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Periodontal status in children with primary immunodeficiencies

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Abstract

Objective: This study aimed to assess associations between neutrophil-related primary immunodeficiencies (PIDs) and the presence of periodontal disease and other oral diseases and response to periodontal treatment.

Background: Presence of neutrophil-related PIDs is thought to be a major risk factor for development of periodontitis.

Methods: This study had both a cross-sectional and cohort design. Twenty-four children (age 4–16) with PIDs and 24 age-matched systemically healthy subjects received a dental clinical examination, including measures of probing pocket depths (PPD), clinical attachment loss (CAL) and bleeding on probing (BOP). Those found to be affected by periodontal disease were offered periodontal treatment and reassessed 6 months later.

Results: Diagnosis of PIDs was associated with increased odds of presence of periodontal disease (p = .008 adjusted for age, gender, plaque, OR = 10.0, 95% CI = 1.83–54.38) and with continuous measures of periodontal disease such as number of PPDs >4 mm, mean PPD and mean CAL (all p < .001) and BOP (p = .001). However, only 7 out of 24 children were diagnosed with periodontitis. PIDs were also associated with a history of oral ulcers (p = .001, OR 12.47, 95% CI 2.71–57.29). An improvement in periodontal parameters (PPD and CAL) was detected following oral hygiene instructions and non-surgical periodontal therapy.

Conclusion: Although children affected by neutrophil-associated PIDs exhibited a higher prevalence of periodontal disease compared with systemically healthy children, severe periodontitis was rarely seen. This suggests that good systemic control of the PIDs may reduce their impact on the periodontium.

KEYWORDS
immunity, neutrophil biology, periodontitis

Josephine Bayliss-Chapman, Hiten Halai and Cheryl Somani contributed equally to the study.

1 | INTRODUCTION

Primary immunodeficiency diseases (PIDs) are rare early-onset and often life-threatening inherited disorders characterised by intrinsic defects in the human immune system.[1] PIDs have been associated with more than 200 gene defects and manifest in over 180 different phenotypes.[2] The prevalence of oral conditions and periodontal diseases is thought to increase dramatically in children affected by PIDs.[3,4] Children with defects in neutrophil activity seem particularly susceptible to develop severe periodontitis in both primary and permanent dentitions, due to the crucial defensive role of neutrophils against periodontopathogenic bacteria.[5,6] Furthermore, their response to periodontal treatment is highly variable, and the presence of periodontitis often leads to early tooth loss,[4,7] with a devastating effect on mastication, aesthetics and quality of life. Furthermore, oral diseases (in particular periodontitis) may also provide an additional systemic inflammatory burden for these subjects, due to microbial entry into the systemic circulation from inflamed gum tissues.[7,8]

Incorporation of periodontal screening has been advocated for early diagnosis and treatment of periodontal diseases in all children and especially for children with neutrophil defects, to prevent disease progression and tooth loss.[9,10] However, most published papers on periodontitis in children with immunodeficiencies are case reports or familial observations[11–15] or reviews,[3,4] A recent systematic review from our group revealed a high prevalence of periodontal diseases in children with PIDs and a modest response to treatment. However, the evidence was mainly based on case reports.[4] Therefore, there is a lack of well-designed studies investigating both the prevalence of periodontitis and oral diseases in general in children with neutrophil defects and their response to treatment. A better understanding of the causative factors may help in early diagnosis and treatment, eventually improving disease management.

The aims of this study were to: (i) compare the periodontal status of children with neutrophil disorders to systemically healthy controls and (ii) assess response to periodontal treatment in children affected by neutrophil disorders. The null hypothesis was that no difference in the prevalence of periodontal disease existed between children with PIDs and systemically healthy children.

2 | MATERIALS AND METHODS

This study consisted of two separate components:

1. Cross-sectional: comparison of the oral health status (and particularly the periodontal conditions) of children with PIDs affecting neutrophil function vs. systemically healthy children.
2. Longitudinal: assessment of response to treatment (oral hygiene instructions and non-surgical periodontal therapy) in children with PIDs affecting neutrophil function.

