scientific reports

Check for updates

OPEN

Japanese nationwide dental survey of hypophosphatasia reveals novel oral manifestations

Rena Okawa[1]✉, Tamami Kadota[1], Hiroshi Kurosaka[2], Hirofumi Nakayama[3], Marin Ochiai[1], Yuko Ogaya[1], Takuo Kubota[3], Takashi Yamashiro[2] & Kazuhiko Nakano[1]

Hypophosphatasia (HPP) is a common inherited skeletal disease. Early exfoliation of primary teeth is known as a dental manifestation of HPP, and sometimes this symptom leads to a diagnosis of HPP. This study aimed to investigate the dental manifestations of HPP in the Japanese population, focusing on dentition and occlusion. A total of 609 dental clinics among general hospitals with dentistry departments were invited to participate. Clinics were sent questionnaires about the number of HPP cases encountered from 2018 to 2022. When clinics indicated that they had treated HPP cases, we proceeded with a second questionnaire about the clinical dental findings of these cases. A total of 103 clinical records of HPP from 30 clinics were collected. Forty percent of non-odonto type cases showed enamel hypomineralization, which was significantly higher than the incidence found in odonto type cases (8.5%) ($P < 0.001$). Non-odonto type cases also exhibited malocclusion (40.0%), poor oral habits (29.1%), and dysphagia (23.6%). The number of dental visits made by HPP patients is increasing because of the development of new treatments and increased disease awareness. Dental symptoms of HPP vary in severity, with particularly severe forms of HPP associated with enamel hypomineralization, malocclusion, poor oral habits, and dysphagia. Patients with HPP require not only medical collaboration but also multidisciplinary dental care according to the severity of the disease.

Keywords Alkaline phosphatase, Dysphagia, Early exfoliation, Enamel hypoplasia, Hypophosphatasia, Malocclusion, Poor oral habits

Hypophosphatasia (HPP) is a common inherited skeletal disease caused by pathogenic variants in the *ALPL* gene that encodes tissue-nonspecific alkaline phosphatase (TNSALP)[1–3]. Impaired bone mineralization is a characteristic feature of HPP, which is caused by low levels of alkaline phosphatase (ALP) activity[4]. Based on the age at which the disease first manifests and the symptoms, HPP is classified into the following six clinical types: perinatal severe, perinatal benign, infantile, childhood, adult, and odonto[5,6]. The diagnostic criteria for HPP include the presence of disordered bone mineralization and premature loss of primary teeth (loss before the age of 4 years) as primary symptoms[7]. HPP is diagnosed based on the presence of one or both primary symptoms, as well as low serum ALP values. Severe forms of HPP (perinatal severe or infantile types) receive general care from medical doctors before or soon after birth[8]. In contrast, in the milder forms of HPP, such as odonto or childhood types, dental signs frequently serve as the initial indications for a diagnosis[9–11].

Our first nationwide dental survey of HPP, conducted in 2013, indicated that most early exfoliation of primary teeth occurs in the mandibular anterior primary incisors of children aged 1–4 years[12]. However, the dental manifestations of severe forms of HPP, which have a poor prognosis for life, were not elucidated. The treatment of HPP has undergone a significant transformation with the advent of ALP enzyme replacement therapy (ERT) asfotase alfa (Strensiq®; Alexion, AstraZeneca Rare Disease, Boston, MA, USA), which was first introduced in 2015. This innovative approach has led to a notable improvement in the survival rate of patients with severe HPP[13–15]. Perinatal HPP is almost always lethal shortly after birth, whereas infantile HPP has an estimated 50% mortality during infancy[16]. Consequently, patients with severe type HPP who are unable to survive without asfotase alfa until tooth eruption are increasingly being referred to dental clinics.

[1]Department of Pediatric Dentistry, Graduate School of Dentistry, The University of Osaka, 1-8 Yamadaoka, Suita, Osaka 565-0871, Japan. [2]Department of Orthodontics and Dentofacial Orthopedics, Graduate School of Dentistry, The University of Osaka, 1-8 Yamadaoka, Suita, Osaka 565-0871, Japan. [3]Department of Pediatrics, Graduate School of Medicine, The University of Osaka, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan. ✉email: okawa.rena.dent@osaka-u.ac.jp

In 2018, we conducted a second nationwide survey of HPP, which revealed that the genetic and dental manifestations of patients with odonto type and non-odonto type HPP are significantly different[17]. An autosomal dominant (AD) inheritance pattern was identified in most odonto type patients, while an autosomal recessive (AR) inheritance pattern was observed in the majority of non-odonto type patients. A higher frequency of premature exfoliation of primary teeth was observed in patients classified as odonto type patients in comparison with those classified as non-odonto type patients. Tooth hypomineralization was detected in 42% of non-odonto type patients, but not in any odonto type patients. In the current cohort of patients with severe HPP who have been treated with asfotase alfa, the eruption of permanent teeth has been observed. These patients with severe HPP present with different dental problems of malocclusion and oral function compared with those with mild HPP who have not been treated with asfotase alfa[11]. Furthermore, educational activities highlighting that early exfoliation of primary teeth may be a dental manifestation of HPP have been conducted in Japan with the objective of increasing awareness of HPP among those involved in pediatric oral health[11,18]. Mild form HPP with mild bone symptoms or only dental symptoms can now be screened by dental practitioners[11]. However, oral management for HPP according to severity is not fully established. The need for orthodontic treatment of malocclusion for early loss of permanent teeth is now increasing. Therefore, we decided to conduct a third dental survey focusing on the dentition and occlusion of HPP patients. The primary objective was to determine the dental manifestations of HPP patients. The secondary objective was to determine the medical background, periodontal status, hypomineralization of tooth, malocclusion and orthodontic treatment, poor oral habits and dysphagia of HPP cases.

Results

Number of HPP cases

A total of 609 dental clinics in general hospitals with dentistry departments, including 28 university dental hospitals with pediatric dentistry departments, were invited to participate. Of these, 359 clinics (58.9%) completed the first questionnaire about the number of HPP cases encountered over a recent 5-year period (2018 to 2022; S1 Fig.). A total of 86 HPP cases were reported by 38 clinics (6.2%). These clinics then received a second questionnaire about clinical dental findings (S2 Fig.). Finally, we obtained the clinical records of 62 HPP cases (60.2% of cases) (29 clinics [4.7%]; 16 dental clinics in general hospitals with dentistry departments and 13 university dental hospitals with pediatric dentistry departments). We included an additional 41 HPP cases (39.8% of cases) from our clinic, and analyzed a total of 103 HPP cases (50 male and 53 female patients).

