ORIGINAL ARTICLE

Salivary IgE in Children With Allergy: A Preliminary Study

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ABSTRACT

Introduction: Atopy is defined as the tendency of a person to produce IgE antibodies as a response to low levels of allergen exposure, such as proteins, which in turn triggers clinical symptoms of allergy such as asthma, rhinoconjunctivitis, or eczema. The diagnosis of allergy can be established by evaluating IgE levels in the serum, but this may cause discomfort in children. Salivary IgE examination is thought to be a less invasive alternative approach. This study aims to acquire data on the role of salivary IgE levels in detecting allergies in children. **Methods:** Subjects in the allergic case group were those with a previous diagnosis of allergy as determined by a paediatrician, had positive risk factors for allergy based on the Early Detection of Allergy Score Card from the Indonesian Paediatric Society, and had positive allergic symptoms based on the ChAt (Children Atopy) questionnaire. None of the criteria were found in the control group. Salivary IgE levels were evaluated in both groups using the ELISA Kit. **Results:** Both groups had 20 subjects, and the median salivary IgE level was normal with 0.26 IU/mL in the case group (min – max: 0.08 – 8.60 IU/mL) and 0.94 IU/mL (min – max: 0.08 – 9.82 IU/mL) in the control group, with a p-value of 0.9869. **Conclusion:** This study found salivary IgE was the same level in both groups. Feasibility of collecting salivary samples is higher from children over 5 years old and who understands commands.

Keywords: Atopy, Allergy, Salivary IgE

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INTRODUCTION

Allergic diseases such as atopic dermatitis, food allergies, asthma, and rhinoconjunctivitis are among the most common chronic diseases occurring in children. Exposure to allergens, including powders, animal dander, house dust, and food can result in increased serum IgE level in an allergic patient when compared to those without atopy (1). Many factors influence the level of IgE in children. Toddlers usually have prolonged exposure to allergen in infancy phase from foods, house dust mites, indoor molds, and animal dander with higher level of specific IgE for those allergens (2). Another study showed that infants with atopic dermatitis has an increase allergen specific-IgE antibodies for cow's milk (86.3%) and 5.8% for house dust mites (3). There are varied value of IgE serum in boys and girls (4). Other risk factors such as breastfeeding and malnutrition are also thought to influence the level of IgE in children thus affecting their susceptibility towards allergic diseases (5).

In 2003, the World Health Organization (WHO) reported that the prevalence of allergic diseases increases every year by around 5-15% (6). There have been many reported invasive or non-invasive methods for detecting children at risk of atopy. The Indonesian Paediatric Society's Allergy-Immunology Working Group utilizes an allergy risk card to detect if a family has a risk for allergy (7). Meanwhile, laboratory tests for blood IgE and skin prick tests are invasive but remain the gold standard to determine whether or not a child has atopy (8). Several studies have examined salivary IgE in children, but with variable results (9,10). However, this examination is non-invasive, and uses only a dropper to extract saliva from the mouth of the child. Although this examination may not be traumatic for a child, the cost to perform such examination remains high.

This study aims to identify the role of salivary IgE levels in detecting the presence of allergies in children. It is expected that there will be higher salivary IgE levels in allergic children compared to non-allergic children, prompting early prevention.

MATERIALS AND METHODS

This is a preliminary study to diagnose allergy from salivary IgE. The examination was carried out at the Faculty of Medicine Universitas Islam Negeri (UIN) Syarif Hidayatullah Jakarta and the analysis was done at the Biochemistry Laboratory, Faculty of Medicine, UIN Syarif Hidayatullah Jakarta. Subjects in this study were children from six month until five years old for both of allergic case and control group. This study used a numerical comparative analytic study in pairs, cross-sectional design. The research was conducted for six months from preparation to sampling (from July to Desember 2019). The sample size were twenty subjects in each of the two groups following parental consent. Subjects from the allergic case group were obtained from an outpatient private clinic and subjects from the control group were from a housing complex neighbouring the clinic.

