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Oral manifestations in selective IgA deficiency

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Abstract: Selective immunoglobulin A (IgA) deficiency is the most common of the primary immunodeficiencies with a frequency of 1/300–1/3000, depending on the screened population. As secretory IgA (SIgA) has a protective role in mucosal surfaces from invasion of microorganisms, it is thought that IgA-deficient subjects are susceptible to periodontal diseases and oral manifestations. Previous studies show contradictory results, concerning the involvement of the individuals' periodontium with IgA deficiency. The aim of this study was to investigate and compare the oral manifestations in IgA-deficient subjects with controls. Eleven selective IgA-deficient subjects aged 3–18 years with serum IgA levels $<10\,mg\,dl^{-1}$ and 11 age–sex-matched healthy children as the controls entered the study. Oral mucosal investigation, dental caries, plaque accumulation and periodontal status were assessed. Serum immunoglobulin levels were measured by single radial immunodiffusion (SRID) method. Saliva immunoglobulins and secretory component levels were measured by enzyme linked immunosorbent assay (ELISA) methods. IgA-deficient patients had serum and saliva IgA levels less than $10\,mg\,dl^{-1}$ and $10\,\mu g\,ml^{-1}$, respectively, but other serum immunoglobulin levels were normal and saliva immunoglobulin M (IgM) levels were increased, compared with controls. There were no significant differences in oral manifestations between IgA-deficient subjects and controls, which may be a result of compensatory increase of saliva IgM or other non-immunological defence factors in saliva. Thus, it is not necessary to evaluate IgA and SIgA in all the patients with oral and dental lesions and it is thought that it is better to investigate other factors.

Key words: oral manifestation; selective IgA deficiency; periodontal disease; secretory IgA

Introduction

Defence against microbes is mediated by the early reactions of innate immunity and the later responses of adaptive immunity. There are two types of adaptive immune responses called humoral immunity (including immunoglobulins) and cell-mediated immunity (1). Immunoglobulin A (IgA) protects the mucosal surfaces from invasion of microorganisms (2).

Selective IgA deficiency is the most common of the primary immunodeficiencies (3, 4), with a frequency of 1/300–1/3000, depending on the population studied (5,6). IgA-deficient patients have very low or no detectable levels of IgA both in saliva and serum. It is classically defined as a serum IgA level less than $10\,mg\,dl^{-1}$ (7, 8). In these patients, serum immunoglobulin G (IgG) and immunoglobulin M (IgM) levels are usually normal or even elevated, so it is called 'selective'. IgA is the major immunoglobulin class in secretions with concentrations around $100–200\,mg\,l^{-1}$ in unstimulated whole saliva followed by IgG (around $20–30\,mg\,l^{-1}$), IgM (around $10\,mg\,l^{-1}$) (9, 10). Secretory IgA (SIgA) is present in a dimeric form with a joining segment and a secretory component (11). SIgA is considered the first line of defence against pathogens that colonise and invade surfaces bathed by secretions. SIgA can neutralise viruses, bind toxins, agglutinate bacteria and prevent bacteria from binding to various food antigens preventing entry into the general circulation. The level of salivary IgA may vary according to salivary flow rate, age, hormonal factors, smoking habits, etc. (2).

In most cases, selective IgA deficiency occurs sporadically, but familial occurrence with autosomal recessive or polygenic patterns of inheritance has been reported (12). Also, it has been reported in children with chromosomal abnormalities, particularly those involving chromosome 18 (deletion or ring formation) (5). An association between IgA deficiency and certain human leukocyte antigen (HLA) types of the major histocompatibility complex (MHC) has been noted. An increased frequency of HLA-AI, HLA-B8 and HLA DR3 in IgA-deficient subjects was reported (13). Also, other investigations have found the connection between the MHC haplotype (HLA-B8, SC01 and DR3) and selective IgA deficiency (14).