2.1 | Patient population

The study was conducted in line with the principles outlined in the Declaration of Helsinki (2008) on experimentation involving human participants. Ethics approval for the conduct of the study was granted by the UK National Research Ethics Service Committee London–Hampstead (ref 15/LO/1090). Each patient's parent or guardian gave informed consent for study participation. Every child was provided with an information sheet for the study (different versions according to age groups, 4–5 years old, 6–9 years old and 10–15 years old) and provided assent to take part in the study. The study was registered on clinicaltrails.gov (ref NCT03069079), and the paper follows the STROBE checklist for reporting observational studies (Appendix S1). Patient visits took place from 7th of March 2017 to 4th of December 2019.

2.2 | Test patients

Twenty-four children affected by neutrophil defects potentially affecting the periodontium were identified from subjects attending the Immunology and Haematology clinics at Great Ormond Street Hospital (GOSH) as well as from the Paediatric department, Royal London Hospital (RLH), Barts Health NHS Trust, following a medical examination.

Inclusion criteria were as follows:

1. Age 4–15 years.
2. Diagnosis of one of the following neutrophil defects (as confirmed by the treating physician):
   a. Disorders of neutrophil numbers [neutropenia was defined as an absolute neutrophil count (ANC) below 1.5×10^9/L; severe neutropenia was defined as an ANC below 0.5×10^9/L], including cyclic neutropenia, congenital neutropenia, severe congenital neutropenia, X-linked Neutropenia or auto-immune Neutropenia.
   b. Disorders of neutrophil function, including Leukocyte Adhesion Defects or other neutrophil disorders/ undefined neutrophil disorders (functional defects demonstrated on testing but genetic basis not yet known).
   c. Combined immunodeficiency syndromes.
3. Participants/parents/guardians willing to give informed consent and sign the consent form.

Exclusion Criteria were as follows:

1. previous bone marrow transplant or treatment with granulocyte colony-stimulating factor (G-CSF) leading to increased neutrophil levels (≥1.5×10^9/L).

2.3 | Control patients

Controls (n = 24) were recruited among children referred for treatment to the Department of Paediatric Dentistry at RLH Barts Health

NHS Trust by their general dental practitioner or the community dental services (usually referred due to the presence of dental caries, dental trauma, medical complications, dental anomalies or dental anxiety). Controls were broadly matched to test patients for age groups (4–5 years old, 6–9 years old and 10–15 years old). Inclusion criteria for control were as follows:

1. Age 4–15 years.
2. Parental or participant-reported systemic health.
3. Participants/parents/guardians willing to give informed consent and sign the consent form.

Exclusion criteria for controls were as follows:

1. Abscesses/sinuses associated with their teeth as they will have pathology associated with their periodontal tissues.
2. Pre-formed metal crowns placed on their teeth (predisposing to plaque retention).
3. Traumatic luxation injuries to their teeth or crown-root fractures of their teeth.

2.4 | Study visits

The flowchart in Appendix S2 shows the study visits.

1. Screening (test only): following informed consent, test participants underwent a screening visit, involving collection of data on clinical and laboratory diagnosis, treatment and dental history. At this visit, a Basic Periodontal Examination (BPE) and assessment of caries (dmft/DMFT) and mucosal diseases were carried out (see 'Clinical examination' section). Saliva and plaque sample and clinical photographs were taken, and a dental treatment plan was made.
2. Baseline (test and control participants): full periodontal examination including the collection of periodontal measurements (and dental radiographs if appropriate), clinical photographs, saliva and plaque samples were taken (if not done at screening visit), as well as gingival crevicular fluid (GCF) samples.
3. Treatment visit(s) (test): this included updates about medical history, adverse events recording, oral hygiene instructions and supra- and subgingival debridement and polishing.
4. 6 months post-treatment re-evaluation visit (test): this included updates about medical history, adverse events recording, dental examination, full-mouth periodontal measurements and oral hygiene instructions. Sampling of saliva, subgingival plaque, gingival crevicular fluid, tooth scaling and polishing.