The inclusion criteria in the case group were children who were previously diagnosed with allergies by a paediatrician with history taking and physical examination, met the criteria for moderate or high allergy risk according to the Indonesian Pediatric Society Allergy Immunology Working Group Early Detection for Allergy Score Card, and had positive score in the ChAt questionnaire (11). The subjects in the control group were healthy children, had no previous diagnosis of allergy from history taking and physical examination by a pediatrician, low risk of developing allergies according to the Early Detection for Allergy Score Card from the Indonesian Paediatric Society, and negative score in the ChAt questionnaire.

Patients with severe malnutrition and steroid consumption were excluded from the study. Nutritional status was determined using the standard WHO paediatric anthropometric software. Breastfeeding status were collected through history taking. Study approval and ethical clearance was obtained from the Faculty of Medicine of UIN Syarif Hidayatullah Jakarta, prior to the start of the study (Reference Number: B-022/F12/KEPK/TL.00/10/2019).

Specimen collection

All specimens were collected from the buccal and sublingual mucosa using a procedure described in a previous study (9). Direct saliva specimens were deposited in a sterile specimen pot and placed in an ice flask at 2-8^{o}C (12). All specimens were transported from the sampling room to a processing laboratory, and were subjected to centrifugation for twenty minutes at 1000 xg and 2^{o}C. The supernatants were collected and stored at -20^{o}C until analysis was performed with human IgE ELISA Kit E-EL-H216 (13).

Sampling Methods

A consecutive sampling technique was utilized in this study. Patients who came into the clinic that met the inclusion criteria were included in the study until the required number of subjects was met.

Tools

Demographic data, informed consent, nutritional status forms, infantometer, stadiometer, weight scale, sterile specimen pots, ice flask, centrifuge, refrigerator -20oC, ELISA reader Sunrise Tecan (14).

Materials

Saliva specimens, distilled water, ice, and human IgE ELISA Kit E-EL-H216(13).

Measurement of salivary IgE levels

Measurement of salivary IgE levels was analysed using a commercial kit of enzyme-linked immunosorbent assay (ELISA). The results are expressed in IU/mL for blood samples (16), but previous studies have also expressed salivary IgE levels in IU/dL (13) or µg/mL.(12) Salivary IgE normal level at 0-23 months old, 2-5 years old, and 6-10 years old are 0-13 IU/mL, 0-56 IU/mL, and 0-85 IU/mL respectively (15).

Statistical analysis

Characteristic baseline data such as age, gender, nutritional status, and exclusive breastfeeding or not, are summarized with univariate analysis. Bivariate analysis was carried out to find the relationship between the nutritional status and exclusive breastfeeding with the salivary IgE level in both groups. Data were analysed using SPSS 22 for Windows and summarized in narration, box plot, bar, and table.

RESULTS

A total of forty three subjects were included in this study, twenty two in the allergic case group and twenty one in the control group. Three children (two from the allergic case group, and one from the control group) dropped out due to refusal in providing saliva specimens, leaving twenty subjects in each of the two groups. Median age from the allergic case group was 23 months old, (min-max: 10-58 months old) and in the control group was 30 months old (min-max: 7-60 months old). There were more males in both group with twelve subjects (60%) in the allergic case group and eleven subjects (55%) in the control group. Good nutritional status was found in sixteen subjects (80%) in the allergic case group and twelve subjects (60%) in the control group. Exclusive breastfeeding was given in eleven subjects (55%) in the allergic case group and ten subjects (50%) in the control group. Bivariate analysis of the two groups are shown in table I. There was no association between age and allergy with p-value= 0.0718 (using logistic regression) or gender and allergy with p-value= 0,7491 (using Chi-square test). There was no significant differences in nutritional status (p-value = 0,1675, using Chi-square test) and history of exclusive breastfeeding between the

Table I: Baseline characteristics and bivariate analysis

Variable	Allergic Case Group n(%)	Control Group n(%)	p value
Age (median age)	23 months old Min-max (15-30 months)	30 months old Min-max (25-50 months)	0.2958
Sex			
Male	12 (60)	11 (55)	0.2822
Female	8 (40)	9 (45)	
Nutritional status			
Good nutritional status	16 (80)	12 (60)	0.1675
Malnutrition	4 (20)	8 (40)	
History of breastfeeding			
Exclusive breastfeeding	11 (55)	10 (50)	0.7515
Non exclusive breastfeeding	9 (45)	10 (50)	

two groups (p-value= 0.7515, using Chi-Square test).

