iDXA machine (GE Healthcare, Madison, WI, USA), revealed a Z-score of −2.5 at the lumbar spine and −1.1 for the total body less head, findings consistent with low bone mineralization for age. Computer Tomography (CT) and Magnetic Resonance Imaging (MRI) were not performed.

Genetic testing identified a heterozygous c.262G>A, p.(Glu88Lys) mutation in the *ALPL* gene, confirming the diagnosis of HPP. The individual was also found to be homozygous for the haplotype c.787C, c.793-31C, c.862+20T, c.862+51A, c.862+58T, c.863-12G, c.863-7C, c.876G. This haplotype has been identified in patients carrying only one mutation in the *ALPL* gene, suggesting that it may be in linkage disequilibrium with a second undetected mutation in the coding regions of the gene [22]. The mutation was inherited from the father, who, along with the paternal grandfather, had experienced premature tooth loss previously attributed to dental caries.

In 2023, a second genetic evaluation was performed at the Laboratory of Human Genetics of the IRCCS Istituto Giannina Gaslini Children's Hospital. Molecular analysis of the *ALPL* gene, performed by next-generation sequencing (NGS) of coding genomic regions and exon-intron junctions (5nt) on the Novaseq platform (Illumina), confirmed the pathogenic heterozygotic variant c.262G>A p.(Glu88Lys) and the presence of haplotype E in homozygous form. This haplotype is rare and more frequently observed in affected individuals; however, according to current knowledge, its clinical significance remains uncertain [22].

It is important to note that the patient and his father each have a 50% chance of passing on the c.262G>A, p.(Glu88Lys) variant to their offspring in each pregnancy. For the purposes of the analysis, only genes related to the clinical indications of the investigation were examined. Data analysis was performed using Sophia DDM software (ILL1XG1G5_CNV_exome pipeline, version 1.0.13, SOPHiA Genetics, Lausanne, VD, Switzerland) to identify nucleotide variants and large deletions/duplications.

A detailed chronological overview of the dental findings, oral healthcare strategies, systemic progression, and multidisciplinary interventions is presented in Table 1. A multidisciplinary approach was adopted, with a pediatric endocrinologist as the team leader. General clinical check-ups were performed every 6–12 months, and orthopedic and radiologic evaluations were performed annually.

Dental follow-up began shortly after the first evaluation and was conducted every three months for six years. At the first recall, additional teeth were already lost (51, 73, 82), and others showed significant mobility (52, 62, 53, 63, 83) (Figs. 3,4). All exfoliated teeth had intact roots, no caries, and no signs of inflammation. Orthopantomography confirmed reduced alveolar bone height, short and tapered roots, and enlarged pulp chambers, which are consistent with the typical dental phenotype of HPP (Fig. 5). The process of exfoliation was often preceded by elongation of the affected tooth, followed by rapid mobility and spontaneous loss within a few days.

Preventive strategies were implemented, including profes-

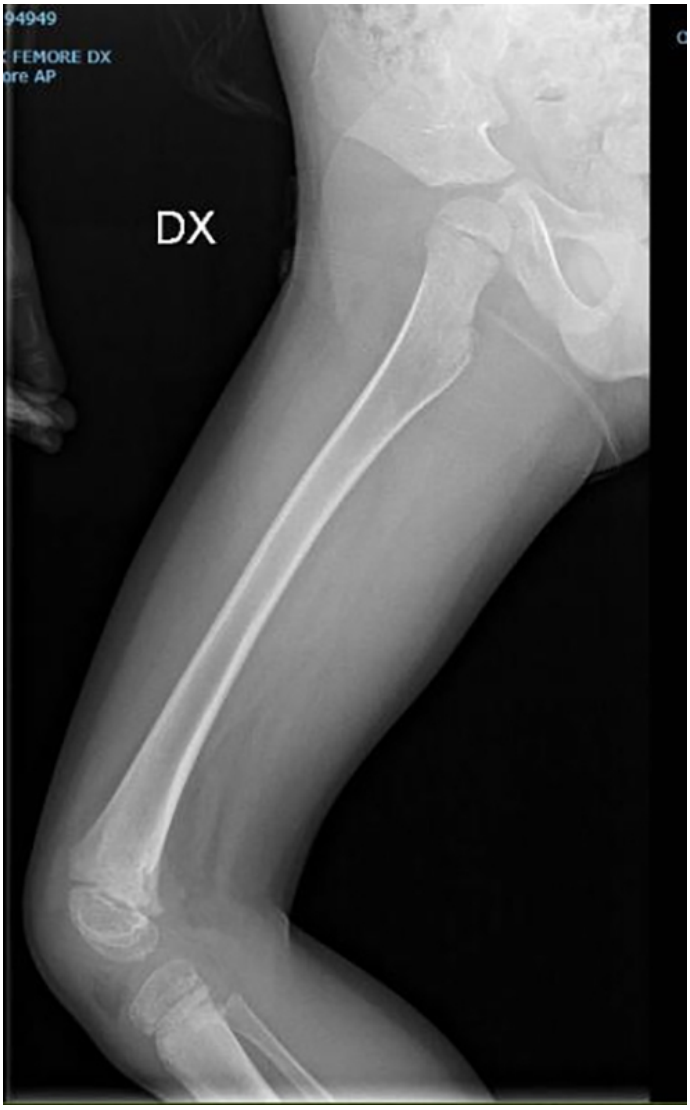

FIGURE 1. Radiograph of the right femur showing irregularities along the lateral contour of the femoral neck and the margin of the distal metaphysis. DX: right (right side); AP: anteroposterior (projection).

