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Oral health status of adult hypophosphatasia patients: A cross-sectional study

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Abstract

Aim: This study evaluated the oral health status of adult patients with hypophosphatasia (HPP).

Materials and Methods: Parameters of oral health assessment comprised decayed/missing/filled teeth (DMFT) index, probing pocket depth and clinical attachment level (CAL) as well as documentation of tooth loss and periodontal health status according to CCD/AAP criteria. Findings were compared with national reference data (DMS V survey) reporting oral health status in age-related controls. Within-group comparisons were made between the HPP patients harbouring one versus two alkaline phosphatase liver/bone/kidney type (ALPL) gene variants.

Results: Of 80 HPP patients (64 female) with a mean age of 46.4 years (range 24–78) and one ($n = 55$) or two ($n = 18$) variants ($n = 7$ lacking testing) within the ALPL gene, those with two variants displayed substantially higher tooth loss rate (14.0 ± 9.3) than those affected by only one ALPL variant (4.1 ± 5.4), who did not differ substantially from healthy DMS V controls. While DMFT score and severe periodontal diseases (PDs) of HPP patients with one variant only increased with progressing age, the two-variant sub-cohort age independently exhibited increased DMFT scores and a higher rate of severe PDs.

Conclusions: HPP patients affected by two variants of the ALPL gene exhibited a higher risk of periodontitis and tooth loss than the general population, while patients with one variant developed clinically relevant oral disease symptoms with progressing ageing. Clinicaltrials.gov identifier: NCT02291497.

KEYWORDS
dental status, hypophosphatasia, inflammation, periodontal disease, tooth loss

Clinical Relevance

Scientific rationale for study: This study adds to clarifying the impact of hypophosphatasia (HPP) on oral health and the lifetime risk of orodental issues in subjects with one versus two alkaline phosphatase liver/bone/kidney type (ALPL) variants.

Principal findings: HPP patients with two variants have a considerably higher risk of periodontitis and tooth loss than general population throughout lifetime. Patients with one ALPL gene variant appear to develop dental manifestation with increasing age.

Practical implications: These findings can support dentists to identify traits of HPP in patients with otherwise unexplained PD and to appropriately guide and treat patients with a genetically confirmed diagnosis of HPP.

1 | INTRODUCTION

Hypophosphatasia (HPP) is a rare genetically determined metabolic disease due to genetic variants within the alkaline phosphatase liver/bone/kidney type (ALPL) gene causing impaired activity of the tissue non-specific alkaline phosphatase (TNSALP) (Rockman-Greenberg, 2013; Mornet, 2015). Cases with dominant and recessive inheritance have been described, displaying a wide spectrum of clinical severity. While prevalence of severe forms has been estimated to be around 1/300,000 in Europe and 1/100,000 in North America, recent data suggest that the prevalence of milder form can be as high as 1 of 508 (Bloch-Zupan, 2016; Seefried et al., 2020; Mornet et al., 2021). Among other findings, defective enzyme activity is associated with extracellular accumulation of the substrates inorganic pyrophosphate, phosphoethanolamine and pyridoxal-5′-phosphate (PLP) (Fedde et al., 1999; Orimo, 2010; Mornet, 2015).

Characteristic clinical signs of HPP are associated with disturbances of bone and teeth mineralization (Feeney et al., 2018) including rickets, skeletal deformities, craniosynostosis and atraumatic premature loss of deciduous teeth in severely affected infants (Petkovic Ramadza et al., 2009; Rothenbuhler & Linglart, 2017; Whyte et al., 2019) as well as fractures, chronic bone and muscle pain, physical fatigue and supposed periodontal disease (PD) in adult life (Schmidt et al., 2017; Seefried et al., 2020; Tilden et al., 2020).