Patients' background

Table 1 summarizes the general and dental information of patients with HPP. The average age at diagnosis of patients with odonto HPP was 43.8 months (range, 17.0–368.0 months), compared with 52.8 months (range, 15.0–115.0 months) for patients with childhood HPP ($P=0.5261$). Forty-five patients (44.1%) were receiving ERT. All patients with perinatal severe, infantile, and adult HPP received ERT, but less than 10% of odonto HPP

Phenotype	Total no. of patients (Male/female) (Rate for all patients)	Age at HPP diagnosis Mean ± SEM (months) [median]	Total no. of patients who received ERT (Rate for all patients in each phenotype)	Age at dental examination Mean ± SEM (years) [median]		Total no. of patients referred from various sources (Rate for all patients in each phenotype)		
				First	Last	Medical	Dental	Others
Perinatal severe	19 (5/14) (18.4%)	0.1 ± 0.1 [0]	19 (100%)	2.1 ± 0.4 [1.7]	6.2 ± 0.7 [6.0]	14 (73.7%)	5 (26.3%)	0 (0%)
Perinatal benign	12 (2/10) (11.7%)	9.0 ± 6.9 [0]	7 (58.3%)	6.4 ± 2.3 [2.6]	11.3 ± 2.6 [7.9]	9 (75.0%)	2 (16.7%)	1 (8.3%)
Infantile	7 (5/2) (6.8%)	6.5 ± 2.9 [3.0]	7 (100%)	4.5 ± 2.2 [1.7]	9.4 ± 2.8 [7.1]	5 (71.4%)	0 (0%)	2 (28.6%)
Childhood	15 (11/4) (14.6%)	52.8 ± 8.1 [51.0]	8 (53.3%)	5.0 ± 0.8 [4.7]	9.2 ± 1.3 [7.8]	8 (53.3%)	5 (33.3%)	2 (13.3%)
Adult	2 (0/2) (1.9%)	490.0 ± 10.0 [490.0]	2 (100%)	45.8 ± 1.5 [45.8]	46.7 ± 2.5 [46.7]	2 (100%)	0 (0%)	0 (0%)
Odonto	47 (26/21) (45.6%)	43.8 ± 7.6 [33.0]	3 (6.4%)	4.0 ± 1.1 [2.8]	6.7 ± 0.8 [5.9]	16 (34.0%)	29 (61.7%)	2 (4.3%)
Unknown	1 (1/0) (1.0%)	-	-	6.8	11.1	0 (0%)	0 (0%)	1 (100%)
Total	103 (50/53) (100%)	39.3 ± 7.8 [26.0]	45 (44.1%)	4.9 ± 0.7 [2.8]	8.5 ± 0.8 [6.6]	54 (52.4%)	41 (39.8%)	8 (7.8%)

Table 1. General and dental information of patients with HPP. ERT, enzyme replacement therapy; HPP, hypophosphatasia; SEM, standard error of the mean.

patients received ERT. The first and last dental visits for patients with perinatal severe HPP were earlier than those for patients with the other phenotypes. The average age at the first dental visit in patients with odonto HPP (4.0 ± 1.1 years) was not significantly different from that of patients with childhood HPP (5.0 ± 0.8 years; $P = 0.0587$). Most odonto HPP patients were referred from dental practitioners while most non-odonto type HPP patients were referred from medical practitioners ($P < 0.001$). Figure 1 shows the distribution of serum ALP values for patients in each clinical type. The mean serum ALP value for patients with odonto HPP was 90.6 U/L, which was significantly higher than those for patients with perinatal severe (4.9 U/L), perinatal benign (9.0 U/L), and infantile (30.1 U/L) types ($P < 0.05$).

Genetic features

Information about the *ALPL* pathogenic variants was obtained for 82 cases (Table 2). The p.Leu520ArgfsTer86 (c.1559delT) pathogenic variant was most frequently detected in 41 cases (50.0%). Of the 17 patients with perinatal severe HPP, 12 (70.6%) were homozygous for the most frequent p.Leu520ArgfsTer86 pathogenic variant and five (29.4%) were compound heterozygous for p.Leu520ArgfsTer86 and another pathogenic variant. In the compound heterozygous cases, the type with p.Leu520ArgfsTer86 in one allele was found in four cases (40.0%) of odonto HPP and in three cases (42.9%) of childhood HPP. The second most frequent pathogenic variant was p.Phe327Leu (c.979 T > C), which was detected in 13 cases (16.0%). Four out of nine patients (44.4%) were found to be compound heterozygous for p.Leu520ArgfsTer86 and p.Phe327Leu in perinatal benign HPP. The third most frequent pathogenic variant was p.Arg184Trp (c.550C > T) in exon 6, which was detected in nine cases (11.1%). Five out of 31 patients with odonto HPP (16.1%) were found to be single pathogenic variants of p.Arg184Trp.

Table 3 shows the inheritance patterns of the 82 probands. Inheritance was AR in 50 patients (61.0%) and AD in 32 patients (39.0%). Significantly more patients had AR inheritance (76.0%) than AD inheritance (24.0%) in the non-odonto type HPP, and AD pathogenic variants were detected in 20 cases (64.5%), with significantly fewer odonto HPP patients demonstrating AR inheritance (35.5%) ($P = 0.0004$).

Dental manifestations

Table 4 summarizes dental problems associated with HPP. Spontaneous early exfoliation or extraction of primary teeth before the age of 4 was reported in 75 cases (73.5%), including 43 odonto HPP patients (43/47 patients, 91.5%); this finding was significant compared with the loss of teeth among the non-odonto types (32/55 patients; 58.2%) ($P < 0.001$). Figure 2 shows the sites of early exfoliation of primary teeth. The mandibular primary central incisors were the most commonly exfoliated teeth. The mandibular primary lateral incisors, followed by the maxillary primary central incisors, were common sites. Patients with perinatal severe HPP had significantly more early exfoliated teeth than those with perinatal benign and odonto HPP ($P < 0.01$) (Fig. 3A). Moreover, there was a significant negative correlation between the number of early exfoliated primary teeth and ALP values

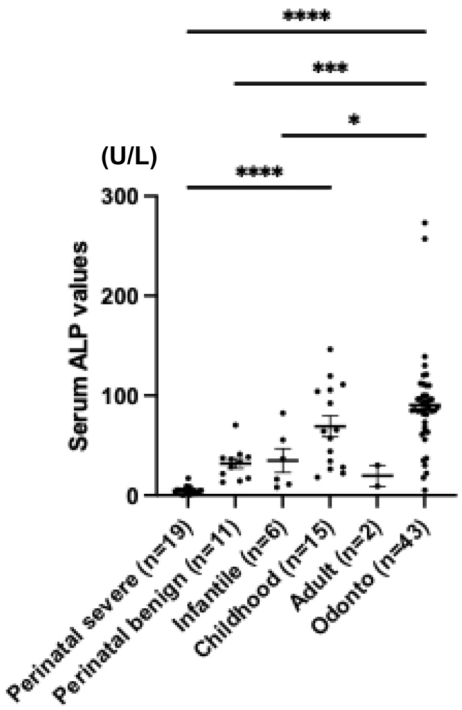

Fig. 1. Distribution of serum alkaline phosphatase (ALP) values of each clinical type of hypophosphatasia. Significant differences were determined using ANOVA with Bonferroni correction. *$P < 0.05$, ***$P < 0.001$, and ****$P < 0.0001$.