IgA is the principal mucosal antibody class. It is synthesised by serum and local plasma cells and has a specific polymeric immunoglobulin receptor-mediated transport mechanism for entry into the body secretions (15). T-cell and cytokine defects often have been extensively sought in IgA deficiency (16). Antigen-stimulated B-cells undergo isotype switch and terminal differentiation into IgA-secreting plasma cells under the influence of cytokines; transforming growth factor-beta (TGF-β) appears to be a key cytokine in this process (17). Serum levels of TGF-β in IgA-deficient sera were less than that of normals (18).

Despite the fact that most IgA-deficient subjects are asymptomatic, IgA deficiency has been associated with an astonishing high number of specific disorders such as respiratory infections, pneumonia, intestinal infections and autoimmune diseases (16, 19–21). Around 30% of the IgA-deficient patients suffer from recurrent upper respiratory tract infections (22, 23). Also, it has been suggested that IgA deficiency must be associated with those of the IgG subclasses, especially IgG2 and IgG4, to be manifested with clinical symptoms (24). Periodontal diseases are characterised by a chronic inflammatory response of the periodontium. The aetiology is complex, involving microbial, immunological and nutritional factors (8, 25). Previously published studies show contradictory results, concerning the involvement of the individual's periodontium with IgA deficiency. Jones and Manson (26), Roitt and Lehner (27) and Scully and Cowson (28) have reported recurrent aphtus, recurrent herpetic infections, tonsillitis, severe gingivitis and candidiasis as oral manifestations that appear in IgA-deficient subjects. However, the susceptibility to periodontal disease was shown not to be elevated in IgA-deficient patients in other studies. Leggot (29), Leggot *et al.* (30) and Porter and Scully (31) have not found oral symptoms in these patients. Immunodeficiency, especially IgA deficiency, represent a useful model in order to study the role of salivary immunoglobulins in oral health and diseases. The aim of this study was to investigate and compare the oral manifestations in IgA-deficient subjects with controls in order to guide dentists to consider IgA deficiency in individuals with periodontal diseases and oral symptoms.

Study population and methods

Patients and controls

Eleven selective IgA-deficient subjects aged 3–18 years (six boys and five girls) and 11 age–sex-matched healthy children as the controls participated in this study. The patients were selected from Immunodeficiency Clinic of Children Medical Center, Tehran University of Medical Science, Iran. Selective IgA deficiency was defined as serum IgA levels less than $10\,mg\,dl^{-1}$ after three times of re-checking with 2–3-month intervals up to 1 year by single radial immunodiffusion (SRID) method. Patients with transient IgA deficiency as a result of viral infections or drugs (cyclosporin, phenitoine, gold, sodium valproate, etc.) were excluded from this study. The control group had normal levels of serum immunoglobulins and did not have any kind of disease during the last 6 months. Weight and height were measured for evaluation of nutritional status in both groups.

Oral examination and analysis

Two trained examiners performed the periodontal and general oral health status of IgA-deficient subjects as well as the control group. Oral mucosal investigation (tonsils, gingival, soft and hard palates, buccal mucosa, lips, tongue and pharynx), dental caries, plaque and periodontal status were assessed.

At the first visit, oral hygiene was instructed to both groups, samples from the saliva and serum were collected and prophylactic considerations, and fluoride therapy were performed as well. The information collected at the first examination was considered as baseline data and the subjects were followed monthly for about a year. The follow-up examinations were carried out monthly and each of the subjects was visited at least six times during a 1-year period. The cases with oral lesions were assessed during the follow-up intervals. Ram fjord index (32) was modified and selected for only the following teeth: 1 6, 2 6, 1 1, 3 1, 3 6, 4 6, because some individuals in both groups had primary teeth. Also, probe technique was applied to identify plaque index and periodontal probe in order to determine periodontal index (33).

Serum collection and analysis

At the first visit, 2 ml of whole blood from each person was collected and stored at −70 °C until analysed. Serum IgG, IgA and IgM levels were determined according to SRID method.