2.5 | Clinical examination

Basic Periodontal Examination (BPE) was performed, consisting of gentle probing between teeth and gums on index teeth. These were the upper right 1 (1.1) and 6 (1.6), upper left 6 (2.6), lower left 1 (3.1) and 6 (3.6) and lower right 6 (4.6) in the permanent dentition, while in their absence upper right C (5.3) and D (5.4), upper left D (6.3), lower left C (7.3) and D (7.4) and lower right D (8.4) were used in the deciduous dentition. BPE of 0 indicates health, 1 indicates bleeding on probing, with no plaque retention factors and no probing pocket depths (PPD) > 3.5 mm, 2 means presence of calculus or plaque retentive factors, but no PPD > 3.5 mm, 3 indicates PPDs 3.5–5.5 mm, while code 4 indicates PPDs > 5.5 mm. The dmft/ DMFT (decayed missing filled teeth) index was calculated for recording caries experience after examination of hard tissues. Mucosal status was investigated by recording the presence of ulcers, blisters, white patches, speckled areas and masses. At the baseline visit, calibrated dental examiners carried out a more detailed assessment, consisting of collection of full-mouth measurements of PPD, clinical attachment loss (CAL), bleeding on probing[16] and assessment of plaque levels (simplified visible biofilm index).[17] Four examiners collected the clinical periodontal measurements from all patients (Appendix S3).

2.6 | Definition of periodontal disease

Based on the periodontal examination, children were diagnosed as:

1. Healthy: no attachment loss (identified as no CAL > 3 mm or CAL > 3 mm in <2 non-adjacent teeth) and no/minimal gingival inflammation (measured as <15 sites bleeding on probing).[18]
2. Gingivitis: no attachment loss (identified as no CAL > 3 mm or CAL > 3 mm in <2 non-adjacent teeth) and presence of gingival inflammation (≥ 15 sites bleeding on probing).[18]
3. Periodontitis: CAL > 3 mm in ≥2 non-adjacent teeth.[19]

When a BPE code 3 or more was detected, bitewings or long cone parallel periapical radiographs using Rinn holders were taken to detect marginal bone levels, according to clinical needs. In the case of patients unable to tolerate bitewings or long cone periapical radiographs, a dental orthopantomogram was requested.

2.7 | Radiographs

When a BPE code 3 or more was detected, bitewings, long cone parallel periapical radiographs or dental orthopantomograms were exposed (if not already available), according to clinical needs. In other cases, available radiographs were examined. The distance between coronal and apical bone levels and cemento-enamel junction (CEJ) (identifiable radiographically) was analysed. 'True' bone loss was defined in cases where the distance between apical bone level and CEJ was >2 mm and not associated with the eruption of teeth,[20] or with radiolucency in the furcation area.

2.8 | Periodontal treatment

All test children were offered an oral hygiene and tooth scaling and polishing session. For children affected by periodontal disease, subgingival debridement was performed according to needs, with the use of local anaesthesia if considered necessary by the treating clinician. The necessary subgingival debridement was performed in 1 to 2 visits using manual (Gracey curettes, Hu-Friedy) and ultrasonic devices (EMS). Caries was treated as necessary in shared care with the general dental practitioners.

2.9 | Sample size calculation

Hypothesising that control patients would have a prevalence of periodontal disease (periodontitis/gingivitis) of 0.5 and that test patients have an Odds Ratio (O.R.) of 80 to have periodontal disease compared with controls (based on Halai et al[4]), a sample size of 24 test and 24 control patients was estimated to give 80% power to detect such O.R. with a cross-sectional design.

2.10 | Statistical and bioinformatic analyses

All data derived from the study were anonymised and entered in a statistical package database. The descriptive analysis includes the prevalence of periodontal diseases in the study cohort (divided by medical diagnosis). The primary study outcome is the presence of periodontal disease (subdivided in gingivitis and periodontitis). Secondary outcomes include clinical parameters (PPD, CAL and FMBS) microbial and inflammatory markers (not reported in this paper) and response to treatment. Explanatory variables are presence (and type) of PID, age, gender, previous treatment and plaque scores. Associations between these factors and periodontal diagnosis were assessed by the two-sample *t* test or ANOVA as appropriate. Normal distribution of clinical parameters was confirmed via Kolmogorov-Smirnov and Shapiro-Wilk tests. Linear and logistic regression analysis adjusted for explanatory variables were carried out as appropriate. Response to therapy was evaluated by comparing clinical periodontal parameters at baseline and follow-ups by paired-sample *t* test, using intention-to-treat analysis. The *p* value set for significance was <0.05.

