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Research Article

Association of Low Salivary Secretory Immunoglobulin A Levels with Symptomatic Allergic Rhinitis in Adolescents and Adults

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Abstract

Over the last decades, the incidence of allergic rhinitis (AR) has revealed a constantly increasing tendency worldwide. In Japan, Japanese cedar pollinosis (JCP) and perennial allergic rhinitis (PAR) mostly due to mite allergens are the predominant types of seasonal and nonseasonal ARs, respectively. We previously reported a relationship between low levels of secretory immunoglobulin A (sIgA) in saliva and clinical AR manifestations in adult patients with JCP. To confirm and extend our previous study, we conducted a cross-sectional study, in which salivary sIgA levels in adolescent and adult patients with symptomatic JCP and PAR were compared with levels in age- and gender-matched non-allergic control individuals during the Japanese cedar pollen dispersing season. The results showing the significantly lower salivary sIgA levels in JCP and PAR patients compared to control individuals led us to the conclusion that there is a negative correlation between salivary sIgA levels and clinical occurrence of AR in adolescents and adults. Moreover, it was also found that age and gender have no significant effect on salivary sIgA levels.

Keywords: Allergic Rhinitis; Immunoglobulin A; Japanese Cedar Pollinosis; Mucosal Immunity; Perennial Allergic Rhinitis; Saliva; Secretory Immunoglobulin A

Abbreviations

AR: Allergic Rhinitis; Fab: Fab Fragment; JCP: Japanese Cedar Pollinosis; PAR: Perennial Allergic Rhinitis; SC: Secretory Component; sIgA: Secretory Immunoglobulin A; IgA: Immunoglobulin A; IgG: Immunoglobulin G; ELISA: Enzyme-Linked Immunosorbent Assay; PBS: Phosphate-Buffered Saline

Introduction

Mucosal surfaces including those of the upper respiratory tract, are the main entry port for potential aeroallergens. Protecting these surfaces is ensured by the mucosal immune system, designated as mucosa-associated lymphoid tissues. Immunoglobulin A (IgA) is the predominant antibody in the mucosal immune system and the primary mediator of mucosal immunity found in mucosal fluids, such as saliva, tears, and respiratory and intestinal secretions [1]. Different from serum IgA which shows a monomeric structure, IgA existing in these secretions is mostly multimeric.

It consists of polymeric IgA and a secretory component (SC) molecule and is referred to as secretory IgA (sIgA) or mucosal IgA

[2,3]. It is commonly thought that sIgA in secretions may bind exogenous antigens, to block their adhesion to and penetration in the mucosa, and thus facilitate their elimination by peristalsis or mucociliary movements, a phenomenon termed immune exclusion [4]. Therefore, sIgA excreted in saliva or other mucosal fluids could be considered to interfere with the interaction between allergens and immunoglobulin E (IgE) antibodies in sensitized individuals, thereby preventing the development of allergy [5]. Moreover, many reviews suggest that selective IgA deficiency, a genetic disorder characterized by a permanent deficiency of IgA (including both monomeric and multimeric IgA), are associated with allergy [6-10]. In these reviews, together with allergic conjunctivitis, urticaria, atopic dermatitis, allergic asthma and food allergy, allergic rhinitis (AR) is reported as one of the most common allergic manifestations observed in IgA-deficient individuals.

Allergic rhinitis is among the main allergic diseases and is clinically characterized by several discomfortable nasal symptoms, such as sneezing, watery rhinorrhea and nasal obstruction, generating a global health problem due to the rapid increase in its prevalence worldwide [11,12]. In Japan, AR has been classified as seasonal AR and nonseasonal or perennial AR (PAR) [13]. Seasonal AR is predominantly caused by inhalating the pollen of the Japanese cedar (*Cryptomeria japonica*) and is thus referred to as Japanese cedar pollinosis (JCP), whereas PAR is most frequently caused by allergens from mites (*Dermatophagoides* spp.) [14,15]. The results of nationwide epidemiological studies on the general Japanese population showed that the prevalences of JCP and PAR in 2008 were 26.5% and 23.4%, respectively, while the rates in 2019 were 38.8% and 24.5%, respectively [16,17]. One of our major concerns has been the possible relationship between AR and deficiency or shortage of sIgA. We recently conducted an exploratory study, in which salivary sIgA levels were compared between a relatively small number of adult patients with JCP (n=20) and a similar number of non-allergic adult controls (n=22). The results of this preliminary investigation showed that the salivary sIgA levels in JCP patients were significantly lower than those observed in controls, suggesting that salivary sIgA shortage and JCP are associated [18].