Traditional clinical nosology distinguishes five different forms of HPP based on the age at clinical onset of the disease and a separate type with mere dental manifestation, that is, odontohypophosphatasia (Mornet, 2007; Millan & Plotkin, 2012; Whyte et al., 2015). Steadily growing evidence derived from clinical investigations however strongly suggests that dental manifestation is an inherent trait of actually all types of HPP and that in certain instances oral manifestation of HPP could be a leading sign of HPP-related metabolic problems, which may eventually become clinically apparent later in life (Bloch-Zupan & Vaysse, 2017).

Indeed, atraumatic, premature loss of deciduous teeth with root attached and only minimal signs of periodontal inflammation is a key symptom of paediatric forms of HPP (Feeney et al., 2018), characterized by a marked hypoplasia of the acellular extrinsic fibre cementum of the exfoliated teeth (Foster et al., 2012; Rodrigues et al., 2012). Furthermore, the dental hard tissues of HPP patients often exhibit dysplasia and anomalies, due to a reduced expression of dentine matrix proteins and the pathological accumulation of pyrophosphate, impairing mineralization of the dentin matrix (Reibel et al., 2009; Suzuki et al., 2009; Rodrigues et al., 2012). HPP-related accumulation of pyrophosphate is supposed to elicit a chronic tissue-destructive inflammatory response and increases the serum levels of proinflammatory cytokines and the total systemic inflammatory load (Beck, Morbach, Richl, et al., 2009; Beck, Morbach, Stenzel, et al., 2009). Additionally, the reduced activity of TNSALP may impair the protective dephosphorylation of bacterial lipopolysaccharides at the interface between mucosal tissues and bacterial biofilms (Bates et al., 2007; Goldberg et al., 2008; Malo et al., 2010, 2014). Both factors in combination may favour the development of periodontitis-promoting bacterial dysbiosis and periodontal inflammation in a periodontium already affected by HPP-related structural deficits. Due to the rarity of the disease, most available information concerning the susceptibility of HPP patients to oral health problems is based on the evaluation of very small cohorts of HPP patients, inevitably limiting their validity (Kramer et al., 2020).

Accordingly, this cross-sectional study aimed at assessing oral health status and orodental medical history of a large cohort of adult HPP patients with a wide spectrum of clinical disease severity and to compare the results with oral health data of the general population derived from the Fifth German Oral Health Study (DMS V) (A. R. Jordan et al., 2016). In addition, comparative analysis of supposed autosomal-recessive versus autosomal dominant disease was intended to better understand the genotype impact on dental manifestations of HPP.

2 | MATERIALS AND METHODS

This cross-sectional investigation is a sub-study of the "HPP burden of disease" project (Clinical Trials gov identifier: NCT02291497). The study protocol was established in accordance with the declaration of Helsinki and the criteria of good clinical practice. It was approved by the ethics committee of the University of Wuerzburg (file # 166/14). All oral examinations of the study participants were performed between November 2014 and October 2015.

2.1 | Study population

The study participants were recruited among HPP patients being cared for at the Department for Osteology, Orthopaedic Hospital, University of Wuerzburg.

The inclusion criteria were as follows:

- adults (≥18 years) with an established diagnosis of HPP, defined by:
- reduced serum/plasma alkaline phosphatase activity below age and sex, and specific reference ranges (measured at least twice with an interval ≥4 weeks);

- at least one of the following findings:
  - genetically verified variant within the ALPL gene;
  - PLP serum values above the upper limit of normal;
  - manifestation of typical clinical symptoms of HPP.

The exclusion criteria were as follows:

- current or previous alkaline phosphatase enzyme replacement therapy;
- current participation in another clinical study.

All study participants provided written informed consent after comprehensive information about the aims and risks of study participation, before any study-related procedures.

2.2 | Oral examination

2.2.1 | Evaluated parameters

For each study participant, the following parameters were recorded for the complete dentition:

1. Number of natural teeth in situ (excluding third molars).
2. Clinical attachment level (CAL).
3. Probing pocket depth (PPD).
4. Decayed missing filled/tooth (DMFT) index.

CAL and PPD were recorded at six sites per tooth (mesiobuccal, buccal, distobuccal, mesiooral, oral and distooral) using a manual periodontal probe (CP-11; Hu-Friedy, USA).