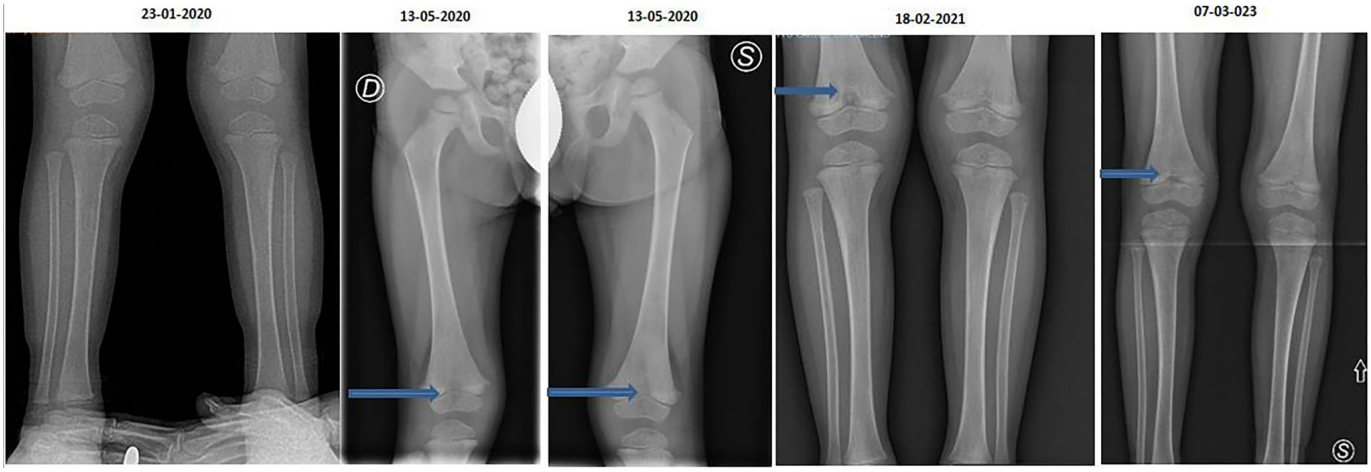

FIGURE 2. Radiographic follow-up at three years demonstrating stable appearance of the distal femoral and proximal tibial metaphysis, with a small lingular radiolucency more evident in the distal femur and less pronounced in the proximal tibia. The blue arrows indicate areas of metaphyseal irregularities and growth plate changes, consistent with mild hypophosphatasia manifestations. Ⓓ: right side; Ⓢ: left side; ⇑: cranial.

TABLE 1. Chronological overview of dental findings, oral healthcare, systemic progression, and multidisciplinary interventions during 6 years of follow-up in the present case.

Age (yr, mon)	Systemic progression	Non-dental interventions	Exfoliated teeth	Teeth currently present in the arch	Erupting teeth	Oral healthcare	Rehabilitation measure
1, 1	Short stature noted, gait instability observed	Initial pediatric evaluation; referral to orthopedics for gait instability	51-61-71-72-81-82			First aid	
2, 2	Biochemical abnormalities detected (low ALP, hypercalciuria, high PEA)	Metabolic work-up by pediatric endocrinology; urine and serum biomarkers	73	54-53-52-62-63-64-74-83-84-85	75	Check-up, scaling and polishing, fluoride varnish	
2, 5	Stable growth, no fractures	Neurologic assessment of motor skills		54-53-52-62-63-64-74-75-83-84-85	65	Check up	Speech therapist evaluation
3, 0	Suspicion of HPP raised	Referral to clinical genetics; preparation for molecular testing	53-63-83	54-52-62-65-64-74-75-84-85	55	Check-up, scaling and polishing, fluoride varnish	
3, 8	Genetic confirmation of *ALPL* mutation	Genetic counseling provided to family; confirmation of *ALPL* mutation	52-62	54-55-65-64-74-75-84-85		Check-up, scaling and polishing, fluoride varnish	Evaluation for dental space maintainers
5, 3	Mild phenotype confirmed, no skeletal deformities	Follow-up by pediatric endocrinology and orthopedics; growth monitoring		54-55-65-64-74-75-84-85	31-32-41-42-46	Pit and fissure sealant, scaling and polishing, fluoride varnish	Orthodontic evaluation
5, 9	Stable skeletal condition, no indication for ERT	Multidisciplinary follow-up including pediatrics, orthopedics, genetics, and dentistry		54-55-65-64-74-75-31-32-41-42-84-85-46	16-36	Pit and fissure sealant	Orthodontic evaluation
6, 6	Normal growth trend maintained	Orthopedic evaluation of gait; no skeletal deformities detected	55	16-54-55-65-64-36-75-74-32-31-41-42-84-85-46	26	Pit and fissure sealant, scaling and polishing, fluoride varnish	Orthodontic evaluation
7, 1	Mild phenotype stable, no systemic progression	Regular pediatric and metabolic follow-up; genetic re-assessment	65	16-54-64-26-36-74-75-32-31-41-42-84-85-46		Check-up, scaling and polishing, fluoride varnish	Orthodontic records collection
7, 10	Ongoing systemic monitoring	Continued multidisciplinary monitoring (pediatrics, orthopedics, genetics, dentistry)		16-54-64-26-36-75-74-32-31-41-42-84-85-46	21	Check-up, scaling and polishing, fluoride varnish	Insertion of a TPA in TMA

ALP: Alkaline Phosphatase; PEA: Phosphoethanolamine; HPP: Hypophosphatasia; ALPL: Liver/Bone/Kidney Alkaline Phosphatase; ERT: Enzyme Replacement Therapy; TPA: Transpalatal arch; TMA: Titanium Molybdenum Alloy.