3 | RESULTS

3.1 | Medical history (test control)

A total of 48 patients were recruited between March 2017 and December 2019. Their demographic characteristics are reported in Table 1. The majority of patient was Caucasian, with an average age around 10 years old. None of these differences were statistically significant between test and control groups.

Test patients were diagnosed with auto-immune neutropenia (n = 5), severe congenital neutropenia (n = 4), congenital neutropenia (n = 1), other neutrophil disorders where functional defects demonstrated on testing but with unknown genetic basis (n = 5), and other syndromes, which included Shwachman-Diamond syndrome (n = 2), Cohen's Syndrome (n = 2), Fanconi's anaemia (n = 2), Clericuzio-type poikiloderma (n = 1), Papillon-Lefèvre Syndrome (PLS) (n = 1) and glycogen storage disease (n = 1) (see Appendix S4). The reported mean age at diagnosis was 4.2 (±3.9) years old, and the average number of years since diagnosis was 5.8 (±3.8). Self-reported family history of PID was positive for 4 test patients and negative for 15, while it was unknown for 5. Two of the patients reported that the parents were consanguineous. Twenty-three out of twenty-four test patients had an absolute neutrophil count less than 1.5×10^9/L (for 10 of them $<0.5 \times 10^9$/L). Only one of the test patients (diagnosed with Papillon-Lefevre Syndrome) had a neutrophil count of 3.2×10^9/L at the baseline study visit. Three of the test patients were on a granulocyte colony-stimulating factor (G-CSF or GCSF), while 6 patients were on weekly antibiotics, 1 on weekly antifungals and 3 patients (who had asthma) used salbutamol inhalers when needed. Although these conditions are associated with a range of other inflammatory/immunological features, these were not investigated in this study, which focussed on neutrophils.

Control patients were systemically healthy, with only 2 reporting a medical history of asthma and the use of salbutamol inhalers. Eight test patients reported previous non-surgical periodontal therapy and 2 reported early loss of teeth not due to trauma. Test and control patients used a combination of electric and manual toothbrush, and the majority (21 test and 15 control patients) reported brushing at least 2/day. A small percentage of patients (6 test and 3 control patients) reported interdental brush use and 7 test and 2 controls reported using mouthwash daily.

TABLE 1 Baseline characteristics of test and control patients

Demographics	Test	Control	Comparison *p*
Gender			
Male	13	15	.770
Female	11	9	
Ethnicity			
Caucasian	13	12	.428
Asian	9	6	
Afro-Caribbean	1	4	
Mixed/Other	1	2	
Age at Visit 1			
4–6 years	6	6	.949
7–9 years	5	5	
10–15 years	13	13	
Average	9.67 ± 3.70	10.04 ± 3.51	.720

3.2 | Oral examination (test-control)

Table 2 reports the results of dental/periodontal examination in test (baseline and 6-month follow-up) and control patients. Out of 24 PID cases, 7 were diagnosed with periodontitis, 8 with gingivitis and 9 with periodontal health. Cases diagnosed with periodontitis included severe congenital neutropenia (n = 2), congenital neutropenia (n = 1), other neutrophil disorders (n = 2), Shwachman-Diamond syndrome (n = 1) and Clericuzio-type poikiloderma (n = 1). The PLS patient and a patient with Cohen's syndrome reported a history of periodontitis and early tooth loss, although they were not diagnosed with periodontitis based on the baseline criteria. Figure 1 shows the clinical photograph and radiograph of neutropenic test patient diagnosed with periodontitis. Controls were diagnosed with either gingivitis (n = 4) or periodontal health (n = 20). Figure 2 shows clinical photographs and radiographs of systemically healthy control patient diagnosed with gingivitis (A and B) and periodontal health (C and D). The visible plaque index (VBI) ranged from 1 to 3 in test and controls (Appendix S5). Diagnosis of PID was associated with periodontal status (health vs. gingivitis vs. periodontitis) (Chi-square p = .002). Logistic regression revealed that patients with PID were found to have a higher prevalence of periodontal disease (periodontitis + gingivitis) (p = .008 adjusted for age, gender, plaque, OR = 10.0, 95% CI = 1.83–54.38) (see Table 3). In agreement with this, associations with PID were found for number of PPDs >4 mm (p = .043), average PPD (p < .001), average CAL (p < .001) and BOP (p = .001), with a border-line association for proportion of PPDs >4 mm (p = .054). Proportion of sites divided by PPDs in test and control subjects is reported in Appendix S6.

