

Oral and Dental Health Status in Patients with Primary Antibody Deficiencies

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ABSTRACT

Primary antibody deficiencies (PAD) are a group of immune system disorders, associated with decreased levels of secretory and protective immunoglobulins. Because of the important role of immunoglobulins in the protection of oral cavity, patients with PADs are more susceptible to dental caries or oral manifestations.

This study was performed to investigate the oral and dental manifestations of PADs patients. In this study, 33 patients with PADs (21 common variable immunodeficiency, 8 X-linked agammaglobulinemia and 4 hyper IgM syndrome) and 66 controls were examined; the number of decayed, missed and filled teeth (DMFT) were investigated.

Aphthous was the most frequent manifestation in PADs patients (38.7%), which was significantly 16.7% higher than the controls ($p=0.03$). The patients with PADs showed significantly higher presentation of other oral and dental manifestations, including herpes sores, candidiasis tonsillitis, gingivitis, calculus, enamel hypoplasia and other ulcerations. The mean DMFT scores were 6.15 ± 3.6 and 1.93 ± 0.4 in PADs patients and controls, respectively ($p<0.001$). Although the patients with common variable immunodeficiency had higher means of DMFT in comparison with other groups of PADs, this difference was not statistically significant.

This study showed significantly higher frequency of oral and dental manifestations in the patients with PADs compared to controls. Therefore, regular examination of oral cavity could be suggested in this group of immunodeficient patients.

Keywords: Aphthous; Common variable immunodeficiency; Dental caries; Immunoglobulin; Oral manifestation; X-linked agammaglobulinemia

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INTRODUCTION

Primary antibody deficiencies (PAD) are the most common type of primary immunodeficiency diseases,

which are characterized by qualitative and quantitative defects in the humoral immune system and are presented with low serum levels of immunoglobulins. These diseases can be developed primarily as a result of genetically heterogeneous disorders with defects during differentiation and development of B-cells. The most common symptomatic diseases of PADs were common variable immunodeficiency (CVID), X-linked agammaglobulinemia (XLA) and Hyper IgM syndrome (HIGM).¹⁻⁶ All symptomatic PADs are susceptible to different bacterial and opportunistic infections, especially in the respiratory and gastrointestinal tract, requiring regular immunoglobulin and antibiotics administration.¹⁻³ However, the patients may be susceptible to a variety of oral manifestations, including aphthous-like ulcerations, oral candidiasis, gingival inflammation (gingivitis), periodontitis and enamel hypoplasia.^{7,8} Oral manifestations are a major risk for patients with PAD and therefore treatment should be started once the diagnosis is made, based on the existence of these manifestations.⁸ This process may decrease the quality of life of affected patients due to inappropriate nutrition.

The present study was performed to investigate the oral health status of patients with PAD in Iran.

PATIENTS AND METHODS

Patients

Thirty three patients with diagnosis of PAD, based on the diagnostic criteria defined by the European Society for Immunodeficiencies (ESID) and the Pan-American Group of Immunodeficiency (PAGID),⁹ who were diagnosed at the Children's Medical Center Hospital (Pediatrics Center of Excellence in Tehran, Iran) were selected during 2002-2009. XLA was confirmed by mutation analysis of bruton tyrosin kinase (*BTK*) gene in agammaglobulinemic male patients with reduced number of B cells (<1%). HIGM was diagnosed by mutation analysis of CD40 ligand (*CD50L*) in the patients with reduced serum levels of IgG and IgA and normal or elevated serum IgM levels. The diagnosis of CVID was made in the patients with decreased serum levels of IgG, IgM, and IgA, with exclusion of other well-defined single gene defects.

Inclusion Criteria

The inclusion criteria for patients' selection were: (1) patients under regular intravenous immunoglobulin

(IVIG) replacement therapy with 400-500 mg/kg every 3-4 weeks; (2) age range between 2 and 20 years (The patients with ages lower than two years were excluded because of the possibility of transient hypogammaglobulinemia of infancy); (3) No hospital admission during last one month; (4) No major stress in previous 3 months; and (5) No evidence of secondary immunodeficiency diseases like AIDS, diabetes mellitus and leukemia.

Control Subjects

Thirty-three eligible patients (28 males, 5 females) among 65 registered patients were studied, while remaining individuals were excluded for reasons like death, age limitations or serious and critical infection involvement. Relatives of the patients admitted to the Department of Pediatrics, School of Dentistry in the same University formed the control group in this designed cross-sectional study. The 66 control subjects (56 males, 10 females) were selected in a way that matched the gender and age of their cases. The control individuals were neither infected with chronic diseases, under clinician observation nor using specific medicaments.