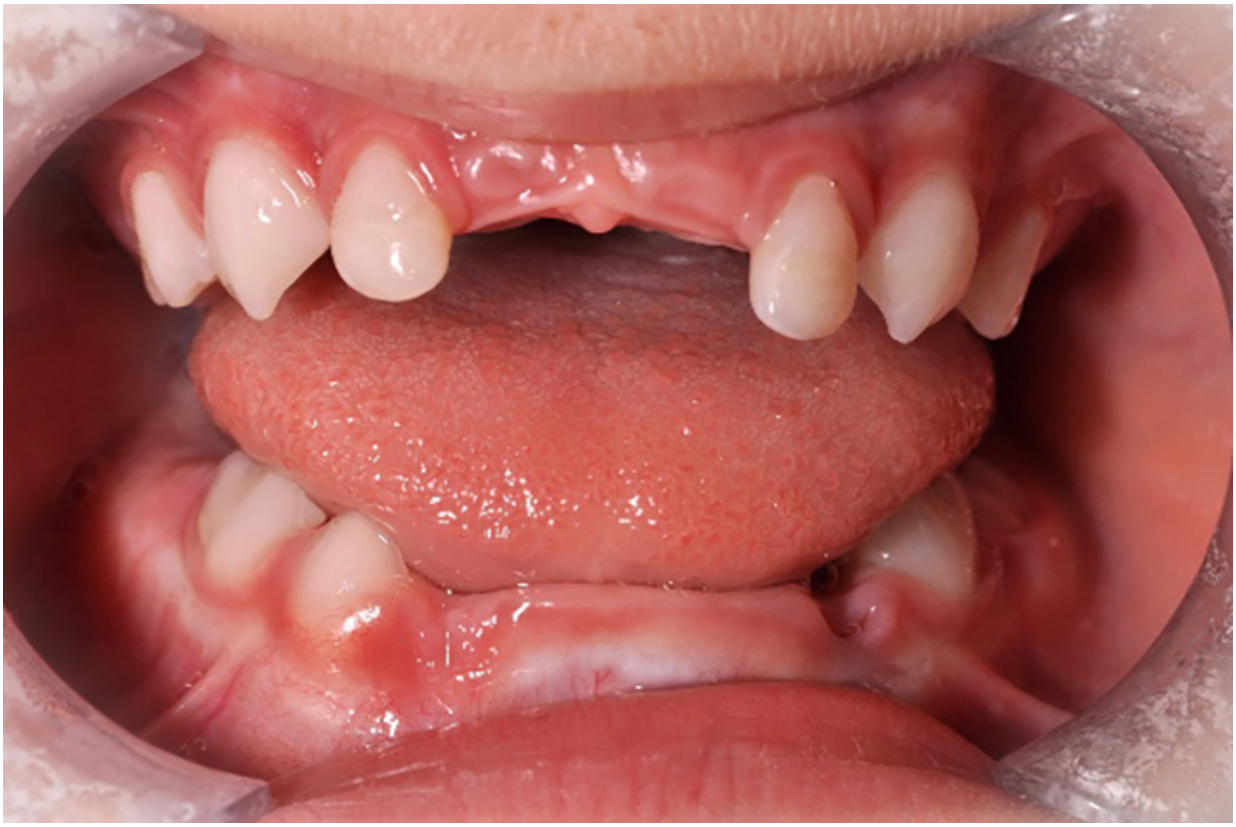

FIGURE 3. Intraoral photograph showing multiple missing primary teeth (5.1, 6.1, 7.1, 7.2, 7.3, 8.1, 8.2) due to premature exfoliation.

FIGURE 4. Exfoliated teeth (6.2, 7.3) showing unresorbed roots exceeding two-thirds of the total root length, with no evidence of carious lesions.

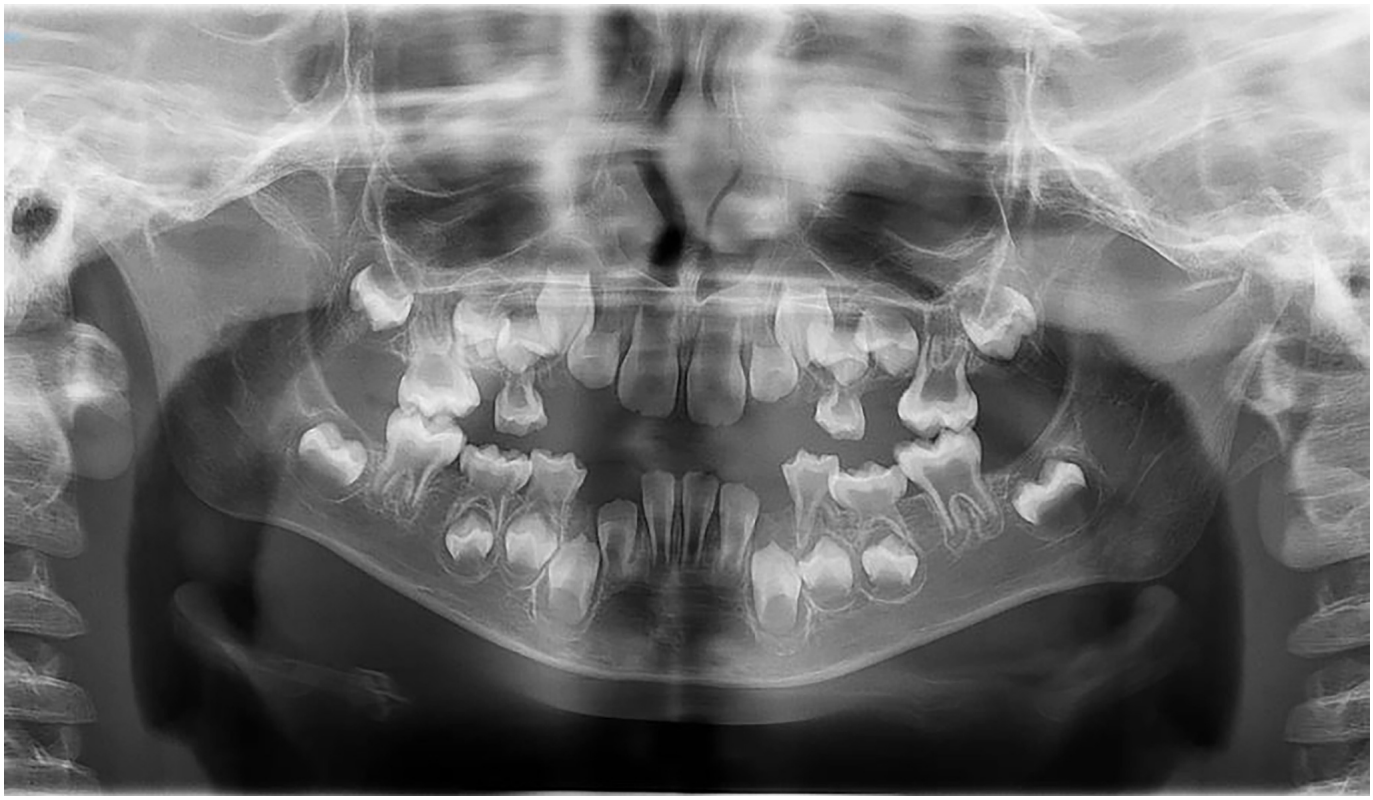

FIGURE 5. Orthopantomography showing reduced alveolar bone height, short and tapered roots, enlarged pulp chambers, and root canals.

sional hygiene every 4–6 months, scaling and polishing, fluoride varnish application, and detailed home hygiene instructions. Parents were advised to use fluoride toothpaste adjusted according to their child's age. At 5 years and 5 months of age, following the eruption of the first permanent molars, pit-and-fissure sealants were applied using a resin-based sealant material, in line with current preventive recommendations [23]. Despite multiple losses of anterior teeth, the child maintained good masticatory efficiency owing to the second primary molars, which preserved vertical dimension and occlusal stability. Speech therapy was introduced for mild psychomotor delay, and the child's phonation improved progressively with no significant deficits in pronunciation.

Orthodontic evaluation was performed at the age of 6 years, after the exfoliation of tooth 55 and eruption of the first permanent molars. Study models and cephalometric analysis guided the decision to monitor the occlusal development and eruption space for the premolars (Figs. 6,7).

At the last general follow-up in November 2024, at 7 years and 5 months of age, the child showed stable growth (123 cm, −0.2 Standard Deviation Score (SDS); 22.3 kg, 40th percentile; Body Mass Index (BMI) 14.7, normal for age) and good overall health. Growth parameters were reported according to the World Health Organization (WHO) growth charts for children, with BMI values interpreted using age- and sex-specific percentiles [24].