To confirm and extend this finding, we undertook the present study, in which salivary sIgA levels for Japanese adolescents and adults were compared among the three age- and gender-matched study groups: (1) patients with JCP; (2) patients with PAR; and (3) randomly selected non-allergic control individuals. Moreover, effects of age and gender on salivary sIgA levels in each study group were analyzed.

Materials and Methods

Study design

This mucosal immunity survey was conducted on adolescent and adult Japanese patients with JCP and PAR, along with non-allergic healthy individuals, at the Wakayama Red Cross Hospital in collaboration with eight otolaryngology clinics in Wakayama Prefecture and Metropolitan Tokyo, Japan. This project was approved by the Review Board of the Life Science Promoting Association, Tokyo (Approval number : 2020-4).

Study population

Three groups of male and female individuals with a Japanese racial background between 14 and 70 years of age were invited to participate in the present study. The participants were patients with JCP and PAR diagnosed clinically and immunologically by otolaryngology/allergology experts who belonged to the participating hospital or clinics. The selected participants were divided into JCP and PAR groups. Healthy individuals with a negative history of allergic diseases, including AR, were randomly recruited from the general public as the age- and gender- matched control group.

Collection of saliva

All saliva samples were collected between 9:00 and 10:00 a.m. in the morning during the season when the Japanese cedar pollens were dispersed. After rising the oral cavity, saliva samples were collected using Salivettes® (Sarstadt AG and Co., Germany). The collected samples were immediately centrifuged at 3,000×g for 5 min at 5°C to remove cells and debris. The supernatants were stored at -70°C until use.

Quantification of sIgA in saliva

Detection and measurement of sIgA in saliva were performed using sandwich ELISA with the EIA SIgA Test® (MBL Corporation, Japan) according to the manufacturer's instruction. In this assay, saliva samples and each concentration of human sIgA standards were incubated at 37°C for 60 min with the anti-human SC-solidified porous polystyrene ball (MBL Corporation) placed in a tube. After washing with PBS, the tube receiving the reaction mixture

was incubated at room temperature for 60 min with a solution containing peroxidase-conjugated anti-human IgA rabbit IgG/Fab (MBL Corporation). After washing with PBS, the addition of O-phenylenediamine used as substrate (0.5ml/tube) detected the antibody binding to the polystyrene ball. Secretory IgA levels in saliva were detected by using a standard curve. The detection intervals were 0.06 to 64 μg/mL for human sIgA.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics version 24 (IBM Corporation, USA). Means with standard deviations of age and gender ratio were compared among the three study groups using the Mann-Whitney U-test and Pearson's χ^2 test, respectively. The Mann-Whitney U-test performed group-comparisons of the medians of salivary sIgA levels. The correlation between individual salivary sIgA levels and the participants' ages was analyzed using the Spearman's rank correlation coefficient. A probability level of < 0.05 was considered statistically significant.

Results and Discussion

Participant profiles

The demographic and clinical characteristics of the enrolled participants are shown in Table 1. Thirty patients with JCP (male/female: 13/17; mean ± SD age: 43.4 ± 17.6 yr) and 32 patients with PAR (male/female:13/19; mean ± SD age: 40.7 ± 16.5 yr) were successfully recruited based on their clinical signs and symptoms. Besides that, 31 of age- and gender-matched non-allergic control participants were also recruited. There were no statistically significant differences in age and gender ratio among these three study groups, i.e. JCP, PAR and control groups, indicating that they are age-and gender-matched.