Same levels of plaque were associated with higher BOP in PID compared with systemically healthy children. In particular, while BOP was similar for test and control children with visible biofilm index of 1 (4.2% vs. 4.7% respectively), clear differences were seen for VBI of 2 (24.9% for test and 2.1% for control children) and VBI of 3 (45.0% for test and 14.4% for control children).

Test patients had a higher prevalence of history of oral ulcers (p = 0.001, OR 12.47, 95% CI 2.71–57.29 adjusted for age, gender and VBI) (example of test patient in Appendix S7). Eight test patients (33.3%) and no controls reported having mouth ulcers at least 1/month. Three patients presented with mouth ulcers at the baseline examination.

3.3 | Radiographic assessment

Radiographs of 18 test and 12 control patients were available for analysis. These radiographs consisted of 21 orthopantomograms, 7 bitewings, 2 lateral oblique radiographs and 1 set of periapical radiographs. In 4 cases, bone levels were not clearly visible on radiographs. Of 7 patients with a clinical diagnosis of 'periodontitis', 4 exhibited signs of bone loss, while 1 did not and 2 radiographs could not be scored.

3.4 | Longitudinal assessment

Twenty test patients received treatment and attended the 6-month re-evaluation appointment. A total of 23 deciduous teeth exfoliated

TABLE 2 Clinical data of test patients (baseline and 6 months) and controls

	Clinical data		Comparisons p	
	Test			
	Controls	Baseline	6-month follow-up	Test baseline vs. C	Test baseline vs. Test follow-up
Number of deciduous teeth	9.12 ± 7.61	7.71 ± 8.23	6.7 ± 8.25	.539	–
Number of permanent teeth	14.37 ± 10.42	15.25 ± 10.52	16.6 ± 9.84	.774	–
Visible biofilm Index	12 (50.0%)	1 5 (22.7%)	7 (35.0%)	.074	–
	7 (29.2%)	2 9 (40.9%)	8 (40.0%)		
	5 (20.8%)	3 8 (36.4%)	5 (25.0%)		
Average PPD (mm)	1.87 ± 0.28	2.35 ± 0.53	1.96 ± 0.33	<.001	.011
Average CAL (mm)	0.84 ± 0.32	1.56 ± 0.74	1.07 ± 0.43	<.001	.015
NUMBER PPDs>4 mm	0	2.95 ± 6.95	0.05 ± 0.22	.043	.078
PROPORTION PPDs>4 mm	0	1.90 ± 4.71%	0.03 ± 0.15%	.054	.065
BOP %	5.96 ± 8.42	27.50 ± 27.81	24.27 ± 24.42	.001	.511
Dx of Periodontitis	0	7/24 (29.2%)	4/20 (20%)	.002	–
Dx of gingivitis	4 (16.7%)	8 /24(33.3%)	6/20 (30%)		–
Dx of periodontal health	20 (83.3%)	9/24 (37.5%)	10/20 (50%)		–
Dx of caries	4 (16.7%)	1 (4.2%)	0	.348	–
Dx of mucosal ulcers	0	3/24 (12.5%)	2/20 (10%)	.234	–
History of ulcers	4 (16.7%)	18 (75.0%)	–	<.001	–

Note: Results of intention-to treat analysis are reported for clinical measurements at the 6-month follow-up.