Saliva collection and analysis

Eating was prohibited for at least 20 min before salivary sample collection. Each person washed his mouth with tap water. After few minutes, the first sample of saliva was collected for 2 min in order to determine the saliva rate. Saliva samples containing 300 µl were stored at −70 °C until analysed, and then they were thawed and centrifuged for 10 min at 9200 ***g*** to remove cells and debris. The supernatant of each sample was diluted in phosphate buffer saline containing 0.05% Tween 20 (1/800 dilution of saliva for determining secretory component and IgA, 1/100 dilution of saliva for determining IgM and IgG).

Polystyrene microtitre plates were kept overnight with an anti-immunoglobulin (obtained from DAKO, Denmark) at 4 °C (four different microplates). Each well of each microplate was coated with 100 µl of rabbit immunoglobulins directed towards human IgM (µ-chain-specific), 2.5 µg ml^{-1}; IgG (γ-chain-specific), 2.5 µg ml^{-1}; IgA (α-chain-specific), 2.5 µg ml^{-1} and secretory component, 5 µg ml^{-1}, separately. Diluted saliva samples were added in a volume of 100 µl to the microtitre wells and incubated for 1.5 h at 37 °C. Among the various incubation steps, the wells were rinsed five times with phosphate-buffered saline containing 0.05% Tween 20. One hundred microtitre of horse radish peroxidase (HRP)-conjugated immunoglobulin fractions of monospecific rabbit antisera (obtained from DAKO, Denmark; human IgM (µ-chain-specific) diluted to 1/1000, IgG (γ-chain-specific) diluted to 1/6000, IgA (α-chain-specific) diluted to 1/4000 and secretory component diluted to 1/2000) were added to the related microtitre wells and incubated for 1.5 h at 37 °C.

After final wash, 100 µl of the substrate (O-phthaldehyde (OPD), 5 mg; Na_2HPO_4 (0.2 M), 6.5 ml; citric acid (0.1 M), 6 ml; H_2O_2, 10 µl) was added to each well of microtitre plate and the absorbance was measured at 492 nm using a microplate autoreader.

Statistical analysis

The statistical calculations were performed with Chi-square and Fisher's exact tests for qualitative variants and *t*-test and Mann–Whitney test were used for quantitative variants. *P*-value of less than 0.05 was considered significant.

Results

Sex, age, height and weight of the IgA-deficient and control groups are shown in Table 1. No differences were found in height and weight between the two groups.

Serum and saliva immunoglobulin levels

Serum IgA, IgG, IgM and salivary immunoglobulins including SIgA, SIgG and SIgM and non-stimulatory secretion rate and also secretory component are shown in Table 2.

The lack of detectable SIgA (<10 µg ml^{-1}) was observed in IgA-deficient patients. Normal levels of serum IgM and IgG were

Table 1. **Sex, age, weight and height in IgA-deficient and control groups**

Variable	IgAd group	Control group	*P*-value
Total	11	11	–
Male	6	6	–
Female	5	5	–
Age (years)			
Mean ± SD	12.09 ± 4.76	11.77 ± 4.93	0.879
Range	3–18	3–19	
Weight (kg)			
Mean ± SD	33.4 ± 10.34	40.23 ± 18.76	0.307
Range	15–46	13–66	
Height (cm)			
Mean ± SD	135.90 ± 19.40	142.54 ± 26.38	0.510
Range	98–160	97–184	

Table 2. **Serum and saliva immunoglobulins levels in IgA-deficient and control groups**

Variable	IgAd group	Control group	*P*-value
Serum IgG (mg dl^{-1})			
Mean ± SD	1351.81 ± 777.54	1009.5 ± 380.02	0.204
Range	550–2500	400–1900	
Serum IgM (mg dl^{-1})			
Mean ± SD	141.27 ± 110.05	159.27 ± 77.16	0.662
Range	20–260	74–340	
Serum IgA (mg dl^{-1})			
Mean ± SD	10 ± 0.03	178.81 ± 102.01	0.0001*
Range	0–<10	70–372	
No stimulatory secretion rate			
Mean	427 µl per 2 min	705 µl per 2 min	0.22
SD	503.50	490.71	
Range	20–1500 µl per 2 min	50–1500 µl per 2 min	
SIgA (µg ml^{-1})			
Mean ± SE	1.95 ± 1.27	104.63 ± 12.63	0.0001*
SIgM (µg ml^{-1})			
Mean ± SD	31.13 ± 25.11	6 ± 6.24	0.004*
SIgG (µg ml^{-1})			
Mean ± SD	14.96 ± 13.78	12.40 ± 10.95	0.63
Secretory component (OD)			
Mean ± SD	1.28 ± 0.43	0.51 ± 0.19	0.0001*