Study group (n)	Age (years)		Gender ratio (male/female)	
Control (31)	36.6 ± 14.3	n.s.	12/19	n.s.
JCP (30)	43.4 ± 17.6	n.s.	13/17	n.s.
PAR (32)	40.7 ± 16.5	n.s.	13/19	n.s.

Table 1: Distribution of the overall participants of the three study groups by age and gender.

Control, without allergic desease; JCP, Japanese cedar pollinosis; PAR, perennial allergic rhinitis.

n.s., not statistically significant ($p > 0.05$, Student's t-test for age and χ^2 -test for gender ratio).

Comparision of sIgA levels among the three study groups

Secretory IgA was detected in the saliva of all 93 participants of the three study groups, including 38 males and 55 females. The mean salivary sIgA levels in both JCP patients (n=31) and PAR patients (n=30), compared to control individuals (n=32), were significantly low ($P < 0.001$ each) (Figure 1). Meanwhile, there was no statistical difference between the mean salivary sIgA levels of the JCP and PAR patients.

Thus, we demonstrate in this study that sIgA levels in adolescent and adult patients with JCP and those with PAR were significantly lower than non-allergic control individuals. These results are compatible to previous data obtained from our exploratory study using a smaller adult JCP patient cohort, in which mean salivary sIgA levels were compared between adult male and female JCP patients and non-allergic controls [18]. The association of salivary sIgA levels with the morbidity of two major ARs prevalent in Japan, JCP and PAR, revealed in the present study is in line with

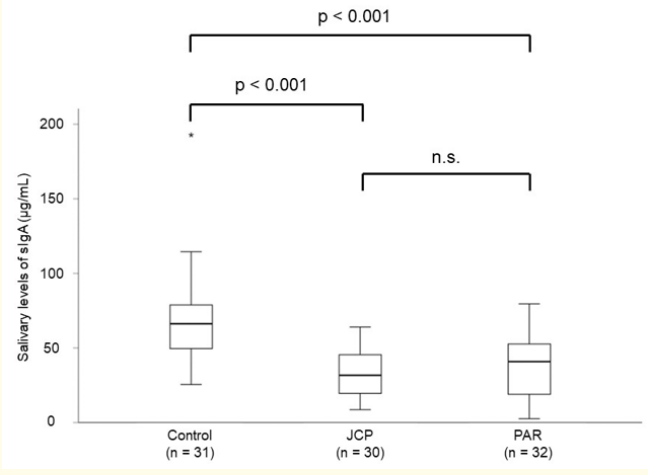


Figure 1: Between-group comparisons of salivary sIgA levels in the overall participants.

The box-plots indicate medians (bold horizontal lines) and interquartile ranges (box boundaries), whereas the whiskers represent 1.5 × interquartile ranges.

The circle and star denote measurements that are ≥ 1.5 and ≥ 3 times the interquartile range, respectively.

n.s., not statistically significant (p > 0.05, Mann-Whitney U-test).

The abbreviations of the three study groups are the same as those in Table 1.