Phenotype	Genotype						Number of patients
	Exon	Allele	Residual activity % WT	Exon	Allele	Residual activity % WT	
Perinatal severe (n = 17)	6	c.550C > T, p.Arg184Trp	0.0–3.1	**12**	**c.1559delT, p.Leu520ArgfsTer86**	0	1
	6	c.563C > T, p.Ser188Pro	ND	**12**	**c.1559delT, p.Leu520ArgfsTer86**	0	1
	9	c.979_980delCTT, F310del	ND	**12**	**c.1559delT, p.Leu520ArgfsTer86**	0	1
	9	c.984_986DEL, p.(Phe328del)	4.5	**12**	**c.1559delT, p.Leu520ArgfsTer86**	0	1
	10	c.1130C > T, p.Ala377Val	0.0–2.3	**12**	**c.1559delT, p.Leu520ArgfsTer86**	0	1
	12	**c.1559delT, p.Leu520ArgfsTer86**	0	**12**	**c.1559delT, p.Leu520ArgfsTer86**	0	12
Perinatal benign (n = 10)	9	c.979 T > C, p.Phe327Leu	97.5	WT		-	1
	5	c.407G > A, p.Arg136His	21.2	**12**	**c.1559delT, p.Leu520ArgfsTer86**	0	1
	7	c.678G > T, p.Met226Ile	ND	**12**	**c.1559delT, p.Leu520ArgfsTer86**	0	1
	9	c.979 T > C, p.Phe327Leu	97.5	10	c.1144G > A, p.(Val382Ile)	0.0	1
	9	c.979 T > C, p.Phe327Leu	97.5	12	c.1366G > A, p.(Gly456Arg)	2.5	1
	9	c.979 T > C, p.Phe327Leu	97.5	**12**	**c.1559delT, p.Leu520ArgfsTer86**	0	5
Infantile (n = 7)	5	c.319G > A, p.Val107Ile	ND	12	c.1403C > T, p.Ala468Val	3.9	1
	5	c.407G > A, p.Arg136His	21.2	**12**	**c.1559delT, p.Leu520ArgfsTer86**	0	1
	6	c.550C > T, p.Arg184Trp	0.0–3.1	IVS9	c.997 + 3A > G	NR	1
	9	c.979 T > C, p.Phe327Leu	97.5	**12**	**c.1559delT, p.Leu520ArgfsTer86**	0	1
	10	c.1013A > G, p.His338Arg	ND	**12**	**c.1559delT, p.Leu520ArgfsTer86**	0	1
	11	c.1307A > G, p.Try436Cys	NR	**12**	**c.1559delT, p.Leu520ArgfsTer86**	0	1
	12	c.1446C > A, p.His482Gln	ND	**12**	**c.1559delT, p.Leu520ArgfsTer86**	0	1
Childhood (n = 15)	5	c.406C > T, p.Arg136Cys	5	WT		-	1
	6	c.550C > T, p.Arg184Trp	0.0–3.1	WT		-	1
	9	c.984_986DEL, p.Phe328del	4.5	WT		-	1
	10	c.1144G > A, p.Val382Ile	0	WT		-	2
	12	**c.1559delT, p.Leu520ArgfsTer86**	0	WT		-	2
	5	c.319G > A, p.Val107Ile	ND	9	c.1403C > T, p.(Ala468Val)	3.9	1
	6	c.526G > A, p.Ala176Thr	67.6	12	c.920C > T, p.(Pro307Leu)	5.3	1
	6	c.572A > G, p.Glu191Gly	NR	**12**	**c.1559delT, p.Leu520ArgfsTer86**	0	1
	6	c.613G > A, p.Ala205Thr	NR	**12**	**c.1559delT, p.Leu520ArgfsTer86**	0	1
	7	c.670A > G, p.(Lys224Glu)	43.0	11	c.1225c > G, p.(Pro409Ala)	37.5	1
	7	*c.787 T > C, p.(Try246His)*	*SNP*	**12**	**c.1559delT, p.Leu520ArgfsTer86**	0	1
	9	c.979 T > C, p.Phe327Leu	97.5	7	c.1144G > A, p.Val382Ile	0	1
	11	c.1307A > G, p.Try436Cys	NR	**12**	**c.1559delT, p.Leu520ArgfsTer86**	0	1
Adult (n = 1)	5	c.1565 T > C, p.Val522Ala	ND	WT		-	1

Continued

Phenotype	Genotype						Number of patients
	Exon	Allele	Residual activity % WT	Exon	Allele	Residual activity % WT	
Odonto (n = 31)	4	c.188G > T, p.Gly63Val	0.8	WT		-	1
	5	c.340G > A, p.Ala114Thr	3	WT		-	1
	6	c.512A > G, p.(His171Arg)	4.3	WT		-	1
	6	c.521C > A, p.Pro174His	ND	WT		-	1
	6	c.550C > T, p.Arg184Trp	0.0–3.1	WT		-	5
	9	c.979 T > C, p.Phe327Leu	97.5	WT		-	1
	10	c.1132G > T, p.Asp378Try	0	WT		-	1
	10	c.1144G > A, p.Val382Ile	0	WT		-	2
	10	c.1183A > T, p.Ile395Phe	ND	WT		-	1
	12	c.1333 T > C, p.Ser445Pro	2.1	WT		-	1
	12	c.1426G > A, p.Glu476Lys	4.3	WT		-	1
	12	**c.1559delT, p.Leu520ArgfsTer86**	0	WT		-	2
	3	c.Ter126G > A	ND	5	c.331G > A, p.(Ala111Thr)	3.4	1
	4	c.211C > T, p. (Arg71Cys)	7.7	7	*c.787 T > C, p.(Try246His)*	*SNP*	1
	4	c.211C > T, p.Arg71Cys	7.7	**12**	**c.1559delT, p.Leu520ArgfsTer86**	0	1
	5	c.407G > A, p.Arg136His	21.2	**12**	**c.1559delT, p.Leu520ArgfsTer86**	0	1
	6	c.550C > T, p.(Arg184Trp)	0.0–3.1	7	*c.787 T > C, p.(Try246His)*	*SNP*	1
	6	c.572A > G, p.Glu191Gly	NR	11	c.1276G > A, p.Gly426Ser	10	2
	7	*c.787 T > C, p.Try246His*	*SNP*	10	c.1144G > A, p.(Val382Ile)	0.0	1
	9	c.979 T > C, p.Phe327Leu	97.5	9	c.984_986DEL, p.Phe328del	4.5	2
	9	c.979 T > C, p.Phe327Leu	97.5	**12**	**c.1559delT, p.Leu520ArgfsTer86**	0	1
	11	c.1225C > G, p.(Pro409Ala)	37.5	**12**	**c.1559delT, p.Leu520ArgfsTer86**	0	1
	12	c.1354G > A, p.Glu452Lys	4.1	12	c.1356G > A, p.Glu452Glu	ND	1
Unknown (n = 1)	5	c.407G > A, p.(Arg136His)	21.2	**12**	**c.1559delT, p.Leu520ArgfsTer86**	0	1
Total							82