(as part of the normal exfoliation process) and 46 additional permanent teeth erupted enough to be probed during the study 6-month follow-up period. Table 2 shows periodontal parameters at baseline vs. re-evaluation, showing statistically significant improvements in periodontal conditions post-treatment, measured as improvements in average PPD (p = .011) and average CAL (p = .015). Changes in number of PPDs >4 mm (p = .078) and percentage BOP were not statistically significant (p = .511). At the 6-month follow-up, only 1 of the patients diagnosed with periodontitis and 1 of the patients diagnosed with gingivitis at baseline reverted to periodontal health (based on the definitions adopted in this study). Figure 3 shows clinical photograph of a test patient at baseline and at the 6-month follow-up post-periodontal treatment, showing a reduction in marginal inflammation.

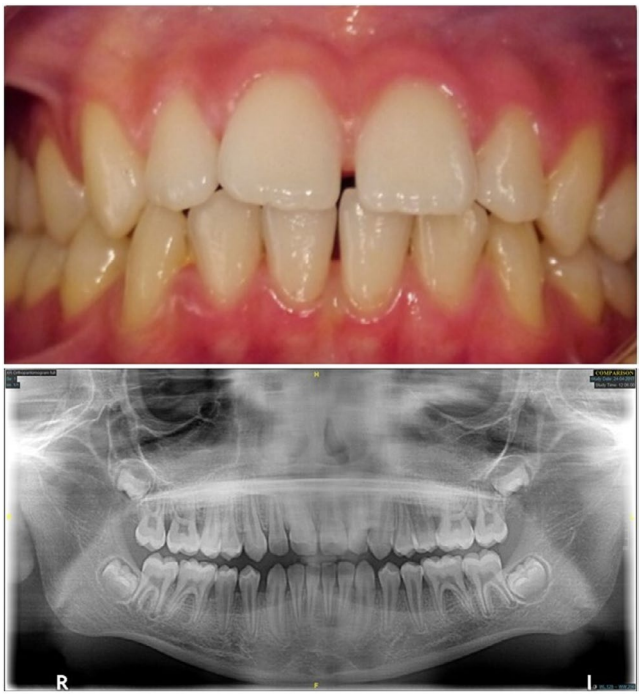

FIGURE 1 Clinical photograph and radiograph of neutropenic test patient diagnosed with periodontitis

4 | DISCUSSION

This study showed that children affected by neutrophil-related primary immunodeficiencies were nearly 10 times more likely to be diagnosed with periodontal disease (gingivitis or periodontitis) compared with systemically healthy age-matched children. This is substantiated by previous reports on periodontal conditions in children and adolescents in the UK. Thirty-eight per cent of the test children and 13% of the control children had a BPE of 3 or higher in the present study, compared with 3% of male and 5% of female 15-year-old children in the Children's Dental Health Survey.[21]

However, periodontal disease prevalence and severity observed in this group of children with PIDs (mean approximately 3 sites with PPD >4 mm per patient) are somewhat less than what was reported in PID patients in previous studies[11,22,23] and summarised in a recent