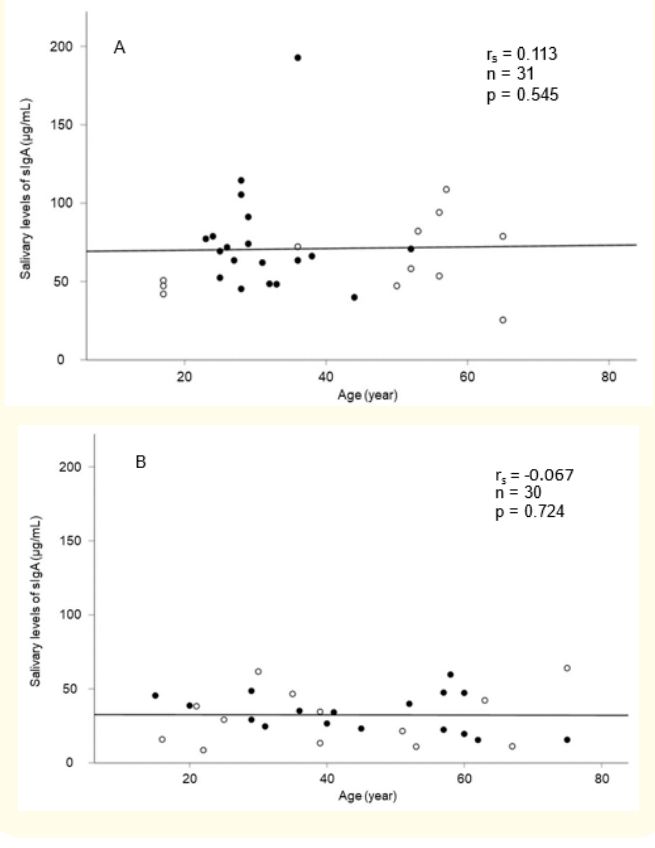
numerous studies on infants or children reporting that low mucosal sIgA levels correlated with the development or severity of AR [19,20] and various other allergic diseases, such as allergic asthma and atopic dermatitis [21-23]. Combining all data thus far obtained from pediatric allergy patients with ours on adolescent and adult AR patients, we are led to the possibility that low sIgA levels contribute to the development of AR throughout the whole course of patient's life.

There are also studies with sensitized infants showing that high sIgA levels are associated with less development of allergic symptoms [2,24]. In connection with these results, Tani-Ishii and his collaborators reported intriguing findings from an exploratory study conducted to confirm their clinical experience that wearing a mouthguard in the dental treatment unexpectedly may have some beneficial effects on patients with JCP [25]. Their results showed that, in adult JCP patients with a shortage of salivary sIgA levels, the one-week placement of mouthguard during a Japan cedar pollen dispersing season significantly improved AR symptoms, along with significant increases in salivary sIgA levels and saliva flow rates [25]. This leads us to the possibility that, like the mouthguard use, nutritional interventions with those dietary supplements, which are known to increase the sIgA level in mucosal fluids (e.g., bovine colostrum, lactoferrins, and probiotics), could be promising options for prevention or management of AR as mentioned in our review [26].

Relation of salivary sIgA levels to age and gender

Supplemental analyses were performed to examine whether the salivary sIgA level undergoes age-and gender-associated change. To our knowledge, no data have been published on the relationship of age and gender with sIgA levels for non-allergic adult individuals, to say nothing of sIgA levels for adult patients with AR or any other allergic disease.

The correlation of salivary sIgA levels with participants' ages in control, JCP and PAR groups are shown in Figures 2A, 2B and 2C, respectively. No correlation was observed between sIgA levels and age in participants of not only the control group but also the JCP and PAR groups.



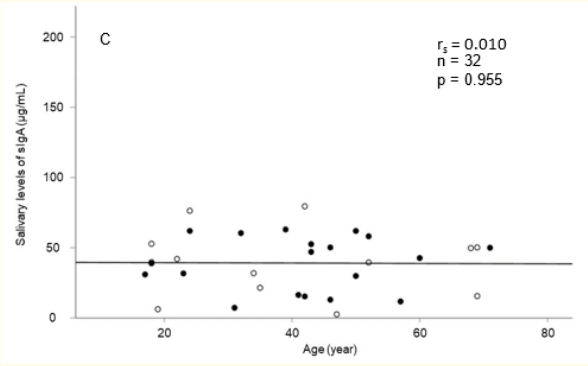


Figure 2: Scatter plots between salivary levels of sIgA (vertical) and participants' age (horizontal) in control (A), JCP (B) and PAR (C) groups.

Black and white circles represent male and female participants, respectively.

The correlation of individual values of salivary sIgA levels and participants' ages was performed by the Spearman's rank correlation coefficient.