TABLE 1 Age and sex distribution, age of first deciduous tooth exfoliation

Baseline data	Total HPP cohort ($n = 80$)	Single ALPL variant ($n = 55$)	Two ALPL variants ($n = 18$)	Without genetic testing ($n = 7$)
Mean age ± SD	46.4	43.7	53.6	49.6
Age, SD	±12.3	±11.3	±13.0	±11.2
Median age	45.5	44.0	52.5	51.0
Age				
Q25%	39.0	37.0	45.8	47.0
Q75%	52.0	49.0	60.5	58.0
ALP activity (U/l)	23.8	25.9	19.0	20.4
ALP, SD	±9.6	±8.9	±10.0	±10.1
Sex				
Male	16 (20%)	13 (23.6%)	3 (16.7%)	0 (0%)
Female	64 (80.0%)	42 (76.4%)	15 (83.3%)	7 (100%)
Mean age reported for first deciduous tooth exfoliation	5.1	5.6	3.6	5.0
Age at first deciduous tooth exfoliation, SD	±0.19	±0.36	±0.16	±0.79

Note: Data are presented as mean ± SD and median (25%; 75% quantile) or percentages.
Abbreviations: ALP, Alkaline Phosphatase; ALPL, alkaline phosphatase liver/bone/kidney type; HPP, hypophosphatasia.

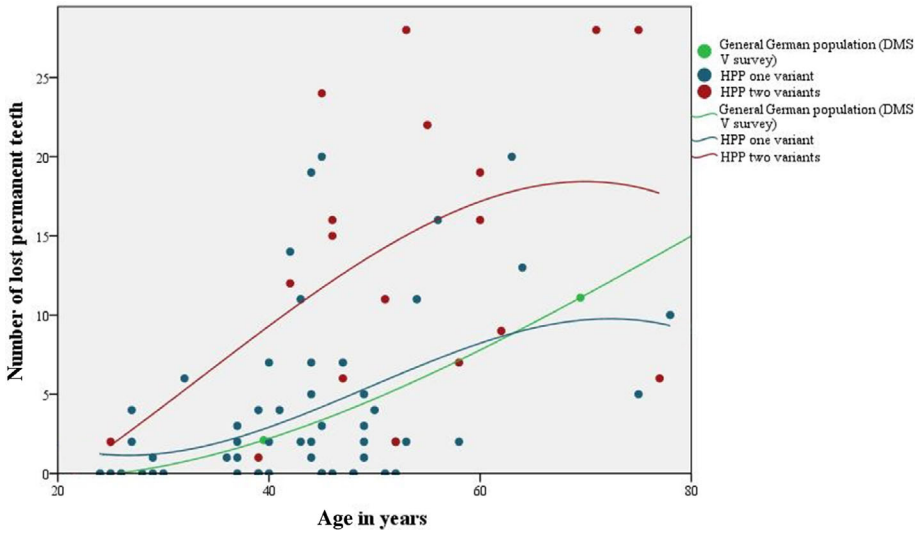

FIGURE 1 Number of lost permanent teeth according to age and number of variants in comparison with general German population (DMS V survey). While data points for DMS V represent available mean values for cohorts, individual patients' data are presented for hypophosphatasia (HPP) groups. The tendency of values with ageing is visualized using moving average trend lines.