Table 2. *ALPL* pathogenic variants in each clinical type of hypophosphatasia. SNP of "c.787 T > C, p.Tyr246His" is displayed in italics. "c.1559delT, p.Leu520ArgfsTer86" is shown in bold. IVS, intervening sequence; ND, pathogenic variant type was not described; NR, pathogenic variant type was reported but no residual activity was detected; WT, wild type.

Phenotype	n	Autosomal dominant	Autosomal recessive	*P* value
Non-odonto	50	12 (24.0%)	38 (76.0%)	$P = 0.0004^{**}$ ($P < 0.01$)
Odonto	31	20 (64.5%)	11 (35.5%)	
Unknown	1	0 (0%)	1 (100%)	
Total	**82**	**32 (39.0%)**	**50 (61.0%)**	

Table 3. Comparison of inheritance patterns between non-odonto and odonto types of hypophosphatasia.

in the primary teeth ($P = 0.030$) (Fig. 3B). Forty percent of non-odonto type cases (22/55 patients) showed tooth hypomineralization at a significantly higher rate than that found in odonto type cases (8.5%; $P < 0.001$).

Table 5 summarizes malocclusions and treatments for occlusion and dentition in HPP patients. Forty percent of non-odonto type cases (22/55 patients) had malocclusions, compared with only 29.8% of odonto type cases. The most common type of malocclusion was crowding, followed by anterior crossbite in both non-odonto and odonto HPP. Partial dentures were more frequently used in odonto HPP patients than in non-odonto HPP patients for space maintenance. However, the proportion of patients with experience of orthodontic treatment was lower than the experience of partial dentures (10.9% in non-odonto HPP patients and 4.3% in odonto HPP patients).

Table 6 summarizes oral habits and dysphagia associated with HPP. Poor oral habits were more common in non-odonto HPP patients (29.1%) than in odonto HPP patients (12.8%). Finger sucking and tongue thrusting were major oral habits in non-odonto HPP patients. Dysphagia occurred more frequently in non-odonto HPP patients (23.6%) than in odonto HPP patients (10.6%). Swallowing food without chewing and washing food down with drinks were recorded in a quarter of non-odonto HPP patients. For these dysphagias, significantly more non-odonto HPP patients (14.5%) were receiving oral function training than odonto HPP patients (2.1%; $P < 0.05$).

Dental problems	Non-odonto (n = 55)	Odonto (n = 47)
Periodontal condition	32 (58.2%)	
Experience of early exfoliation of primary teeth (before the age of 4 years)	Perinatal severe 15/19 (78.9%) Perinatal benign 4/12 (33.3%)[b]	43 (91.5%)[a]
Loss of permanent teeth	Infantile 5/7 (71.4%)	1 (2.1%)
Deep periodontal pocket (over 4 mm)	Childhood 8/15 (53.3%)[c]	10 (21.3%)
Mobility of teeth	Adult 0/0 (0%) 3 (5.5%) 14 (25.5%) 20 (36.4%)	21 (44.5%)
Tooth		
Hypomineralization	22 (40.0%)	4 (8.5%)[a]
Enamel	2 (3.6%)	0 (0%)
Dentin		
Soft tissue		
Upper labial frenulum	0 (0%)	1 (2.1%)
Lingual frenulum	2 (3.6%)	1 (2.1%)
Others	1 (1.8%)	1 (2.1%)
Eruption disturbances		
Ectopic eruption	4 (7.3%)	0 (0%)
Palate		
High palate	4 (7.3%)	1 (2.1%)
Cleft palate	1 (1.8%)	1 (2.1%)

Table 4. Dental problems associated with hypophosphatasia. [a]The rate of the category is significantly higher than that of another category ($P < 0.001$). [b]The rate of each phenotype is significantly lower than that of another category ($P < 0.01$). [c]The rate of each phenotype is significantly lower than that of another category ($P < 0.05$).

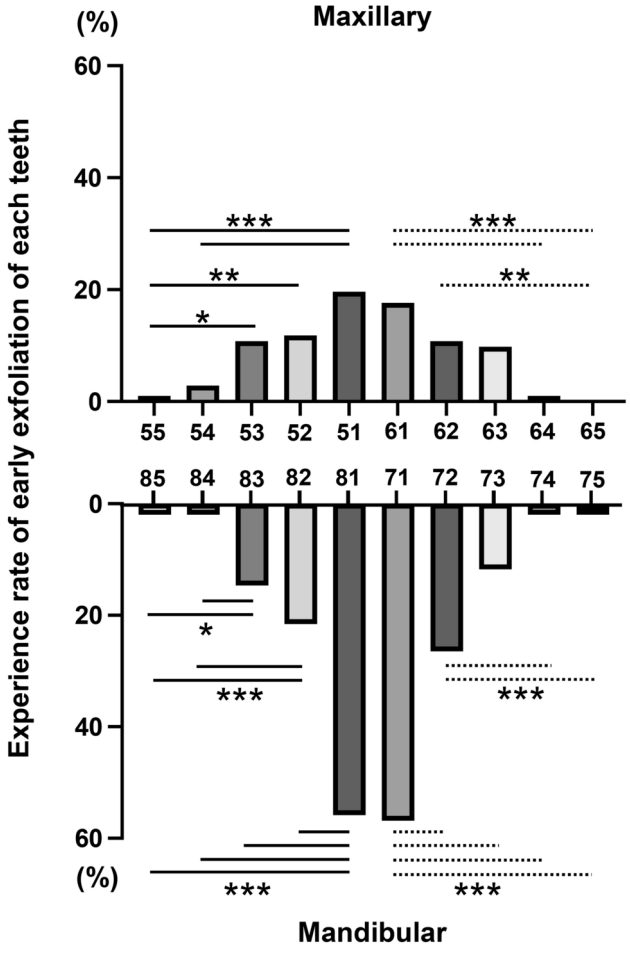

Fig. 2. The sites of early exfoliation of primary teeth. Significant differences were determined using ANOVA with Bonferroni correction. The x-axis indicates the tooth number of the primary tooth in the FDI dental notation system. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, and ****$P < 0.0001$.