Study Protocol

The study was approved by the Ethics Committee of Tehran University of Medical Sciences and informed consent was obtained from all patients.

Demographic data, type of PAD, time of diagnosis, duration of treatment and clinical features of each patient were evaluated and recorded in a designed questionnaire.

Each patient with confirmed PAD and his/her controls were referred to the Department of Pediatric Dentistry for the assessment of oral manifestations using dental mirror under the artificial light of a torch. During the examinations, all teeth surfaces were dried with a gauze roll and different oral and dental manifestations, including aphthous, herpes sores, candidiasis, tonsillitis, gingivitis, dental calculus, enamel hypoplasia and other dental ulcerations were assessed in cases and control individuals.

The caries teeth were documented with single or multiple decayed or restored surfaces, cavity developments or discolorations at the tooth surface with visible tooth substance loss. The teeth filled with amalgam or tooth-colored restorations were regarded as restored ones. The missing teeth were recorded with the

observation of the missing teeth area together with the parents' explanations of the causes. The number of Decayed, Missing and Filled Teeth (DMFT) was added up to calculate the DMFT index. Chalky white or yellowish lesions when simply separated from the tooth surfaces were considered as sub- or supra-gingival calculus. Gingival inflammation was defined as the inflamed tissues of tooth surrounding area with signs of redness, irritation, burning and gingival bleeding during tooth brushing when matched by the patient responses. It should be noted that, the oral and dental manifestations could be correlated with race, gender and age factors which were regarded in this examination.

The case and control specimens were encouraged to receive dental treatments when necessary with special stress on the restoration of the decayed teeth.

Statistics

Frequency and percentage of different oral manifestations were calculated for both case and control individuals. Based on matched case and control specimens, the data were subjected to Generalized Estimating Equation (GEE) model using linear regression analysis for the dependent quantitative variables like DMFT or Logit regression for the calculation of Odds ratio in dependant qualitative variables like exhibiting specific manifestation.

RESULTS

Among 33 studied patients with PAD, 21 cases were CVID, 8 patients were diagnosed as XLA and 4 were patients diagnosed as HIGM. The mean age of patients was 12.39 ± 4.92 years and that of control subjects was 12.12 ± 4.94 years. Detailed results of demographic data in each group of patients are presented in the table 1.

Among all studied PADs individuals, 38.7% of cases presented aphthous, which was significantly higher than 16.7% in the control subjects ($p = 0.033$). Herpes sores was a finding in 48.4% of PADs cases, whilst only 3% of controls showed such manifestation ($p < 0.001$). Oral candidiasis and tonsillitis were seen in 32.3% and 35.5% of patients, respectively, which were significantly higher than 4.5% and 6.1%, respectively in the control subjects (p -value of 0.002 and 0.006, respectively). More than 50% of patients

suffered from gingivitis which was significantly higher than 18.2% in the control group ($p = 0.002$). Furthermore, calculus was observed in 51.6% of PADs cases, which was significantly higher than 18.2% of controls (p -value=0.005). Other ulcerations in the control group was significantly lower than cases (6.1% vs. 54.8%, $P < 0.001$). Although 16.1% of patients showed enamel hypoplasia, it was not seen in any control subject ($p = 0.012$). The mean DMFT scores were 6.15 ± 3.6 and 1.93 ± 0.4 in PAD patients and controls, respectively ($p < 0.001$). Although CVID patients showed higher means of DMFT, the mean DMFT values were not significantly different among various types of PAD (Table 1).

DISCUSSION

Dental caries is a multifactorial bacterial infectious disease, in which streptococcus mutans and poor oral hygiene could be considered as etiologic factors. Whilst the host's immune system is responsible for controlling the caries activity, and the secreted immunoglobulin A (IgA) from saliva could prevent caries development.¹⁰

According to the findings of this study, although there is no difference between various types of PAD, the patients with antibody deficiencies showed higher rate of all oral dental manifestations, compared to healthy individuals. Defects in the immune system may alter the salivary secreted IgA volume.¹¹ Furthermore, when *streptococcus mutans* is infiltrated in the body, it may increase the specific IgA antibodies in the saliva or milk, preventing caries development consequently.¹² It was shown that other oral ulcers as well as dental caries are increased in all types of immune system disorders.¹³ However, some of previous studies suggested low or no correlation between immunodeficiency and dental caries or periodontal disease.^{14,15}