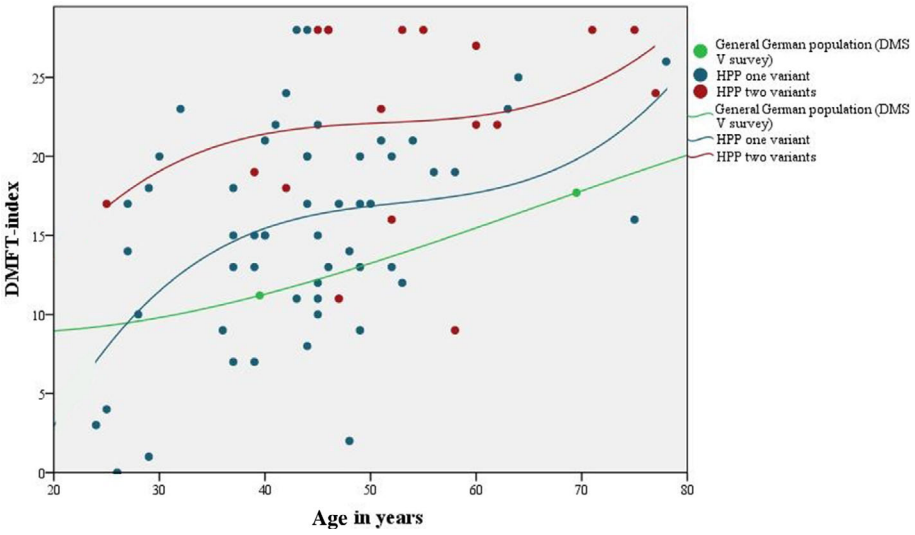

FIGURE 2 Recorded decayed/missing/filled teeth (DMFT)-index scores according to age and number of variants in comparison with general German population (DMS V survey). While data points for DMS V represent available mean values for cohorts, individual patients' data are presented for hypophosphatasia (HPP) groups. The tendency of values with ageing is visualized using moving average trend lines.

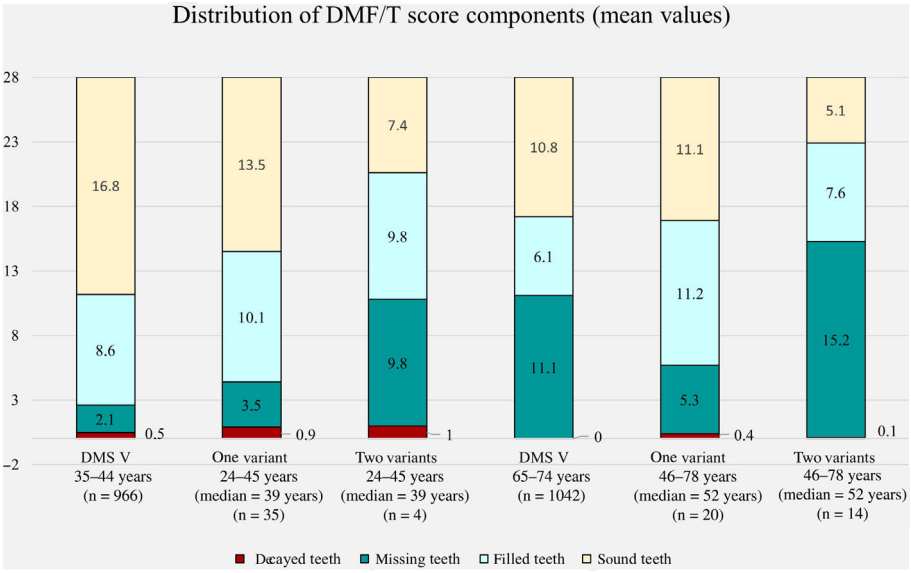

FIGURE 3 Distribution of the individual decayed/missing/filled teeth (DMFT) components decayed teeth, missing teeth, filled teeth and sound teeth in the age subgroups 24–45 years and 46–78 years of both hypophosphatasia (HPP) study groups and in two age-related control groups (35–44 years/65–74 years) of the general German population (DMS V survey)

The extent of tooth loss, tooth decay and fillings was assessed using the DMFT index (Petersen, Baez & Wold Health Organization, 2013).

Recorded CAL and PPD data were used to classify the periodontal health status of the study participants according to a classification established by a working group of the Centers for Disease Control and Prevention (CDC) and the American Academy of Periodontology (AAP) distinguishing (I) mild or no periodontitis, (II) moderate periodontitis and (III) severe periodontitis (Page & Eke, 2007). Serum alkaline phosphatase activity was assessed at the time of enrolment.