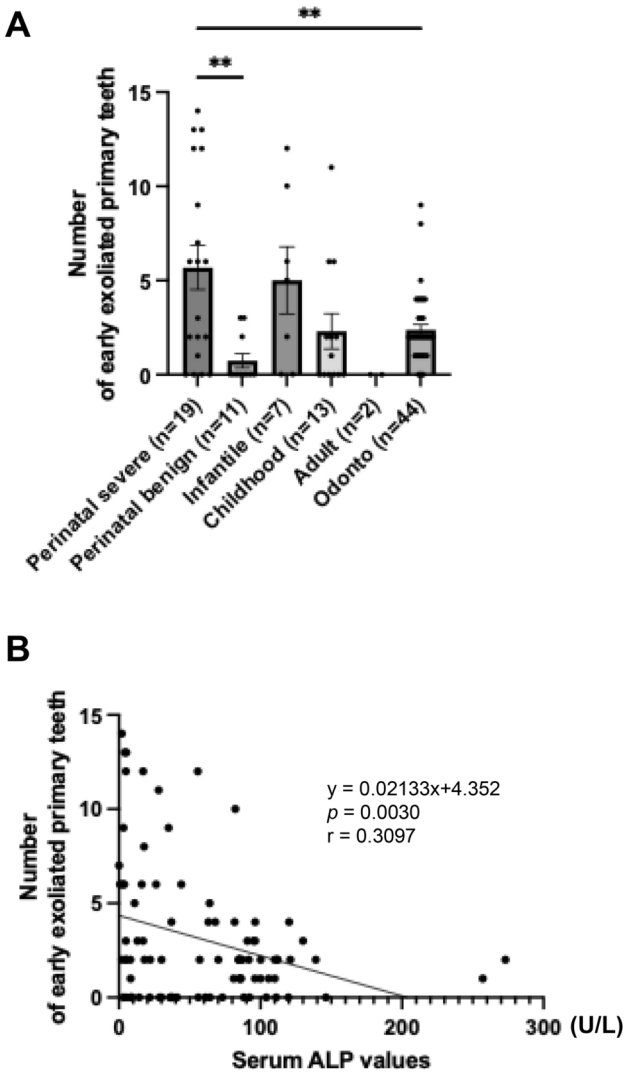

Fig. 3. (**A**) Number of early exfoliated primary teeth in each phenotype of hypophosphatasia (n = 96). Significant differences were determined using ANOVA with Bonferroni correction. $^{**}P < 0.01$. (**B**) Correlation of serum alkaline phosphatase (ALP) value and numbers of early exfoliated primary teeth. A significant negative correlation was found between serum ALP values and the number of early exfoliated primary teeth in patients with hypophosphatasia (correlation coefficient = − 0.3097).

Discussion

The number of respondents increased from 19 cases in seven dental clinics in the first survey 10 years ago, to 52 cases in 23 dental clinics in the second survey 5 years ago, and finally to 103 cases in 43 dental clinics in the current survey. Nine patients were diagnosed with HPP in our clinic in the first survey, 14 patients in the second survey, and 41 patients in the third survey. The number of patients with mild form HPP has increased because of the availability of dental screening for HPP, and ERT has made dental visits possible for patients with severe form HPP[11,12,17–19]. This survey was conducted for the dental sector, and the distribution of the disease types showed that a quarter of the patients had severe form HPP, including perinatal severe and infantile types, whereas half of the patients had odonto type HPP. The frequency is reported to be 1/150,000 for the severe form and 1/6,500 for the mild form[20–22]. It can be concluded that many potential mild cases exist. A limitation of this study is that the initial survey likely did not cover all HPP patients who visited dental clinics. The response rate was approximately 60% and it is possible that some of the clinics that did not respond to the first survey had HPP cases. Another limitation is the reliability of the information presented in the responses. In the second questionnaire, guidelines for school dentist activities presented by the Japan Association of School Dentists were adopted to avoid variations in responses regarding dentition and occlusion.

The age of diagnosis and the age of the first dental examination were almost identical for odonto HPP patients in this study. Patients with non-odonto type HPP were often referred to dental practitioners by medical practitioners, while one-third of odonto HPP patients were diagnosed by dental practitioners. The age of diagnosis of childhood HPP was earlier than that of odonto HPP, although there was no significant difference in serum ALP values at the time of diagnosis of HPP. These factors suggest that dental symptoms appear prior to

	Non-odonto (n = 55)	Odonto (n = 47)
Malocclusions	22 (40.0%)	14 (29.8%)
Maxillary protrusion	2	1
Mandibular protrusion	2	3
Anterior crossbite	3	5
Crowding	9	6
Edge-to-edge bite	2	1
Deep bite	1	1
Open bite	2	1
Diastema	1	0
Posterior crossbite	3	0
Others	1	0
Treatment		
Space maintenance (partial denture)	13 (23.6%)	18 (38.3%)
Orthodontic treatment	6 (10.9%)	2 (4.3%)
Multi-bracket technique	1	0
Orthodontic plate	1	1
Aligner	1	1
Appliance with auxiliary spring	1	0
Other	3	1
Undergoing treatment planning	6	3

Table 5. Malocclusions and treatment for dentition and occlusion in hypophosphatasia.

	Non-odonto (n = 55)	Odonto (n = 47)
Oral habits	16 (29.1%)	6 (12.8%)
Finger sucking	6	2
Tongue thrusting	5	0
Oral breathing	2	1
Lip incompetence	1	0
Low set of tongue	1	0
Bruxism	3	1
Other	4	2
Dysphagia	13 (23.6%)	5 (10.6%)
Swallowing food without chewing	5	1
Washing food down with drinks	6	3
Sticking tongue out when eating	2	0
Difficulty swallowing and food accumulating in mouth	3	1
Chewing sound	0	1
Eating with mouth open	1	0
Other	3	2
Training	8 (14.5%)	1 (2.1%)[a]
Lip training	1	1
Tongue exercises	2	0
Dysphagia rehabilitation	4	0
Diet guidance	2	0
Other	1	0

Table 6. Poor oral habits and dysphagia associated with hypophosphatasia. [a]The rate of each phenotype is significantly lower than that of another category ($P < 0.05$).

systemic symptoms in mild form HPP. Studies have reported that as age increases, symptoms spread throughout the body[23,24]. Dental practitioners should detect HPP early to facilitate diagnosis and growth management by a pediatrician.