Table 2 showed that there were no significant differences in mean salivary sIgA levels between male and female participants of the control group, as well as of the two AR patient groups (JCP and PAR groups). Moreover, it was also indicated that mean salivary sIgA levels in the JCP and PAR groups were still lower significantly than those in the control group, even when between-group comparisons were made with male and female participants alone (Table 2).

There are numerous reported studies, which were conducted to investigate the correlation of age and gender with the salivary level of IgA in healthy children and/or adults. In these studies, although gender was not associated with salivary IgA, age-dependent changes of the salivary IgA level was observed [27-33]. The discrepancy between the results of these studies and ours may be due to the molecular characteristics of salivary IgA that possibly contains monomeric IgA besides polymeric IgA referred to as sIgA. Thus, we demonstrate in the present study for the first time that age and gender have no effect on the salivary level in adolescents and adults whether they are allergic or not.

Study group	Number of participants		Median (μg/mL)		Range (μg/mL)		Between-gender difference (p-value)
	Male	Female	Male	Female	Male	Female	
Control	12	19	55.87	69.38	25.51 - 108.76	39.95 - 192.82	0.417
JCP	13	17	29.23	34.20	8.66 - 64.07*	15.51 - 59.70**	0.414
PAR	13	19	39.76	42.69	2.64 - 79.55*	7.28 - 63.02**	0.887

Table 2: The median levels and ranges of salivary sIgA in male and female participants of control, JCP and PAR groups.

*p< 0.05 and **p < 0.01 against control assessed by the Mann-Whitney U test.

Conclusion

Date obtained in this study lead us to the conclusion that salivary sIgA levels in adolescent and adult patients with symptomatic JCP and PAR significantly decreased compared with the levels in age- and gender- matched non-allergic control individuals. It was also found that age and gender have no significant effect on the salivary sIgA level not only in the control cohort, but also in the JCP and PAR patient cohorts.

Conflict of Interest

The authors declare no conflict of interest.

Bibliography

1. Cerutti A., *et al*. "Immunoglobulin responses at the mucosal interface". *Annual Review of Immunology* 29 (2011): 273-279.

2. Bo ttcher M., *et al*. "Total and allergen-specific immunoglobulin A levels in saliva in relation to the development of allergy in infants up to 2 years of age". *Clinical and Experimental Allergy* 32 (2003): 293-298.

3. Kaetzel CS. "The polymeric immunoglobulin receptor : bridging innate and adaptive immune responses at mucosal surfaces". *Immunological Review* 206 (2005): 83-99.

4. Corthe sy B. "Role of secretory immunoglobulin A and secretory component in the protection of mucosal surfaces". *Future Microbiology* 5 (2010): 817-829.

5. Boyaka PN. "Inducing mucosal IgA: A challenge for vaccine adjuvants and delivery systems". *Journal of Immunology* 199 (2017): 9-16.

6. Hammarstrom L., *et al*. "Selective IgA deficiency (SIgAD) and common variable Immunodeficiency (CVID)". *Clinical and Experimental Immunology* 120 (2000): 225-231.

7. Cunningham-Rundles C. "Physiology of IgA and IgA deficiency". *Journal of Clinical Immunology* 21 (2001): 303-309.

8. Janzi M., *et al*. "Selective IgA deficiency in early life: Association to infections and allergic diseases during childhood". *Clinical Immunology* 133 (2009): 78-85.

9. Morawska I., *et al*. "The epidemiology and clinical presentations of atopic diseases in selective IgA deficiency". *Journal of Clinical Medicine* 10 (2021): 3809.

10. Cinicola BL., *et al*. "Selective IgA deficiency and allergy: A fresh look to an old story". *Medicina* 58 (2022): 129.

11. Van Cauwenberge P., *et al*. "Consensus statement on the treatment of allergic rhinitis". *Allergy* 55 (2000): 116-134.

12. Bousguet N., *et al*. "Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA2LEN and AllerGen)". *Allergy* 63.86 (2008): 8-160.