Dental examination revealed well-shaped arches, good functional occlusion, stable first permanent molars, and no evidence of caries or gingival inflammation in the oral cavity (Fig. 8). Orthodontic management aimed at preserving arch integrity during the mixed dentition phase began in July 2025 with the insertion of a transpalatal arch (TPA) made of titanium molybdenum alloy (TMA). The appliance was placed after reaching two-thirds root maturation of teeth 16 and 26. The purpose was to achieve molar derotation and partial distalization (Fig. 9) and maintain eruption space for teeth 15 and 25.

Throughout the six years of observation, the patient's skeletal phenotype remained mild and stable, and enzyme replacement therapy (ERT) with asfotase alfa was not indicated, as it was considered unnecessary. Multidisciplinary follow-up involving endocrinologists, orthopedists, dentists, orthodontists, speech therapists, and urologists ensured coordinated care, while preventive and interceptive orthodontic strategies effectively preserved the oral health and function.

3. Discussion

This case highlights how the premature, nontraumatic loss of primary teeth can serve as the first visible sign of a systemic disorder such as HPP. Although uncommon, this finding should alert pediatric dentists to investigate beyond local oral conditions and consider systemic or genetic causes. In young children, exfoliated teeth with intact roots, in absence of trauma, inflammation, or caries, are highly suggestive of systemic disease and may enable early diagnosis and coordinated care [25, 26].

HPP presents with remarkable clinical variations [1, 2]. In the present case, the phenotype was mild, with short stature, gait instability, and repeated premature tooth loss, but without fractures or overt bone deformities. This variability highlights

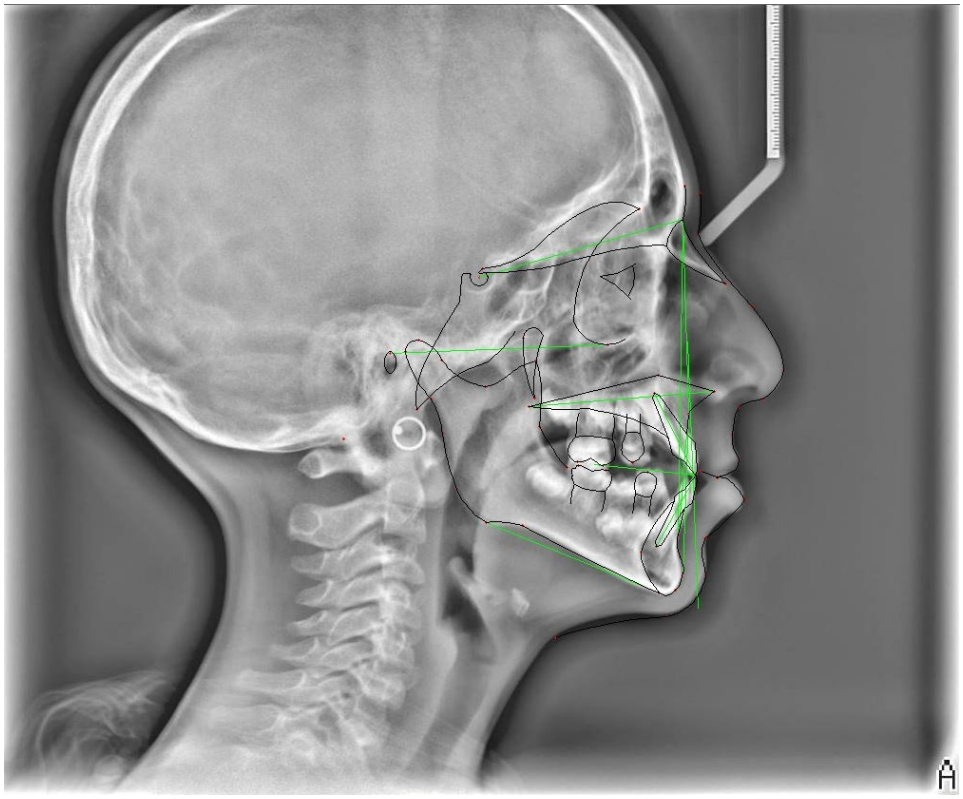

FIGURE 6. Lateral cephalometric radiograph with cephalometric analysis of the patient at 6 years of age used for skeletal and dental evaluation. The black lines represent the traced anatomical contours used as structural references in the analysis, whereas the green lines indicate the cephalometric planes that were measured for the angular and linear assessments.

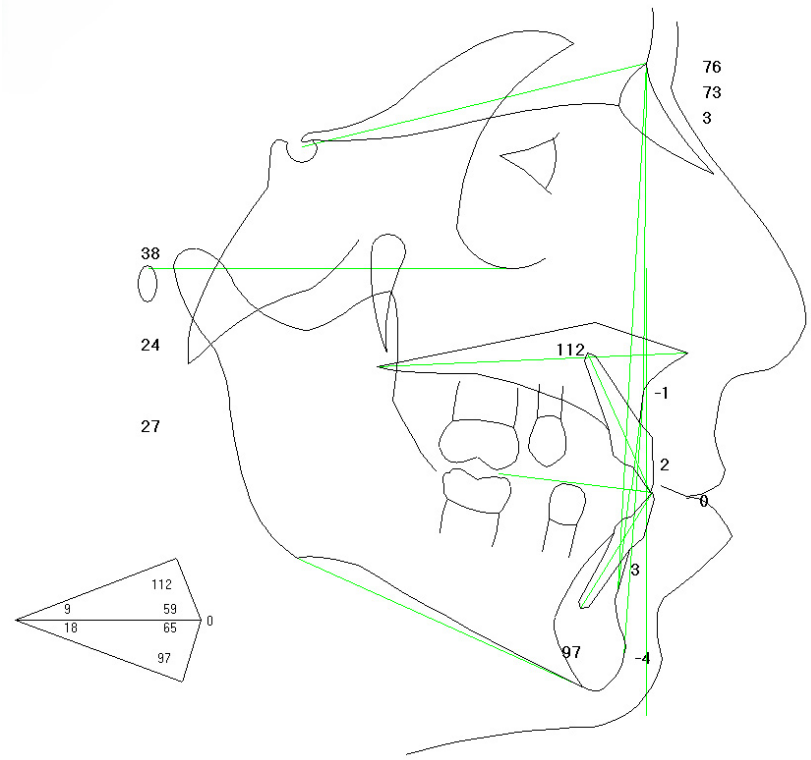

FIGURE 7. Cephalometric analysis according to the Bennet–McLaughlin method, showing a skeletal Class I relationship with a retrognathic maxilla and mandible, normo-bite vertical pattern, and mild proclination of the lower incisors. The black lines represent the traced anatomical contours used as structural references in the analysis, whereas the green lines indicate the cephalometric planes that were measured for the angular and linear assessments.