*$P < 0.05$ is significant.

found in the IgA-deficient and control groups. Decreased levels of SIgA ($P < 0.0001$) and increased levels of SIgM ($P = 0.004$) were found in IgA-deficient patients as compared with the controls. No difference was found in salivary flow rate between IgA-deficient population and controls. Increased level of secretory component was observed in IgA-deficient individuals, compared with controls ($P < 0.0001$).

Clinical parameter in oral examinations

Oral ulcer, microbial plaque accumulation, decayed, missed and filled teeth (DMF) amounts and periodontal situations are shown in Table 3. The results show that there were no significant differences between both groups.

Discussion

The results of this investigation confirm those of the other study (8), suggesting that oral manifestations including microbial plaque accumulation, dental caries, periodontal lesions or diseases and oral mucosal infections are not significantly different in IgA-deficient patients comparing with control group. The results are discussed in the following subsections.

Table 3. **Clinical data in IgA-deficient and control groups**

Variable	IgAd group	Control group	*P*-value
Oral ulcer			
Aphtus	0	3	0.24
Herpes	3	0	0.49
Candida	0	1	1
Tonsillitis	42	40	0.349
Glossitis rhomboidea	0	6	0.349
Fissured tongue	6	0	0.349
Geographic tongue	6	0	0.349
Microbial plaque			
Mean ± SD	1.1970 ± 0.6742	0.7121 ± 0.6916	0.112
DMF amounts (mean ± SE)			
D	477 ± 1.62	3.88 ± 1.17	0.07
M	1.10 ± 0.39	0.68 ± 0.38	0.11
F	4.42 ± 2.07	2.53 ± 0.73	0.22
Periodontal situation			
Mean ± SD	1.1515 ± 0.979	0.50 ± 0.650	0.081

Oral manifestations

Previously, Bathall and Bjorkander (34) reported that hypogammaglobulinaemic patients might be a risk group in periodontal disease. Other studies showed that immunodeficients individuals, regardless of their impaired immune system, have no greater frequency of severe periodontal diseases than the immunocompetent population (35). In this study, oral manifestations showed no differences between IgA-deficient subjects and control group. During a 1-year follow-up period, some oral symptoms including geographical or fissured tongue, rhomboid glossitis, tonsillar hyperplasia either in IgA-deficient or control group were observed, but there were no statistically significant differences between the patients and controls. The results are in agreement with some studies (8, 29–31) and in disagreement with several other researches (26–28), which have reported recurrent aphtuses, recurrent herpetic infections, tonsillitis, pharyngitis, severe gingivitis and candidiasis as oral manifestations in IgA-deficient patients, but some of these studies had no control group. It is believed that the absence of oral manifestations in IgA-deficient patients may be a reflection of compensatory and protective effects of increased SIgM. Also, other immunological factors such as phagocytic system, cellular immunity and saliva and non-immunological factors such as peroxidase, lysozyme, etc., have compensatory roles. The controversial results in previous studies may be caused by genetic and/or nutritional factors in different societies. Nutrition and nutritional status can have profound effects on immune function. Malnutrition is strongly associated with impaired immunity and infectious diseases. In order to clarify nutritional status in this study, weight and height were measured. No differences were observed in weight and height

between the two groups. Thus, IgA deficiency in these patients could not be caused as a result of malnutrition. There were no differences observed in DMF indices between the two groups. The role of salivary immunoglobulins (IgA, IgG and IgM) in caries aetiology is not yet clearly identified. The role of salivary IgA in the protection against dental caries has been investigated in many studies, both in children and adults. The results of these studies were variable, with positive, negative or no correlation found between total salivary IgA and dental caries (36). In a 2-year study of immunoglobulin-deficient patients, Robertson *et al.* (35, 37) reported a lower caries problem and gingival inflammation in immunoglobulin-deficient patients, compared with normal individuals. Some investigations reported a high frequency of harbouring *Streptococcus mutans* and a greater susceptibility to dental caries in immunoglobulin-deficient patients (38, 39). In contrast, other investigations found only minor changes in oral microbial content of immunoglobulin-deficient individuals (40–42), and susceptibility to caries and periodontal diseases did not increase (37, 38, 41).