13. Fujieda S., *et al*. "Examination, diagnosis and classification for Japanese allergic rhinitis : Japanese guideline". *Auris Nasus Larynx* 39 (2012): 553-556.

14. Okubo. K., *et al*. "Japanese guidelines for allergic rhinitis 2017". *Allergology International* 66 (2017): 205-219.

15. Sakashita M., *et al*. "Prevalence of allergic rhinitis and sensitization to common aeroallergens in a Japanese population". *International Archives of allergy and Immunology* 151 (2010): 255-261.

16. Okubo k., *et al*. "Japanese guidelines for allergic rhinitis 2014". *Allergology International* 63 (2014): 357-375.

17. Matsubara A., *et al*. "Epidemiological survey of allergic rhinitis in Japan 2019". *Nippon Jibiinkoka Gakkai kaiho (Tokyo)* 123 (2020): 485-490.

18. Yamamoto T., *et al*. "The relationship between allergic pollinosis and low salivary levels of secretory IgA in adults". *Acta Scientific Nutritional Health* 4 (2020): 16-21.

19. Lu dví ksson BR., *et al*. "Correlation between serum immunoglobulin A concentrations and allergic manifestations in infants". *Journal of Pediatrics* 121 (1992): 23-27.

20. Cortesina G., *et al*. "Mucosal immunity in allergic rhinitis". *Acta Otolaryngology (Stockholm*) 113 (1993): 397-399.

21. Calvo M., *et al*. "Evaluation of secretory IgA in childhood respiratory diseases". *Allergologia et Immunopathologia* 16 (1988): 157-161.

22. Gleeson M., *et al*. "Development of bronchial hyperreactivity following transient absence of salivary IgA". *American Journal of Respiratory and Critical Care Medicine* 153 (1996): 1785-1789.

23. Aghamohammadi A., *et al*. "IgA deficiency: correlation between clinical and immunological phenotypes". *Journal of Clinical Immunology* 29 (2009): 130-136.

24. Sandin A., *et al*. "High salivary secretory IgA antibody levels are associated with less late-onset wheezing in IgE-sensitized infants". *Pediatric Allergy and Immunology* 2 (2011): 477-481.

25. Tani-Ishii N., *et al*. "Effect of salivary secretion with mouthguard use on seasonal allergic rhinitis symptom improvement". *Journal of Oral Bioscience* 62 (2020): 205-211.

26. Yamamoto T., *et al*. "The function of secretory immunoglobulin A (sIgA) in saliva protecting against microbial infections and allergic diseases and potential measures to enhance sIgA secretion". *Japanese Pharmacological Therapy* 49 (2021): 533-562.

27. Kugler J ., *et al*. "Secretion of salivary immunoglobulin A in relation to age, saliva flow, mood states, secretion of albumin, cortisol, and catecholamines in saliva". *Journal of Clinical Immunology* 12 (1992): 45-49.

28. Widerstro m L., *et al*. "Increased IgA levels in saliva during pregnancy". *Scandinavian Journal of Dental Research* 92 (1984): 33-37.

29. Jafarzadeh A., *et al*. "Salivary IgA and IgE levels in healthy subjects : relation to age and gender". *Brazilian Oral Research* 24 (2010).

30. Miletic ID., *et al*. "Salivary IgA secretion rate in young and elderly persons". *Physiological Behavior* 1 (1996): 243-248.

31. Smith DJ., *et al*. "Effect of age on immunoglobulin content and volume of human labial gland saliva". *Journal of Dental Research* 71 (1992): 1891-1894.

32. Challacombe SJ., *et al*. "Age- related changes in immunoglobulin isotypes in whole and parotid saliva and serum in healthy individuals". *Oral Microbiology and Immunology* 10 (1995): 202-207.

33. Evans P., *et al*. "Social class, sex and age differences in mucosal immunity in a large community sample". *Brain Behavior and Immunity* 14 (2000): 41-48.