2.3 | Data analysis

Descriptive statistical analysis comprised means and SD as well as absolute frequencies and corresponding proportions. Between-group comparisons were made between the HPP patients harbouring one versus two ALPL gene variants. Normal distribution of the data was assessed by the Shapiro–Wilk test. Normally distributed data were subsequently analysed using the *t*-test for independent samples. Data lacking normal distribution were evaluated using the Mann–Whitney *U*-test. The level of significance was set to $p \leq .05$. Inferential statistical analyses and graphical representation of data were performed using Microsoft Excel and the IBM SPSS Statistics 23.0 for Windows software package.

Findings were compared with national German reference data (DMS V survey) reporting oral health status in two age range cohorts of 35–44 years and 65–74 years, respectively (A. R. Jordan et al., 2016; R. A. Jordan, Bodechtel et al., 2014). In order to best match these reference groups, a differential analysis of the HPP patient cohort was conducted, distinguishing younger (up to 45 years) and senior adults (>46 years).

TABLE 2 Detailed periodontal data, including percentage of affected sites with probing pocket depth (PPD)/clinical attachment level (CAL) above defined severity thresholds and severity variables according to (Holtfreter et al., 2015)

	Age, years	Total HPP cohort	One genetic variant	Two genetic variants
Percentage of sites/mouth with CAL ≥ 3 mm (%)	24–45	41.5 (±23.1)	39.1 (±22.0)	62.1 (±28.3)
	46–78	63.1 (±26.6)	54.9 (±26.3)	76.8 (±19.4)
	Total	51.7 (±26.9)	44.8 (±24.6)	72.6 (±22.2)
Percentage of sites/mouth with CAL ≥ 5 mm (%)	24–45	6.9 (±18.2)	4.1 (±10.2)	33.0 (±45.3)
	46–78	18.7 (±22.4)	13.1 (±18.6)	23.9 (±15.0)
	Total	12.5 (±21.0)	7.3 (±14.3)	26.5 (±25.4)
Percentage of sites/mouth with PPD ≥ 4 mm (%)	24–45	3.7 (±6.8)	3.5 (±7.2)	6.4 (±4.2)
	46–78	10.3 (±16.1)	6.8 (±13.3)	11.3 (±10.7)
	Total	6.8 (±12.5)	4.7 (±9.8)	9.9 (±9.4)
Percentage of sites/mouth with PPD ≥ 6 mm (%)	24–45	0.7 (±2.0)	0.6 (±2.0)	1.6 (±1.9)
	46–78	2.5 (±6.4)	1.5 (±4.0)	1.8 (±3.3)
	Total	1.6 (±4.7)	0.9 (±2.9)	1.7 (±2.9)
Percentage of teeth/mouth with CAL ≥ 3 mm (%)	24–45	22.1 (±22.9)	22.2 (±23.8)	22.9 (±19.9)
	46–78	40.0 (±21.5)	36.0 (±18.3)	51.0 (±21.2)
	Total	30.6 (±23.8)	27.1 (±22.8)	43.0 (±24.0)
Percentage of teeth/mouth with CAL ≥ 5 mm (%)	24–45	8.3 (±20.6)	4.7 (±13.6)	39.9 (±42.9)
	46–78	21.2 (±24.6)	16.2 (±21.2)	26.7 (±19.2)
	Total	14.4 (±23.3)	8.9 (±17.5)	30.4 (±26.8)
Percentage of teeth/mouth with PPD ≥ 4 mm	24–45	10.6 (±15.1)	9.4 (±14.3)	22.5 (±20.3)
	46–78	17.5 (±19.3)	15.2 (±15.6)	26.2 (±26.6)
	Total	13.9 (±17.4)	11.5 (±14.9)	25.2 (±24.3)
Percentage of teeth/mouth with PPD ≥ 6 mm	24–45	2.5 (±7.7)	2.1 (±7.7)	6.5 (±8.9)
	46–78	9.3 (±21.1)	4.8 (±12.4)	8.4 (±13.9)
	Total	5.7 (±15.8)	3.1 (±9.6)	7.8 (±12.3)

Note: Data are presented as mean (±SD).
Abbreviation: HPP, hypophosphatasia.