Seventy percent of odonto HPP patients in this study showed an AD inheritance pattern. Pathogenic variants of "Arg167Trp" (c.550C > T, p. Arg184Trp in exon 6) were detected in 30% of odonto HPP cases with heterozygous

pathogenic variants. This pathogenic variant was previously reported to have dominant negative effects[25]. Compound heterozygous or homozygous pathogenic variants were recognized in all severe type HPP cases (perinatal severe and infantile types). Eighty percent of severe form HPP patients had one or two "c.1559delT" pathogenic variants. The most frequent "c.1559delT" pathogenic variant, carried by 1/450 of general Japanese population, results in complete loss of enzymatic activity[20,21,26,27]. The percentage of compound heterozygote pathogenic variants with the "c.1559delT" variant in one allele was similar in the childhood and odonto types of HPP. In odonto HPP patients with compound heterozygous pathogenic variants, the TNSALP mutant from at least one of the alleles might have residual enzymatic activity. We consider that odonto HPP at diagnosis may change into childhood or adult type HPP during later life, and that the clinical classification of HPP is part of a continuous spectrum, with the laboratory data of odonto HPP overlapping with that of other mild forms[28]. Notably, odonto HPP with compound heterozygous pathogenic variants, especially "c.1559delT" on one side, should be carefully monitored for systemic symptoms.

The most common dental manifestation of HPP, early exfoliation of primary teeth before the age of 4 years, was significantly less common in non-odonto type HPP than in odonto HPP. However, there was a significant difference in the number of early exfoliated teeth between perinatal severe HPP and odonto HPP. There was a significant tendency for the number of early exfoliated primary teeth to decrease with increasing ALP values in primary teeth. All the patients with severe form HPP received ERT soon after diagnosis, suggesting that ERT cannot prevent early exfoliation of primary teeth in severe form HPP[29]. This study revealed that early exfoliation of primary teeth occurs predominantly in the incisors. The formation of the primary incisors begins at week 7 of fetal life and is complete at 1.5 years after birth[30]. Hence, ERT is not expected to affect the primary incisors. A systematic review of 20 articles and two case reports cited three studies that showed a decrease in premature loss of primary teeth[19,31–33]. However, despite general improvements in oral health outcomes, three studies described cases of further loss of primary teeth following the implementation of ERT[32,34,35]. It was apparent the lost teeth had already formed and erupted, and had displayed periodontal compromise in the form of significant mobility prior to ERT[32,35]. In this study, the age at the first and last dental examinations was lower in patients with perinatal severe HPP than in the other phenotypes. This means that the improved life prognosis of the severe form of the disease with ERT allowed for their dental visits, and patients with severe type HPP who received the therapy from birth are in the eruption phase of the permanent teeth. Further time is needed to evaluate the effects of ERT to the permanent teeth. In this study, hypomineralization of enamel was also revealed as a dental manifestation in non-odonto type HPP. Unlike bone, teeth consist of hard tissues that do not remodel[36]. ERT may not have the same effect on teeth as it does on bone in improving mineralization. Prosthetic treatment should be considered to protect the tooth structure in cases of severe hypomineralization of the enamel.

In addition to the increase incidence of severe form HPP, the number of cases of mild form HPP has increased because of increased awareness and recognition of this disease in Japan. Abnormalities in the occlusion and dentition of HPP patients based on severity need to be identified and dental approaches should be developed. In this survey, 40.0% of patients with non-odonto type HPP exhibited malocclusion, which was higher than that found for odonto type HPP. Causes of malocclusion include general dental and jawbone problems. Dental symptoms specific to HPP such as early disturbed formation of cementum or jaw malformation are thought to be the cause of malocclusions[17]. Crowding was the most frequently detected malocclusion in both odonto and non-odonto HPP. We suggest that crowding is caused by space loss from the early loss of primary teeth or a small jawbone. As space maintenance for the early exfoliation of primary teeth, the use of partial dentures is strongly recommended[11]. However, the use of partial dentures in non-odonto type HPP is lower than that of odonto type HPP, even though many teeth are missing. Severe type HPP is sometimes accompanied by intellectual disability[37], which may make the use of dentures problematic. The multi-bracket technique, a typical orthodontic treatment method, applies a strong force to the teeth and uses the mechanism of bone metabolism to move the teeth. Orthodontic treatment in HPP patients should be undertaken with caution because of their fragile periodontal tissues[9,11,38]. Orthodontic treatment for HPP patients may be limited because of concerns about bonding brackets to hypomineralized enamel and the risk of damaging enamel when brackets are removed. However, we found no case reports about orthodontic treatment for HPP patients. The bone disease X-linked hypophosphatemia (XLH) is known to occur more frequently than HPP. Conventional medical therapy (a combination of active vitamin D and oral phosphate) is considered essential for orthodontic treatment of patients with XLH because tooth movement is accompanied by bone remodeling[39]. In patients with HPP, orthodontic treatment should be carefully considered and planned based on the severity of the phenotype and malocclusion. Additional clinical evidence and insights are necessary for the effective orthodontic management of malocclusion in HPP patients.

We focused on the association between poor oral habits and dysphagia and HPP, given that we could find no surveys or case reports addressing this topic. We found that 30.0% of non-odonto type patients had poor oral habits, which was higher than the rate in odonto type patients. Finger sucking was most common in non-odonto type HPP patients. Finger sucking transmits significant force to the anterior teeth, leading to inclination of the teeth in healthy children. In HPP patients with fragile periodontal tissues, excessive force on the anterior teeth may lead to exfoliation. Tongue thrusting was also commonly observed, possibly caused by the loss of the primary incisors. When primary incisors are missing and a space is made between the upper and lower jaws, the tongue must move forward into the space to create negative pressure in the oral cavity when swallowing food[11,40]. Moreover, one-fourth of non-odonto type HPP patients had dysphagia, which was a higher frequency than that of odonto type patients. Hofmann et al. reported dysphagia and recurrent vomiting in severe type HPP patients accompanied by profound muscular hypotonia with markedly delayed neuromotor skills[41]. Muscle weakness with hypotonia and neurologic complications have been reported as one of the clinical features of HPP[42]. We consider that these muscle and neurologic manifestations of the oral and maxillofacial region cause dysphagia.

The non-odonto type HPP patients also received more training, including swallowing rehabilitation, than odonto type HPP patients. These findings indicate the need for oral function training based on the severity of HPP.