No differences in microbial plaque and periodontal status were observed between the two groups. This might be a result of good oral hygiene and care in these patients and controls. Both groups were trained at the beginning of this study. Defect of the immune system such as HIV-associated immunodeficiency (43–45) and severe combined immunodeficiency (44) can lead to increased incidence of periodontal diseases. Thus, the impaired host defence system in IgA-deficient individuals, which is mainly observed in the B-lymphocyte section, may not be severe enough to affect the periodontium (30, 35, 37) and the above mentioned population seems not to be in need of an extensive periodontal prophylaxis and care.

Oral hygiene is one of the most important factors in the maintenance of oral homeostasis and oral health. The mechanical removal of plaque by tooth brushing and flossing can almost completely prevent caries and periodontal disease (45, 46).

Salivary flow rate

The results of this study show no differences in salivary flow rates between IgA-deficient subjects and controls in order to confirm previous studies (8, 47, 48). There was no problem in salivary secretion in IgA-deficient patients as compared to controls. Thus, differences among immunoglobulin levels cannot be considered as a result of difference in salivary amount or volume between the two groups. No difference was observed in salivary volume. As a matter of fact, non-immunological factors accumulate in saliva for oral mucosal protection. Salivary immunoglobulins protect the mucosal and teeth surfaces from invasion and colonisation by bacteria, viruses and other antigens. A group of salivary proteins – lysozyme, lactoferrin and peroxidase – act in conjunction with other components of saliva to limit the growth of bacteria or kill them directly in support of periodontium.

Secretory and non-secretory immunoglobulins

The results of the present study show a decrease in serum IgA, normal serum IgM and IgG in IgA-deficient patients as compared to the controls. The lack of detectable serum and salivary IgA were observed in IgA-deficient individuals as compared to controls. No difference was observed in SIgG between the two groups; as a matter of fact, the main source of SIgG is serum. SIgG may already be derived from serum leakage through gingival or pocket fluid (49, 50), although oral mucosal plasma cells can produce IgG, but IgG cannot be secreted into saliva and this finding is in agreement with the study of Engstrom *et al.* (8). IgA is the first-line defence mechanism on mucous membranes and its deficiency causes an immune defect for which IgG tends to compensate. Also IgG hypergammaglobulinemia was reported as the most frequent accompanying serological abnormality in IgA deficiency. It may be caused by compensatory increased production, but may also reflect more profound immunlogical dysregulation in the disease (51). Also, It is reported that patients with symptomatic IgA deficiency frequently present IgG subclass deficiency and are more likely to have recurrent respiratory infections and greater changes in pulmonary function (52).

Elevated level of SIgM was observed in unstimulated whole saliva, which supports the previous study (8, 9) and confirms the hypothesis of a compensatory IgM increase in selective IgA deficiency (53). An enhanced local synthesis of IgM at mucosal surfaces is frequently observed in patients with selective IgA deficiency (9, 54) and IgA-deficient patients presented SIgM in levels much higher than the healthy children.

Secretory component

Secretory component was significantly higher in IgA-deficient group than controls. It might be caused by the lack of SIgA consumption, thus increased secretory component in IgA-deficient group was observed and it demonstrated that our patients were able to produce secretory segment.

There were no significant differences in oral manifestations between IgA-deficient subjects and controls, which may be a result of compensatory increase of saliva IgM or other non-immunological defence factors in saliva. Thus, it is not necessary to evaluate IgA and SIgA in all the patients with oral and dental lesions and it is thought that it is better to investigate other factors.

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