3 | RESULTS

3.1 | Baseline characteristics

Overall data included dental status from 80 HPP patients, 64 of whom were female. Genotype was available for 73 subjects with 55 of them having a single ALPL variant and 18 exhibiting two variants within the ALPL gene, while in seven persons without genetic testing, diagnosis was based on clinical and laboratory data. Average patient age in the overall cohort was 46.4 years (±12.3) with a slight imbalance towards higher age in the cohort of patients with two variants (53.6 ± 13.0 years) as compared with those with one genetic variant (43.7 ± 11.3 years). Average patient-reported age at first deciduous tooth exfoliation was 5.6 years (±0.36) in those patients with one variant but only 3.6 years (±0.16) in the group with two variants. Details regarding age and sex distribution within the overall cohort and the two genotype groups are provided in Table 1.

3.2 | Number of lost permanent teeth

The number of lost permanent teeth in the overall cohort was 6.7 ± 8.1. Progressive loss of permanent teeth with ageing in the single ALPL variant group appeared largely similar to the findings reported for the general population. By contrast, tooth loss in the group with two variants was 14.0 ± 9.3 and significantly higher than those with one ALPL variant with 4.1 ± 5.4 ($p < .001$). Compared with the single-variant HPP group and the general population, tooth loss rate was substantially elevated across all age groups for those HPP patients harbouring two ALPL variants. Loss of permanent teeth for the different groups in correlation to ageing is shown in Figure 1.

3.3 | DMFT index

Average DMFT index in the overall HPP cohort was 17.0 (±7.4). Particularly, HPP patients with two variants and supposed autosomal-

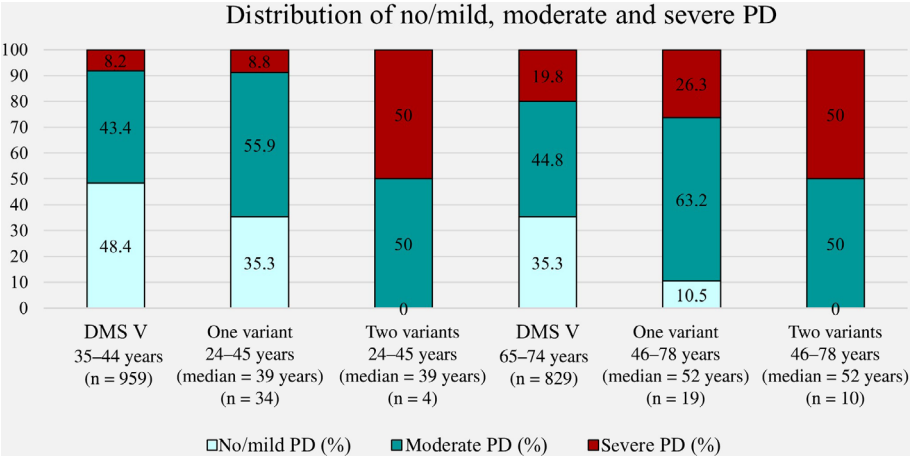

FIGURE 4 Periodontal disease (PD) severity according to Centers for Disease Control and Prevention/American Academy of Periodontology case definition of periodontitis reflecting age and number of alkaline phosphatase liver/bone/kidney type variants in comparison with the general German population (DMS V)

recessive disease exhibited significantly worse DMFT index values (22.4 ± 6.2) across all age groups compared with both, HPP patients with one variant (15.3 ± 6.7) ($p = .003$) and DMS V reference data. Specifically, for those HPP patients with one ALPL variant at younger age, index values (DMFT 14.5) were only slightly elevated compared with the age-related DMS V reference cohort (DMFT 11.2), whereas with progressing ageing, values deteriorated, eventually approximating the results obtained in those patients with two variants. The results of the DMFT assessment are shown graphically in Figure 2.