Conclusion

The improvement in life expectancy with ERT and increased awareness of HPP among pediatric oral health professionals has led to an increase in dental visits by HPP patients. In non-odonto type HPP, in addition to the early exfoliation of primary incisors, enamel dysplasia was observed. The proportion of cases with abnormal occlusion that underwent orthodontic treatment was found to be low, possibly because of their fragile periodontal tissues and cementum dysplasia. Poor oral habits and dysphagia, which were frequently observed in this study, may be induced by the loss of primary incisors. This result suggests the need to recommend not only the use of partial dentures but also evaluation of oral function and oral function training in HPP patients. Patients with HPP require multidisciplinary care and the cooperation of dental specialists in diagnostics and treatment.

Materials and methods

Collection of clinical records of patients with HPP

A nationwide survey was conducted to analyze the oral manifestations of patients diagnosed with HPP. A total of 609 dental clinics among general hospitals with dentistry departments, including 28 university dental hospitals with departments of pediatric dentistry, were invited to participate in this study. The clinics were sent questionnaires by mail about the number of HPP cases encountered over a recent 5-year period, from 2018 to 2022 (Supplementary Fig. 1). Upon receipt of responses indicating that clinics had treated HPP cases, a second questionnaire requesting information about the clinical dental findings of each HPP case was sent by mail (Supplementary Fig. 2). Additionally, clinical records of 41 HPP patients who had presented to our clinic were collected. All responses were based on medical records.

Clinical analysis

The second questionnaire (Supplementary Fig. 2) was evaluated and recorded in terms of chronological age at the time of the initial and final examinations, sex, phenotype, medical information at diagnosis (chronological age at diagnosis, serum ALP value [IFCC: International Federation of Clinical Chemistry and Laboratory Medicine methods], urinary phosphoethanolamine, *ALPL* pathogenic variants), family medical and dental histories, systemic abnormalities, treatment with ERT, the reason for the patient's visit to the dental clinic, collaboration with medical and dental practitioners, the presence of early exfoliation of primary and permanent teeth (positions and age at loss), other dental abnormalities (periodontal condition, hard and soft tissue condition, eruption), dentition and occlusion (malocclusions, palate morphology, and experience of denture use), poor oral habits, feeding processes, feeding/swallowing functional training, orthodontic treatment, and height and weight. Phenotypes were classified into six clinical disease forms of HPP (perinatal severe, perinatal benign, infantile, childhood, adult, and odonto)[6,7]. Non-odonto types included five phenotypes (perinatal severe, perinatal benign, infantile, childhood, adult). Residual activity of each *ALPL* pathogenic variant was obtained at the ALPL gene variant database (https://alplmutationdatabase.jku.at/table/, accessed on 5 August 2024).

Ethical considerations

The study protocol was approved by the ethics committee of the Osaka University Graduate School of Dentistry (approval number R4-E31), and the study was conducted in accordance with the Declaration of Helsinki (64th World Medical Association General Assembly, Fortaleza, Brazil, 2013). All data were completely anonymized before being accessed for this study. The ethics committee waived the requirement to obtain informed consent from patients. This was a retrospective observational study completed by attending dentists using only existing medical records. Informed consent was obtained from the responding dentists through an opt-out process on our hospital website.

Statistical analysis

Statistical analyses were conducted using GraphPad Prism 10 (GraphPad Software Inc., La Jolla, CA, USA). Intergroup differences of serum ALP values were analyzed using analysis of variance (ANOVA) with Bonferroni correction. Results were considered significantly different at $P < 0.05$. Fisher's exact test was also used to analyze differences between groups in terms of inheritance patterns, dental conditions, and the early exfoliation of primary teeth. Pearson's correlation analysis was performed to find the correlation between serum ALP values and the early exfoliation of primary teeth.

Data availability

The data extracted from the included studies and the data used for the analyses are available upon request from the corresponding author.

Received: 13 September 2024; Accepted: 18 February 2025
Published online: 25 February 2025

References

1. Mornet, E. Hypophosphatasia. *Best Pract. Res. Clin. Rheumatol.* **22**, 113–127 (2008).
2. Whyte, M. P. Hypophosphatasia: An overview for 2017. *Bone.* **102**, 15–25 (2017).