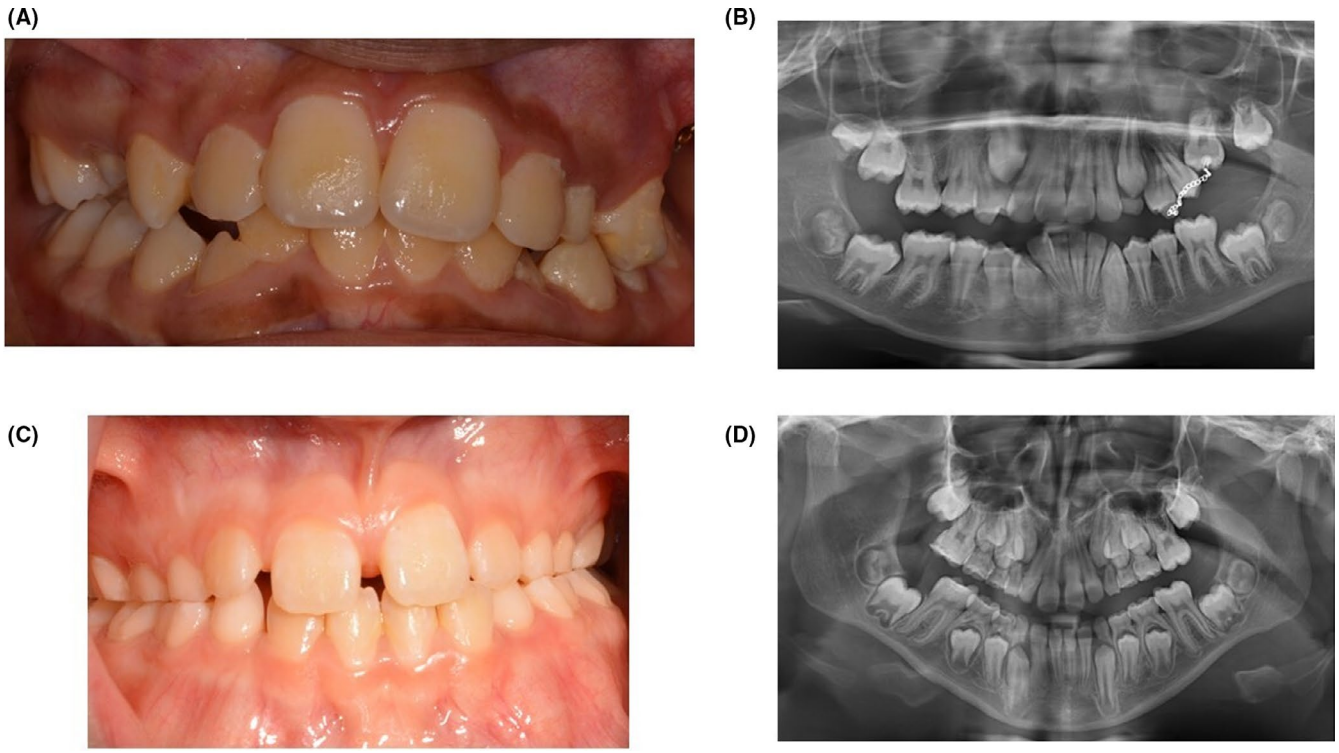

FIGURE 2 Clinical photographs and radiographs of systemically healthy control patient diagnosed with gingivitis (A,B) and periodontal health (C,D)

TABLE 3 Results of logistic regression analysis for association between PID diagnosis, age, gender and Visible dental biofilm index and presence of periodontal disease

							95% CI for EXP(*B*)	
	B	SE	Wald	df	Sig	Exp(*B*)	Lower	Upper
Step 1								
Age	0.172	0.126	1.866	1	.172	1.187	0.928	1.520
Gender	0.634	0.868	0.533	1	.465	1.885	0.344	10.337
PID diagnosis	2.302	0.864	7.088	1	.008	9.990	1.835	54.379
Visible dental biofilm index	1.197	0.555	4.645	1	.031	3.311	1.115	9.834
Constant	−6.627	2.368	7.833	1	.005	0.001		

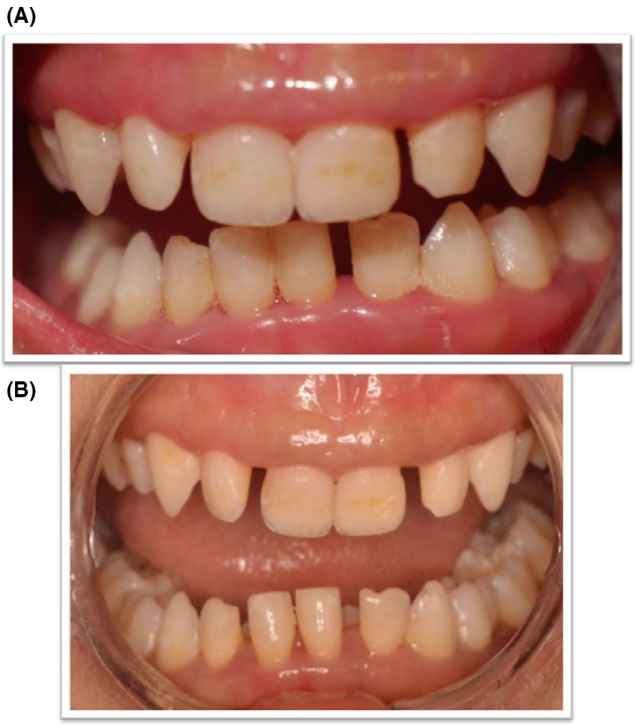

FIGURE 3 Clinical photographs of test patient at baseline (A) and at 6-month follow-up (B), following periodontal treatment