Regarding specific components of the DMFT index at different age groups revealed overall worse values with progressing age for all cohorts, that is, the DMS V reference population and HPP patients with one or two variants. In all groups, this was predominantly due to an increase in the number of missing teeth (MT). Similarly, inferior scores in those patients with two ALPL variants were predominantly attributable to an increased rate of MT both at younger (9.8 vs. 2.1) and at higher age (15.2 vs. 11.1). Conversely, in the age range of 24–45 years, untreated caries represented by the D component of the DMFT index were about twice as prevalent in the HPP study participants, almost irrespective of the number of variants (one variant decayed teeth [DT] = 0.9 ± 0.3, two variants DT = 1.0 ± 0.7) when compared with 35–44-year-old controls of the general German population (DT = 0.5). For the 46–78 years age range group, the proportion of the D component was considerably smaller with no obvious differences between HPP study participants with one or two variants or between both of them versus healthy DMS V-based controls aged 65–74. Figure 3 illustrates the distribution of the individual DMFT components for the age groups 24–45 years and 46–78 years of the study participants compared with partially age-matched groups from the DMS V cohort.

3.4 | Periodontal health according to CDC/AAP case definition of periodontitis

The periodontal health status according to the CDC/AAP case definition of periodontitis could be calculated for 74 of the 80 study patients based on their recorded CAL and PPD scores. Three patients were completely toothless and three more felt uncomfortable with the test and declined to have it done. Detailed results following established recommendations (Holtfreter et al., 2015) are provided in Table 2. In addition, Figure 4 depicts a comparison of the findings with data from the DMS V cohort.

In HPP study patients with two variants, severe PD was highly prevalent in both the younger age sub-cohort ranging from 24 to 45 years and in the older age group 46–78 years. Conversely, in those with only one ALPL variant, periodontal health status in the 35–44-year-old was similar to the periodontal status in controls from the national reference population (DMS V survey data). However, at older age in the HPP sub-cohort aged 46–78 years with one variant, PD was considerably more frequent with 89.5% of them exhibiting moderate or severe periodontitis, which is much higher than what is documented for controls from the reference population at 65–74 years of age (64.6%).

Comparing HPP patients with no/mild, moderate and severe PD revealed a trend to lower residual Alkaline Phosphatase activity levels with increased PD severity, but this was not statistically significant ($p = .244$).

4 | DISCUSSION

Orodental manifestations are considered an inherent aspect of the phenotypic picture of HPP. Still, systematic data regarding the clinical presentation of HPP associated oral signs and symptoms specifically in adults are scarce. Considering the high proportion of HPP patients with dental manifestations on the one hand and the well-known diagnostic delay specifically regarding the identification of adult patients with HPP (Högler et al., 2019), expanding the knowledge and awareness of dental manifestations of the disease appears pivotal to improving that situation.

Accordingly, this study provides an overview of oral health status and common findings in adult HPP patients, covering a wide range of clinical disease severity. The results of this study confirms that early loss of primary teeth at an average age of 3.6 years is a typical finding

in autosomal-recessive disease (Bloch-Zupan & Vaysse, 2017; Hughes et al., 2017), while patients with only one genetic variant only lost their first tooth at an average age of 5.6 years, that is, heterozygous HPP patients in this study did not experience early exfoliation of primary teeth, which is a hallmark of odonto HPP. Conversely, dental manifestation in heterozygous HPP patients included here mainly consisted of PD.

Further, this study substantiates the perception (Bloch-Zupan, 2016; Okawa et al., 2019) that ALPL variants on both alleles are associated with an increased prevalence of missing permanent teeth even in adult HPP patients across all age groups. However, it is not discernible from available information if individual teeth are missing due to an increased rate of periodontal issues causing tooth loss or a consequence of more frequent extractions of DT. Conversely, tooth loss is not a generalized finding in adult HPP patients with only one ALPL variant, specifically at younger adult age, but it appears that with progressing age, their overall dental health status deteriorates disproportionately in comparison to the reference cohort. This is reflected in both the DMFT score and the periodontal health assessment according to CDC/AAP case definition of periodontitis. DMFT index in the single ALPL variant HPP patients at higher age approached score values similar to those observed in the group with two variants. Similarly, the proportion of patients with moderate or severe PD was substantially higher in the single ALPL-variant cohorts compared with the general population. While this increased rate of PD is already obvious in the younger patient cohort (24–45 years) as compared with 35–44-year-old persons from the general population, the difference becomes even more pronounced in the higher age (46–78 years) single ALPL-variant cohort compared with 65–74 years old from the general population. In that regard, the results also confirm that PD is critical in severe HPP, that is, in patients with two variants, with 100% of them exhibiting moderate to severe PD in all age groups.