Our findings strongly suggest that the patients with PAD are at greater risks for developing dental caries which are in agreement with previous study by Legler *et al* who showed more caries surfaces in patients with immunodeficiency than control individuals; they also showed higher gingival inflammation scores in immunodeficient patients compared to the controls.¹⁶

Table 1. Oral and dental manifestations of 33 patients with primary antibody deficiency, comparing with their age-sex matched controls

Topics	CVID	XLA	HIGM	PADs	Controls	<i>p</i> -value (among PADs)	<i>p</i> -value (PADs comparing with controls)
No.	21	8	4	31	66	-	-
Sex(male/female)	15/6	8/0	4/0	27/6	54/12	-	-
Current age(±SD)	12.4(±5.3)	11(±4.7)	12.5(±5.8)	12.39(±4.9)	12.12(±4.9)	-	-
IgG(mg/dl)	56.17±14.5	25.0±11.9	129.4±27.7	64.3±27.3	730.7±129.4	-	-
IgA(mg/dl)	10.69±3.7	9.5±3.3	27.4±11.2	14.2±7.9	40.7±26.6	-	-
IgM(mg/dl)	6.28±4.0	14.6±5.2	139.6±17.1	10.9±8.3	73.8±21.0	-	-
CD3+lymphocyte (%)	55.0±22.7	65.2±21.4	59.3±14.2	59.3±20.4	69.3±25.6	-	-
CD4+lymphocyte (%)	35.0±8.9	32.6±13.3	33.2±7.4	34.7±10.2	33.8±5.9	-	-
CD8+lymphocyte (%)	31.7±11.8	31.6±11.0	36.0±13.9	32.9±16.0	34.5±7.3	-	-
CD19+lymphocyte (%)	7.5±2.6	1.2±0.4	13.4±8.6	8.1±5.3	12.7±4.1	-	-
Aphthous	5(0.23)	4(0.5)	3(0.75)	12(0.38)	11(0.16)	0.98	.033
Herpes sores	9(0.42)	4(0.5)	3(0.5)	15(0.48)	2(0.03)	0.92	<0.001
Candidiasis	7(0.33)	3(0.37)	0	10(.32)	3(0.04)	0.36	.002
Tonsillitis	6(0.28)	2(0.25)	3(0.75)	11(0.35)	4(0.06)	0.16	.006
Gingivitis	11(0.52)	3(0.37)	2(0.5)	16(0.51)	12(0.18)	0.77	.002
Other ulcer	10(0.47)	4(0.5)	3(0.75)	17(0.54)	4(.06)	0.60	<0.001
Enamel hypoplasia	4(0.19)	1(0.12)	0	5(0.16)	0	0.52	.012
Dental calculus	11(0.52)	3(0.37)	2(0.5)	16(0.51)	12(0.18)	0.23	.005
DMFT index(±SD)	6.8(±3.6)	4.7(±2.7)	5.2(±4.6)	6.15(±3.6)	1.93(±0.4)	0.33	<0.001

PADs: Primary antibody deficiencies; CVID: Common variable immunodeficiency; XLA: X-linked agammaglobulinemia; HIGM: Hyper IgM syndrome; DMFT: The number of Decayed, Missing and Filled Teeth

Increased gingival inflammation in immunodeficient individuals may be due to the upper respiratory tract infections and nasal congestion, which compel them to breath via mouth. Although Legler *et al* and Cole *et al* showed higher frequency of *Streptococcus mutans* species and more caries incidence in hypogammaglobulinemia patients,^{16,17} other studies indicated limited alterations in oral microbial content of patients with hypogammaglobulinemia compared to normal individuals^{13,15,17,18} or their susceptibility to caries development.

The increased dental caries and infections in PAD patients can be related to nutritional habits, differences in their lifestyle or to dental neglect as the patients and their parents are more concerned about the main disorder. As antibiotics are frequently used for managing PAD, the dental caries activity is suppressed with the use of these medications. The necessity of preventive dental

treatments for PAD patients was clear; however, the management of disease and the patients' nutrition cannot be easily maintained. Although this study does not investigate the effect of treatment, we also emphasize the role of immunoglobulins in preventing dental caries in our patients. In our study, higher mean scores of DMFT was reported for PAD patients, whilst the difference was not statistically significant among CVID, XLA or HIGM groups which may be due to the limited number of studied patients.

Considering our results, we speculate that periodical oral and dental monitoring could help PAD patients as a part of their management and follow-up, because a higher incidence of oral manifestations related to immunodeficiency may interfere with the treatment course of the defects, causing them to become more intensified.

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