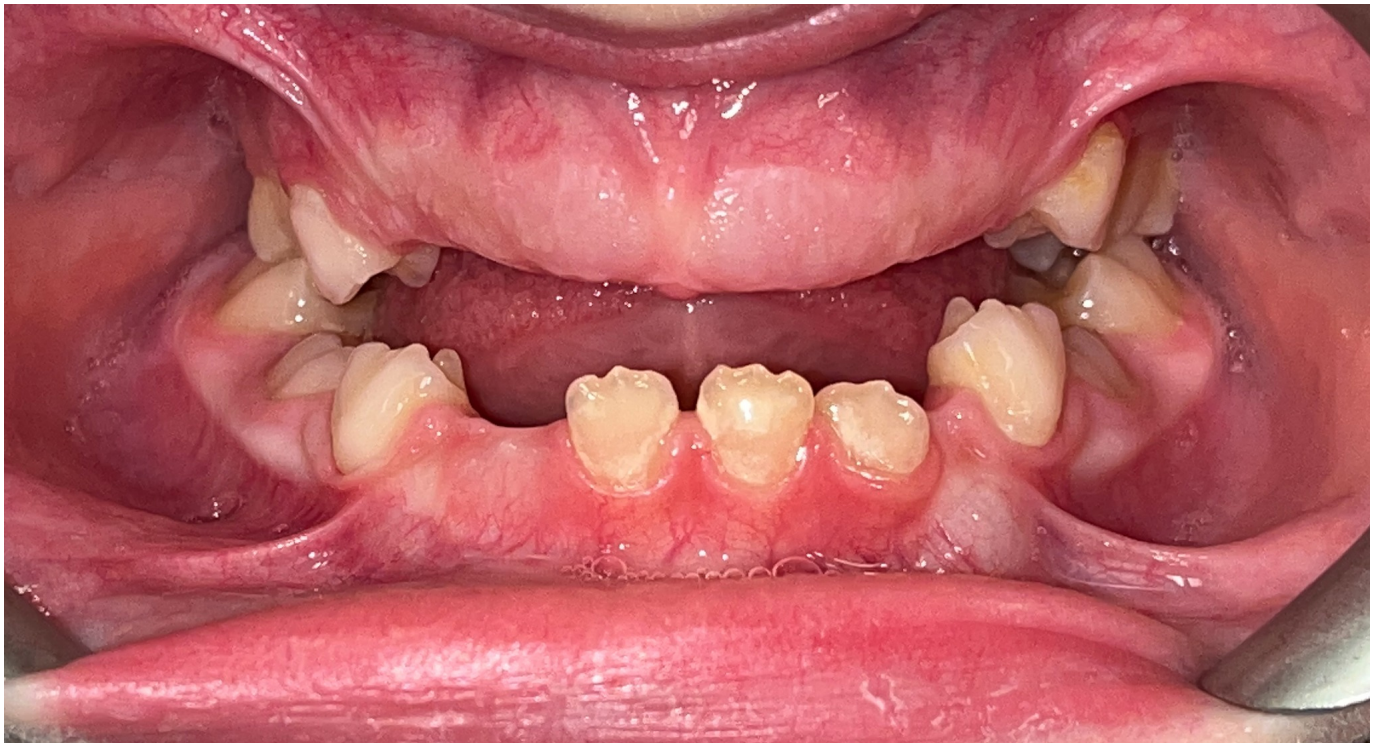

FIGURE 8. Intraoral photograph after 5 years of follow-up showing the initial mixed dentition, well-formed arches, and good alignment of the first permanent molars.

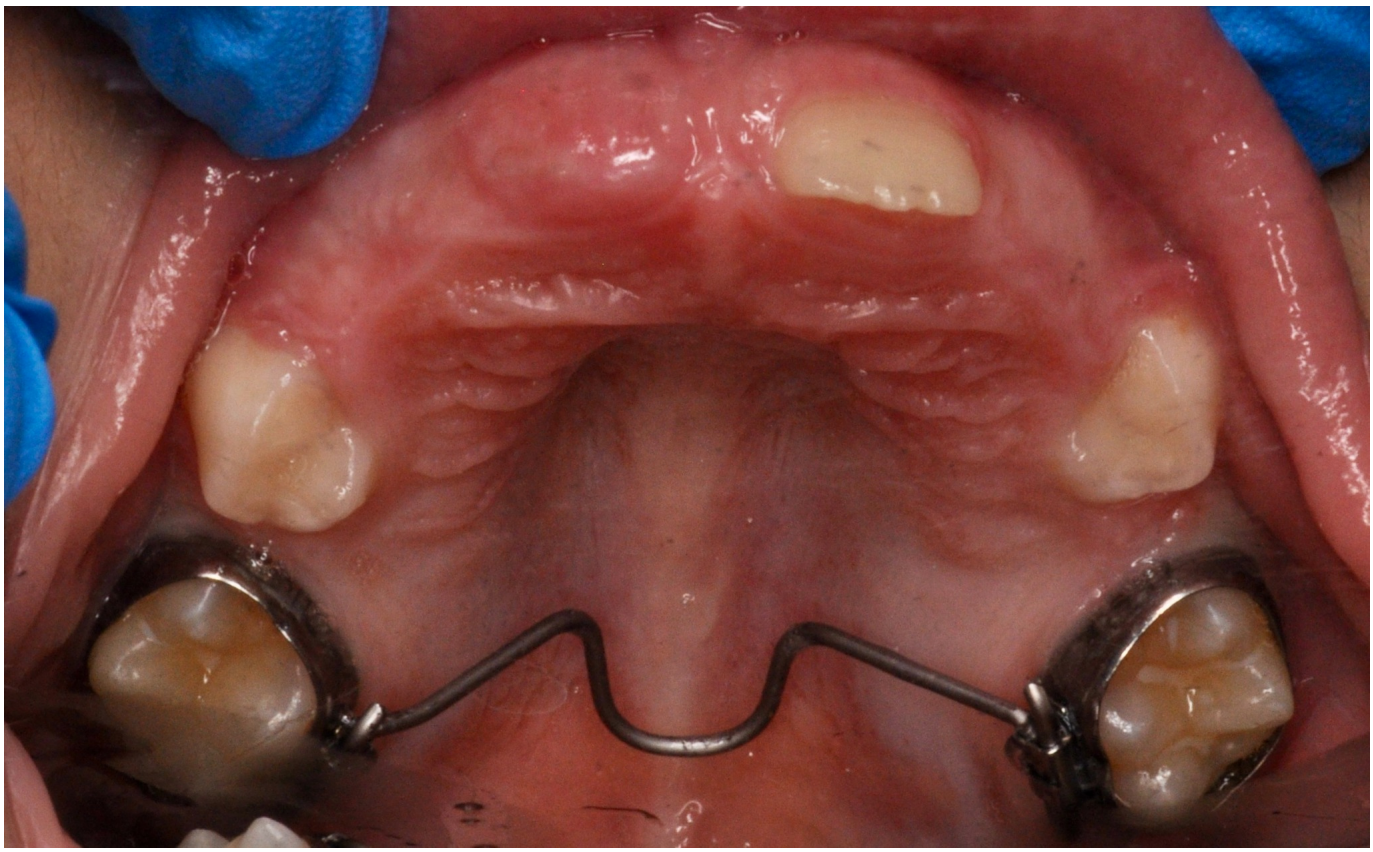

FIGURE 9. Intraoral photograph in the maxillary occlusal view showing the placement of a Transpalatal arch (TPA) in Titanium Molybdenum Alloy (TMA) on the permanent first molars.