systematic review from our group.[4] A reason for this difference may be the good standard medical and dental management of patients included in the present study. Patients were diagnosed with PID at the average age of 4.2 years, and some were treated with G-CSF as well as antibiotics and antifungals. A third of test patients had previously received non-surgical periodontal therapy in secondary care (GOSH or RLH). Daily oral hygiene may be influential as 38% (n = 9) of patients additionally used mouthwash and 25% (n = 6) of used interdental brushes at baseline. Also, there may be an element of publication bias in the literature, consisting mainly of case reports and case series, where only when severe periodontitis associated with PID is published.

PID children in the present study had high prevalence and history of mouth ulcers (affecting 75% of test patients and 17% of control patients based on self-report). The prevalence in controls is in agreement with previous studies on recurrent aphthous stomatitis (RAS) in the general population[24,25] Children with systemic diseases seem to consistently have higher prevalence of oral ulcerations.[26,27] Possible mechanisms of reported associations between PIDs and oral ulcerations[22,28-30] involve an immunopathic process involving cytolytic activity in response to HLA or foreign antigens,[31,32] trauma, stress, menstruation, nutritional deficiencies, food allergies and endocrinopathies. The immunopathogenesis of recurrent oral ulceration may involve differentiation of cytotoxic T cells and production of TNF-α[33] and other cytokines, such as interleukin-2.[34] As neutrophils are also important in regulating other leukocytes, their reduced number may influence this process.[35,36]

Non-surgical periodontal therapy and oral hygiene instruction appeared to be effective in these patients, with statistically significant reductions in PPD and CAL. The number of PPDs >4 mm was reduced from a mean of nearly 3 to 0.05 per patient after treatment. However, children with PIDs had consistently higher BOP in the presence of visible biofilm index of 2 or 3 compared with healthy children. This suggests a stronger response to plaque accumulation in children with PIDs, resulting in more pronounced gingival inflammation. Non-surgical therapy was also safe in this patient cohort, as no serious adverse events were recorded. However, it is important to bear in mind that often prophylactic antibiotic cover may be required.

Limitations of this study include potential selection bias, as not all approached patients with PID or their families were willing to participate. Control patients were recruited from the paediatric new patient clinic and may not be a truly representative sample. Furthermore, they did not receive any periodontal treatment. In addition to this, examiners were not blind to medical diagnosis. A per-protocol definition previously suggested by the European Federation of Periodontology and taking into account attachment loss[19] was used for diagnosis of periodontitis, to balance the highly likelihood of 'false pockets' in children.[37] A strength of this study is the relatively large sample study compared with previous studies on this topic and the cross-sectional design, which allowed comparison with a reference group of systemically healthy age-matched children.

Overall, this study suggests that neutrophil-related PIDs are associated with higher prevalence of periodontal diseases. However, in the cases seen here, periodontal severity was not very advanced,

presumably due to early interceptive treatment for both systemic conditions and gingival conditions are carried out. Future studies should focus on understanding the molecular mechanisms of associations between PIDs and both periodontal disease and oral mucosal lesions, as better prevention and management may improve the quality of life of children affected by PIDs.

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CONFLICTS OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

AUTHOR CONTRIBUTIONS

Prof L. Nibali contributed to conception, design, data acquisition, analysis and interpretation, drafted and critically revised the manuscript. Drs. J. Bayliss-Chapman, H. Halai, C. Somani, C. Davies and P. Ancliff contributed to data acquisition and interpretation and critically revised the manuscript. Prof N. Donos contributed to conception, design and critically revised the manuscript. All authors gave their final approval and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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