In contrast to imputations made in previous manuscripts regarding an increased susceptibility of HPP patients for tooth decay (Mornet, 2007), results of this evaluation do not suggest a major caries problem in HPP patients as compared with the situation in the general population. The higher number of MT found in HPP patients may rather be attributed to the increased prevalence of severe PD documented in this study. While an elevated risk of periodontitis development in HPP patients affected by two variants has already been reported by other authors (van den Bos et al., 2005; Beck, Morbach, Richl, et al., 2009; Beck, Morbach, Stenzel, et al., 2009; Reibel et al., 2009; Rodrigues et al., 2012; Okawa et al., 2019), the increased prevalence of severe and moderate periodontitis in individuals harbouring only one variant in an ALPL gene, as detected by this investigation, has been unknown so far. Indeed, our data actually expand the perception of heterozygous HPP reflecting mainly odonto-type HPP with early exfoliation of primary teeth. Conversely, heterozygous HPP can also manifest primarily with pain and musculoskeletal symptoms in adulthood without premature loss of primary teeth. However, following data reported here, even those patients with only one ALPL variant require lifelong diligent dental care specifically for an increased risk of PD with progressing age.

The underlying mechanisms for this observation, however, remains elusive. In contrast to HPP patients with two variants, the physiological formation of root cementum and other structural elements of the periodontium appears unaltered in individuals affected by only one variant. Subtle long-term impairments of alkaline phosphatase enzyme activity however may already suffice to increase the total systemic inflammatory load by means of a chronic systemic increase of proinflammatory metabolites and theweakening of the mucosal barrier function, which in return may both favour the initiation of a periodontitis-promoting dysbiosis within the oral microbiota (Hajishengallis, 2015). In that regard, dentists play a key role regarding raising a suspicion and triggering further specific diagnostic steps in adults with otherwise unexplained PD.

There are certain limitations to this study that must be kept in mind when interpreting the results. Importantly, this study provides unprecedented, quantitated data on dental manifestation and PD in a large cohort of HPP patients, while comparisons of the study data with the DMS V cohort should only be considered a first attempt to compare HPP patients with controls from the general population. In that regard, a specific, age- and sex-matched control group would have been a better option, but this was beyond the scope of the current study. In addition, the patient group investigated here is derived from a cohort of patients seeking care at the orthopaedic clinic and may thus not be representative of the general HPP population, specifically since the cohort under scrutiny did not comprise any so-called odonto-HPP patients.

Assessments underlying this study were accomplished before ERT was approved, so none of the participants had been treated with asfotase alfa. Available paediatric data suggest that ERT may to some extent improve dental status in children (Kiselnikova et al., 2020; Okawa et al., 2020) but there are not any clinical data to speculate if and how ERT might be beneficial for orodental HPP manifestation in adults.

However, findings and results presented here should help guide clinical care for patients with HPP and should also be considered fundamental for forthcoming, more detailed scientific evaluations of adult dental HPP manifestations.

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CONFLICT OF INTEREST

LS has received honoraria for lectures and advice from Alexion/AstraZeneca, Amgen, KyowaKirin, Lilly, Medi, MSD, Novartis, Theramex and UCB, research grants to the institution (University of Wuerzburg) from Alexion, Kyowa Kirin and Novartis. MW and US report no conflict of interest during the course of the study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was approved by the ethics committee of the University of Wuerzburg (file #166/14).

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