the importance of considering HPP as a possible diagnosis, even in the absence of severe skeletal features.

The differential diagnosis of premature exfoliation in children is broad and includes rare genetic syndromes such as Papillon-Lefèvre syndrome, Chediak-Higashi syndrome, Down syndrome, Langerhans cell histiocytosis, hypophosphatemic rickets [27, 28]; immune system deficiencies, including Human Immunodeficiency Virus (HIV) [29]; neoplastic diseases, such as Acute Myeloid Leukemia (AML); self-injurious behaviors, as seen in Lesch-Nyhan syndrome; connective tissue disorders, including Ehlers–Danlos syndrome; mucocutaneous dyskeratosis, congenital adrenal hyperplasia, and others [3]. In unexplained cases, especially when parents deny trauma, clinicians must rule out child abuse before establishing a diagnosis. In the present case, biochemical markers (low ALP, hypercalciuria, and increased PEA) and genetic confirmation of an *ALPL* mutation confirmed the diagnosis of HPP. The family history further supported the hereditary nature of the condition.

Therapeutic strategies for HPP depend on the severity of the disease. ERT with asfotase alfa has demonstrated clear benefits in severe perinatal and infantile forms, improving bone mineralization, growth, and survival [5, 30, 31]. Previous studies have highlighted the beneficial effects of ERT also on dental outcomes [32]. However, our patient presented with a mild and stable skeletal phenotype, and ERT was not indicated. Individualized preventive care, regular monitoring, and interceptive orthodontics preserved function, occlusion, and oral health, supporting the value of a conservative approach in mild cases.

From a dental perspective, maintaining oral function and guiding craniofacial growth are the primary goals. Preventive measures such as professional hygiene, fluoroprophylaxis, fissure sealing, and parental education are essential [15, 33]. Regular orthodontic evaluation helps preserve the eruption space for permanent dentition [34, 35], while interceptive appliances, such as the TPA, can prevent crowding and maintain occlusal balance.

For this patient, different orthodontic and prosthetic-rehabilitative treatment options were considered. First, the use of a functional bite plate, like the Cervera functional appliance (PCF), was hypothesized to control the occlusal plane. This therapeutic hypothesis was rejected because the patient was too young to guarantee correct collaboration, and the follow-ups demonstrated good spontaneous control of the occlusal plane [36]. The second treatment option was the use of a myofunctional device. Once again, this therapeutic option was not adopted because rehabilitative speech therapy proved sufficient efficacy in guaranteeing correct swallowing and avoiding the onset of dyslalia. The third prosthetic-rehabilitative option involved the use of a flexible nylon removable partial denture [37]. This option was not considered because the child and family did not experience esthetic-relationship discomfort, and the functions of the stomatognathic system did not appear to be compromised. In addition, the masticatory function has always remained sufficient and managed to guarantee the intake of a balanced diet in terms of food variety and consistency. It was not possible to insert dental space maintainers in the upper arch due to the early exfoliation of 55 and 65 compared to the eruption of 16 and 26, which were already mesiorotated at the time of eruption. Finally, a TPA in TMA was placed to derotate and partially distalize the maxillary first permanent molars once sufficient root maturation had been reached. This approach allowed us to regain and maintain the eruption space for the maxillary premolars, thereby preventing future crowding. Similar orthodontic strategies have been reported to be effective in managing space deficiencies [38, 39].

Beyond functional considerations, premature loss of anterior teeth can affect esthetics, feeding, phonation, and self-esteem, potentially leading to social stress for both the child and the family. Clear communication, preventive follow-up, and early speech therapy helped minimize these impacts in our patient, highlighting the importance of addressing psychosocial and clinical needs in the long-term management of HPP.

In the long-term oral management of pediatric HPP, oral rehabilitation must extend beyond functional preservation, aiming to anticipate and adapt to the dynamic changes in craniofacial growth. Although HPP often manifests in childhood, evidence suggests that this condition may have important long-term consequences for permanent dentition [40]. In adults with HPP, premature tooth loss is frequent. In one cohort, 63% had lost at least one permanent tooth, and 19% had lost eight or more, with lower serum ALP levels significantly associated with both tooth loss and periodontal breakdown [41]. Moreover, elevated serum PLP levels are associated with poor oral health outcomes, including higher Decayed, Missing and Filled Teeth (DMFT) scores, deeper probing depths, and greater attachment loss [42]. A recent case report described progressive tooth loss during orthodontic treatment in an adult with HPP, suggesting that mechanical stress may exacerbate dental fragility [43]. In adolescent and adult patients with HPP, long-term tooth preservation is often compromised, and prosthetic or implant rehabilitation may be necessary. Several case reports have described the use of removable partial dentures or implant-supported prostheses, although reduced bone mineralization poses significant challenges to surgical stability and osseointegration [44]. In our patient, looking ahead to adolescence, treatment planning will prioritize the preservation of arch integrity and occlusal balance throughout growth, while prosthetic or implant rehabilitation will be considered only if natural dentition cannot be maintained.

These findings indicate that the early dental alterations observed in pediatric HPP cases could predispose patients to long-term complications, such as periodontitis and premature loss of permanent teeth, emphasizing the need for careful monitoring and preventive strategies from childhood onward. Therefore, patients and their families should be informed about these potential complications and strongly motivated to maintain optimal oral health through regular dental check-ups and strict adherence to preventive and therapeutic care plans recommended by the dental professionals.

This case highlights three innovative aspects: early recognition of HPP through dental signs, identification of a rare haplotype, and successful long-term orthodontic management preserving occlusion and function.