3. Whyte, M. P. Hypophosphatasia - aetiology, nosology, pathogenesis, diagnosis and treatment. *Nat. Rev. Endocrinol.* **12**, 233–246 (2016).
4. Millán, J. L. & Whyte, M. P. Alkaline Phosphatase and Hypophosphatasia. *Calcif. Tissue Int.* **98**, 398–416 (2016).
5. Mornet, E. Hypophosphatasia. *Orphanet J. Rare Dis.* **2**, 40 (2007).
6. Whyte, M. P. et al. Hypophosphatasia: Validation and expansion of the clinical nosology for children from 25 years experience with 173 pediatric patients. *Bone.* **75**, 229–239 (2015).
7. Michigami, T. et al. Clinical practice guidelines for hypophosphatasia. *Clin. Pediatr. Endocrinol.* **29**, 9–24 (2020).
8. Whyte, M. P., Wenkert, D. & Zhang, F. Hypophosphatasia: Natural history study of 101 affected children investigated at one research center. *Bone.* **93**, 125–138 (2016).
9. Bloch-Zupan, A. Hypophosphatasia: Diagnosis and clinical signs - a dental surgeon perspective. *Int. J. Paediatr. Dent.* **26**, 426–438 (2016).
10. Okawa, R., Kadota, T., Matayoshi, S. & Nakano, K. Dental manifestations leading to the diagnosis of hypophosphatasia in two children. *J. Dent. Child. (Chic)* **87**, 179–183 (2020).
11. Okawa, R. & Nakano, K. Dental manifestation and management of Hypophosphatasia. *Jpn. Dent. Sci. Rev.* **58**, 208–216 (2022).
12. Okawa, R., Nakano, K., Matsumoto, M., Kawabata, K. & Ooshima, T. Oral manifestations of patients with hypophosphatasia. *Ped. Dent. J.* **22**, 155–162 (2012).
13. Whyte, M. P. et al. Enzyme-replacement therapy in life-threatening hypophosphatasia. *N. Engl. J. Med.* **366**, 904–913 (2012).
14. Okazaki, Y. et al. Lethal hypophosphatasia successfully treated with enzyme replacement from day 1 after birth. *Eur. J. Pediatr.* **175**, 433–437 (2016).
15. Kitaoka, T. et al. Safety and efficacy of treatment with asfotase alfa in patients with hypophosphatasia: Results from a Japanese clinical trial. *Clin. Endocrinol. (Oxf)* **87**, 10–19 (2017).
16. Whyte, M. P. et al. Asfotase alfa treatment improves survival for perinatal and infantile hypophosphatasia. *J. Clin. Endocrinol. Metab.* **101**(1), 334–342 (2016).
17. Okawa, R. et al. Japanese nationwide survey of hypophosphatasia reveals prominent differences in genetic and dental findings between odonto and non-odonto types. *PLOS ONE.* **14**, e0222931 (2019).
18. Michigami, T. et al. Hypophosphatasia in Japan: ALPL mutation analysis in 98 unrelated patients. *Calcif. Tissue Int.* **106**, 221–231 (2020).
19. Okawa, R., Kokomoto, K., Yamamura-Miyazaki, N., Michigami, T. & Nakano, K. Oral findings in patient with lethal hypophosphatasia treated with enzyme replacement therapy. *Ped. Dent. J.* **27**, 153–156 (2017).
20. Watanabe, A. et al. Prevalence of c.1559delT in ALPL, a common mutation resulting in the perinatal (lethal) form of hypophosphatasia in Japanese and effects of the mutation on heterozygous carriers. *Hum. Genet.* **56**, 166–168 (2011).
21. Ozono, K. & Michigami, T. Hypophosphatasia now draws more attention of both clinicians and researchers: A commentary on Prevalence of c. 1559delT in ALPL, a common mutation resulting in the perinatal (lethal) form of hypophosphatasias in Japanese and effects of the mutation on heterozygous carriers. *J. Hum. Genet.* **56**(174), 176 (2011).
22. Mornet, E., Yvard, A., Taillandier, A., Fauvert, D. & Simon-Bouy, B. A molecular-based estimation of the prevalence of hypophosphatasia in the European population. *Ann. Hum. Genet.* **75**, 439–445 (2011).
23. Mori, M., DeArmey, S. L., Weber, T. J. & Kishnani, P. S. Case series: Odontohypophosphatasia or missed diagnosis of childhood/adult-onset hypophosphatasia? - Call for a long-term follow-up of premature loss of primary teeth. *Bone Rep.* **5**, 228–232 (2016).
24. Okawa, R., Kokomoto, K. & Nakano, K. Dental effects of enzyme replacement therapy in case of childhood-type hypophosphatasia. *BMC Oral. Health.* **21**, 323 (2021).
25. Lia-Baldini, A. S. et al. A molecular approach to dominance in hypophosphatasia. *Hum. Genet.* **109**, 99–108 (2001).
26. Orimo, H. et al. Importance of deletion of T at nucleotide 1559 in the tissue-nonspecific alkaline phosphatase gene in Japanese patients with hypophosphatasia. *J. Bone Min. Metab.* **20**, 28–33 (2002).
27. Michigami, T. et al. Common mutations F310L and T1559del in the tissue-nonspecific alkaline phosphatase gene are related to distinct phenotypes in Japanese patients with hypophosphatasia. *Eur. J. Pediatr.* **164**, 277–282 (2005).
28. Farman, M. R. et al. The Global ALPL gene variant classification project: Dedicated to deciphering variants. *Bone.* **178**, 116947 (2024).
29. Okawa, R., Miura, J., Kokomoto, K. & Nakano, K. Evaluation of avulsed primary incisor in 3-year-old girl with hypophosphatasia who received enzyme replacement therapy. *Ped. Dent. J.* **28**, 136–140 (2018).
30. Schour, I. & Massler, M. The development of the human dentition. *J. Am. Dent. Assoc.* **28**, 1153–1160 (1941).
31. Smart, G., Jensen, E. D., Poirier, B. F. & Sethi, S. The impact of enzyme replacement therapy on the oral health manifestations of hypophosphatasia among children: A scoping review. *Eur. Arch. Paediatr. Dent.* **24**(4), 429–440 (2023).
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. *Clin. Case Rep.* **8**(5), 911–918 (2020).
33. Schroth, R. J., Long, C., Lee, V. H. K., Alai-Towfigh, H. & Rockman-Greenberg, C. Dental outcomes for children receiving asfotase alfa for hypophosphatasia. *Bone.* **152**, 116089 (2021).
34. Whyte, M. P. et al. Asfotase alfa for infants and young children with hypophosphatasia: 7 year outcomes of a single-arm, open-label, phase 2 extension trial. *Lancet Diabetes Endocrinol.* **7**(2), 93–105 (2019).
35. Takagi, M. et al. Odontohypophosphatasia treated with asfotase alfa enzyme replacement therapy in a toddler: A case report. *Clin. Pediatr. Endocrinol.* **29**(3), 115–118 (2020).
36. Wölfel, E. M. et al. Effects of infantile hypophosphatasia on human dental tissue. *Calcif. Tissue. Int.* **112**, 308–319 (2023).
37. Taketani, T. Neurological symptoms of hypophosphatasia. *Subcell. Biochem.* **76**, 309–322 (2015).
38. Hamada, M. et al. Ankylosed primary molar in a japanese child with hypophosphatasia. *Dent. J. (Basel)* **9**, 3 (2020).
39. Haffner, D. et al. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. *Nat. Rev. Nephrol.* **15**, 435–455 (2019).
40. Kydd, W. L., Akamine, J. S., Mendel, R. A. & Kraus, B. S. Tongue and lip forces exerted during deglutition in subjects with and without an anterior open bite. *J. Dent. Res.* **42**, 858–866 (1963).
41. Hofmann, C. et al. Unexpected high intrafamilial phenotypic variability observed in hypophosphatasia. *Eur. J. Hum. Genet.* **22**, 1160–1164 (2014).
42. Kishinani, P. S. et al. Monitoring guidance for patients with hypophosphatasia treated with asfotase alfa. *Mol. Genet. Metab.* **122**, 4–17 (2017).

Acknowledgements

This research was supported by a grant from JSPS (Japan Society for the Promotion of Science) KAKENHI, grant number 24K02651. We also thank Helen Jeays, BDSc, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Author contributions

R.O. conceptualization, data curation, formal analysis, resources, visualization, writing – original draft. T.Ka. investigation, data curation, formal analysis, visualization, writing – review and editing. H.K. conceptualization,

methodology, writing – review and editing. H.N.: data curation, investigation, resources, validation, writing – review and editing. M.O.: data curation, writing – review and editing. Y.O. data curation, writing – review and editing. T.Ku. data curation, investigation, resources, supervision, validation, writing – review and editing. T.Y. supervision, validation, writing – review and editing. K.N. conceptualization, methodology, investigation, resources, writing – review and editing, supervision, project administration.

Funding
This research was funded by a grant from JSPS (Japan Society for the Promotion of Science) KAKENHI, grant number 24K02651. The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Declarations

Competing interests
The authors declare no competing interests.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-91043-7.

Correspondence and requests for materials should be addressed to R.O.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.