Despite its strengths, this case report has some limitations. First, it describes a single patient, which restricts the gener-

alizability of the findings to the general population. Second, advanced imaging modalities such as CT or MRI were not performed, limiting the characterization of the skeletal phenotype. Finally, although a rare homozygous haplotype was identified in association with the *ALPL* mutation, its clinical significance is uncertain. These aspects should be considered when interpreting the observations and underline the need for further studies with larger patient cohorts.

4. Conclusions

Early non-traumatic loss of primary teeth is an unusual finding that should always prompt systemic evaluation, particularly for conditions such as hypophosphatasia. Pediatric dentists play a key role in recognizing these early signs, enabling timely diagnosis and multidisciplinary management. Preventive strategies, regular monitoring, and individualized management are essential for preserving oral function, occlusion, and overall well-being in affected children.

ABBREVIATIONS

HPP, Hypophosphatasia; ALP, Alkaline Phosphatase; *ALPL*, *Liver*/*Bone*/*Kidney Alkaline Phosphatase*; TNSALP, Tissue-nonspecific Alkaline Phosphatase; PPi, Pyrophosphate; PLP, Pyridoxal-5′-Phosphate; AMP, Adenosine Monophosphate; PEA, Phosphoethanolamine; IRCCS, Istituto di Ricovero e Cura a Carattere Scientifico; CT, Computer Tomography; MRI, Magnetic Resonance Imaging; NGS, Next Generation Sequencing; SDS, Standard Deviation Score; BMI, Body Mass Index; PCF, Cervera functional appliance; TPA, Transpalatal arch; TMA, Titanium Molybdenum Alloy; ERT, Enzyme replacement therapy; WHO, World Health Organization; HIV, Human Immunodeficiency Virus; AML, Acute Myeloid Leukemia; DMFT, Decayed, Missing, and Filled Teeth.

AVAILABILITY OF DATA AND MATERIALS

All relevant clinical data supporting the findings of this case report are included in the manuscript. Additional information is available from the corresponding author upon reasonable request to protect patient confidentiality.

AUTHOR CONTRIBUTIONS

CC and NL—conceived and designed the case report and revised the manuscript. CC, CDB and AM—were responsible for acquiring clinical and diagnostic data. CDB, GR and LC—wrote the draft of the manuscript. All authors contributed to the editorial changes in the manuscript. All authors have read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical committee approval was not required for this case report, in accordance with the Declaration of Helsinki and applicable national regulations governing clinical research. According to Italian legislation (Legislative Decree 211/2003) and national guidance issued by the Italian Medicines Agency, single case reports that do not involve experimental interventions are not classified as clinical research studies and therefore do not require formal Ethics Committee approval. This case report is retrospective and purely descriptive in nature; neither the diagnostic process, nor the therapeutic approach, nor the clinical management of the patient were in any way influenced by the subsequent decision to describe the case in a scientific publication. This position is consistent with international recommendations from the International Committee of Medical Journal Editors and the Committee on Publication Ethics, which identify informed consent as the primary ethical requirement for single case reports. Written informed consent for treatment and publication was obtained from the patient's parents. The patient was managed in accordance with national and international guidelines and the principles of good clinical practice.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Hughes SL, Parkes RC, Drage N, Collard M. Early tooth loss in children: a warning sign of childhood hypophosphatasia. Dental Update. 2017; 44: 317–318, 320–321.

[2] Rajput HAS, Ahmed A, Bilgrami A, Haider B, Nasir Khan J, Afnan M. The diagnosis and initial management of children presenting with premature loss of primary teeth associated with a systemic condition. Cureus. 2024; 16: e62402.

[3] Spodzieja K, Olczak-Kowalczyk D. Premature loss of deciduous teeth as a symptom of systemic disease: a narrative literature review. International Journal of Environmental Research and Public Health. 2022; 19: 3386.

[4] Sharma G, Whatling R. Case report: premature exfoliation of primary teeth in a 4-year-old child, a diagnostic dilemma. European Archives of Paediatric Dentistry. 2011; 12: 312–317.

[5] Rathbun JC. Hypophosphatasia; a new developmental anomaly. American Journal of Diseases of Children. 1948; 75: 822–831.

[6] Mornet E. Hypophosphatasia. Orphanet Journal of Rare Diseases. 2007; 2: 40.

[7] Mornet E, Yvard A, Taillandier A, Fauvert D, Simon-Bouy B. A molecular-based estimation of the prevalence of hypophosphatasia in the European population. Annals of Human Genetics. 2011; 75: 439–445.

[8] Mornet E, Taillandier A, Domingues C, Dufour A, Benaloun E, Lavaud

N, *et al.* Hypophosphatasia: a genetic-based nosology and new insights in genotype-phenotype correlation. European Journal of Human Genetics. 2021; 29: 289–299.

[9] Whyte MP. Hypophosphatasia—aetiology, nosology, pathogenesis, diagnosis and treatment. Nature Reviews Endocrinology. 2016; 12: 233–246.

[10] Mornet E. Genetics of hypophosphatasia. French Journal of Pediatrics. 2017; 24: 5S51–5S56.

[11] Villa-Suárez JM, García-Fontana C, Andújar-Vera F, González-Salvatierra S, de Haro-Muñoz T, Contreras-Bolívar V, *et al.* Hypophosphatasia: a unique disorder of bone mineralization. International Journal of Molecular Sciences. 2021; 22: 4303.

[12] Bianchi ML. Hypophosphatasia: an overview of the disease and its treatment. Osteoporosis International. 2015; 26: 2743–2757.

[13] Seefried L, Genest F, Hofmann C, Brandi ML, Rush E. Diagnosis and treatment of hypophosphatasia. Calcified Tissue International. 2025; 116: 46.

[14] Im M, Cho SY. Hypophosphatasia in childhood: diagnosis to management. Osteoporosis and Sarcopenia. 2025; 11: 38–42.

[15] Okawa R, Nakano K. Dental manifestation and management of hypophosphatasia. The Japanese Dental Science Review. 2022; 58: 208–216.

[16] Michigami T, Ohata Y, Fujiwara M, Mochizuki H, Adachi M, Kitaoka T, *et al.* Clinical practice guidelines for hypophosphatasia. Clinical Pediatric Endocrinology. 2020; 29: 9–24.

[17] Khan AA, Brandi ML, Rush ET, Ali DS, Al-Alwani H, Almonaei K, *et al.* Hypophosphatasia diagnosis: current state of the art and proposed diagnostic criteria for children and adults. Osteoporosis International. 2024; 35: 431–438.

[18] Högler W, Langman C, Gomes da Silva H, Fang S, Linglart A, Ozono K, *et al.* Diagnostic delay is common among patients with hypophosphatasia: initial findings from a longitudinal, prospective, global registry. BMC Musculoskeletal Disorders. 2019; 20: 80.

[19] American Academy on Pediatric Dentistry Council on Clinical Affairs. Guideline on management of dental patients with special health care needs. Pediatric Dentistry. 2008; 30: 107–111.

[20] Lira Dos Santos EJ, Mohamed FF, Kramer K, Foster BL. Dental manifestations of hypophosphatasia: translational and clinical advances. JBMR Plus. 2025; 9: ziae180.

[21] Cárdenas-Aguilera JG, González-López V, Zarante-Bahamón AM, Prieto-Rivera JC, Baquero-Rodríguez R, Chacón-Acevedo KR, *et al.* Diagnosis, treatment, and follow-up of patients with hypophosphatasia. Endocrine. 2025; 87: 400–419.

[22] Fauvert D, Brun-Heath I, Lia-Baldini AS, Bellazi L, Taillandier A, Serre JL, *et al.* Mild forms of hypophosphatasia mostly result from dominant negative effect of severe alleles or from compound heterozygosity for severe and moderate alleles. BMC Medical Genetics. 2009; 10: 51.

[23] Ahovuo-Saloranta A, Forss H, Walsh T, Nordblad A, Mäkelä M, Worthington HV. Pit and fissure sealants for preventing dental decay in permanent teeth. The Cochrane Database of Systematic Reviews. 2017; 7: CD001830.

[24] WHO Multicentre Growth Reference Study Group. WHO child growth standards based on length/height, weight and age. Acta Paediatrica. 2006; 450: 76–85.

[25] Heggie C, Al-Diwani H, Arundel P, Balmer R. Diagnosis and initial management of children presenting with premature loss of primary teeth associated with a systemic condition: a scoping review and development of clinical aid. International Journal of Paediatric Dentistry. 2024; 34: 871–890.

[26] Cao Y, Zhang F, Huang X, Jiang A, Jiang S, Wu M. Decade-long delayed diagnosis of hypophosphatasia until next generation tooth loss: case reports on dental rehabilitation, diagnostic challenges and clinical implications. Frontiers in Oral Health. 2025; 6: 1585188.

[27] de Arruda JAA, Sousa-Neto SS, Abreu LG, Schuch LF, Souza VG, Alves TVL, *et al.* Oral manifestations of Chediak-Higashi syndrome: a systematic review. Disease-a-Month. 2023; 69: 101356.

[28] Vocale C, Montevecchi M, D'Alessandro G, Gatto M, Piana G, Nibali L, *et al*. Subgingival periodontal pathogens in down syndrome children without periodontal breakdown. A case-control study on deciduous teeth. European Journal of Paediatric Dentistry. 2021; 22: 309–313.

[29] Blignaut E, Rossouw TM, Becker PJ, Mavuso DS, Feucht UD. Gingival recession and localized aggressive periodontitis among HIV-infected children and adolescents receiving antiretroviral therapy. The Pediatric Infectious Disease Journal. 2019; 38: e112–e115.

[30] Baroncelli GI, Angiolini M, Ninni E, Galli V, Saggese R, Giuca MR. Prevalence and pathogenesis of dental and periodontal lesions in children with X-linked hypophosphatemic rickets. European Journal of Paediatric Dentistry. 2006; 7: 61–66.

[31] Dahir KM, Dunbar NS. Medical management of hypophosphatasia: review of data on asfotase alfa. Current Osteoporosis Reports. 2025; 23: 14.

[32] Kiselnikova L, Vislobokova E, Voinova V. Dental manifestations of hypophosphatasia in children and the effects of enzyme replacement therapy on dental status: a series of clinical cases. Clinical Case Reports. 2020; 8: 911–918.

[33] Ministero della Salute Italiano. National guidelines for the promotion of oral health and the prevention of oral diseases in childhood and adolescence. 2014. Available at: https://www.salute.gov.it/imgs/C_17_pubblicazioni_2073_allegato.pdf (Accessed: 15 June 2025).

[34] Soxman JA. Space maintenance. In Soxman JA (ed.) Handbook of clinical techniques in pediatric dentistry (pp. 229–243). 2nd edn. John Wiley & Sons, Ltd.: Hoboken, NJ, USA. 2021.

[35] Shakti P, Singh A, Purohit BM, Purohit A, Taneja S. Effect of premature loss of primary teeth on prevalence of malocclusion in permanent dentition: a systematic review and meta-analysis. International Orthodontics. 2023; 21: 100816.

[36] Tzemach M, Aizenbud D, Einy S. Early orthodontic treatment for growth modification by functional appliances—pros and cons. Refuat Hapeh Vehashinayim. 2014; 31: 25–31, 61. (In Hebrew)

[37] Nadelman P, Bedran N, Magno MB, Masterson D, de Castro ACR, Maia LC. Premature loss of primary anterior teeth and its consequences to primary dental arch and speech pattern: a systematic review and meta-analysis. International Journal of Paediatric Dentistry. 2020; 30: 687–712.

[38] Tsetsilas M, Konermann AC, Keilig L, Reimann S, Jäger A, Bourauel C. Symmetric and asymmetric expansion of molars using a Burstone-type transpalatal arch. Biomechanical and clinical analysis. Journal of Orofacial Orthopedics. 2015; 76: 377–390.

[39] Mieszala C, Schmidt JG, Becker K, Willmann JH, Drescher D. Digital design of different transpalatal arches made of polyether ether ketone (PEEK) and determination of the force systems. Applied Sciences. 2022; 12: 1590.

[40] Jørgensen FF, Hermann X, Hepp N, Sonnesen L. Oro-dental characteristics in patients with adult-onset hypophosphatasia compared to a healthy control group—a case-control study. Journal of Oral Rehabilitation. 2025; 52: 64–74.

[41] Sinha P, Gabor R, Haupt-Harrington R, Deering L, Steiner RD. Dental manifestations in adult hypophosphatasia and their correlation with biomarkers. JIMD Reports. 2022; 63: 434–445.

[42] Dudde F, Fildebrandt D, Smeets R, Gosau M, Amling M, Beikler T, *et al.* Role of PLP-level as a predictive marker for oral health status in adult hypophosphatasia. Clinical Oral Investigations. 2024; 28: 419.

[43] Tokuchi S, Kawano T, Ntege EH, Murahashi M, Ide K, Maruyama N, *et al.* Adult-onset hypophosphatasia diagnosed after consecutive tooth loss during orthodontic treatment: a case report. Journal of Medical Case Reports. 2024; 18: 626.

[44] Yang Y, Liu Z, Wei L, Taylor TD, Xiao H. Prosthodontic rehabilitation of a patient with hypophosphatasia using dental implants: a case report with seven years follow-up. Journal of Prosthodontics. 2021; 30: 742–746.

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