Saphiro Wilk test was used to test for normality distribution because of the small sample size. Means of salivary IgE in the allergic case group and control group were 1.145±1.99 and 2.19±2.73 respectively. Comparison of salivary IgE concentrations in both groups were analysed using the Mann-Whitney U-test with a p-value = 0.9869 (p> 0.05), The median salivary IgE level in the allergic case group and the control group were 0.26 IU/mL (min – max: 0.08 – 8.60 IU/mL) and 0.94 IU/mL (min – max: 0.08 – 9.82 IU/mL) respectively. There is no significant difference of salivary IgE level between the two groups (Figure 1).

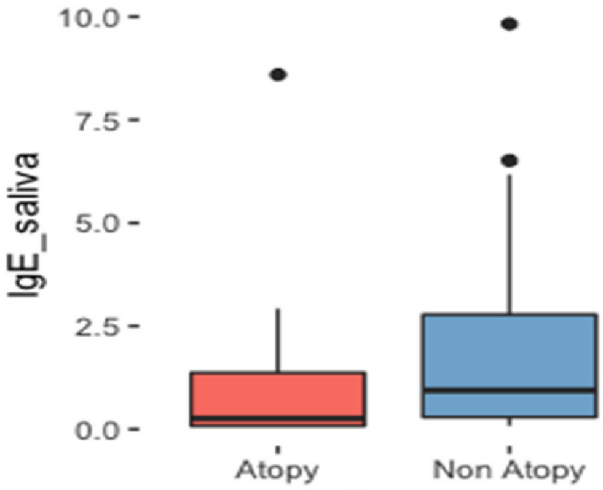

Figure 1: Salivary IgE level in case and control group

DISCUSSION

Many tools can detect sensitization of allergen like skin tests (skin prick test, intradermal test, or patch test), total serum IgE (2,19), a radioallergosorbent test (RAST) for specific IgE antibodies (19), allergen-specific IgE assays such as multiplex assays, cellular assays: basophil activation test (BAT), allergen provocation test, and many more (2). The non invasive tools like ChAt questionnaire or salivary IgE can be an alternative to detect allergy in children. Salivary IgE is considered a less invasive method compared to other tools, but the results still vary (9).

The baseline characteristics found that the subjects in the control group were older than the allergic case group although there were in the range six months until five years old. Several studies found that salivary IgE in neonates (10) and children (20) are low compared to adults. Allergies can be detected with serum IgE and SPT under 6 months old (atopic dermatitis) who were followed until the age of 5 years (3). Another study found that a persistent value total serum IgE ≥ 200 kU/L since infancy is strongly associated with allergies toward food and mite which can develop into eczema in infants, and rhinitis and asthma in early childhood (21).

In this study there were more males in the allergic case group. The salivary IgE in males and females were both in the normal value. The other study found that the total serum IgE level was not significantly different between male and females (21) but another study found that the mean value of total IgE in males was higher than in females with p <0.001)(4). A previous study found that males had a higher total IgE serum than females, and a significantly higher prevalence of asthma, rhinitis, and atopic dermatitis than females (22). This was also evident in another study where males were more allergic in early childhood whilst females were more allergic in early adulthood (23).

Nutritional status was considered as a potential confounding factor in this study. Previous studies reported that malnourished children had lower levels of serum IgE (16,25-30). Forte et al. (31) found that median serum IgE level were lower in malnourished children than control. This finding was not apparent in other studies. Wahyuni et al. (32) showed that children with low z score of BMI had reduced eosinophil count but no difference in the IgE level. Salivary IgE showed no clear pattern based on nutritional status, but the production of gastric acid and flow of saliva is reduced in malnourished children which may affect the amount of antibodies extracted (33).

Non-breastfeeding is commonly associated with atopic disease. Breastmilk is thought to facilitate early maturation of intestinal barrier and provides a passive barrier to potential antigenic molecules (34). Chiu et al. found that children who were exclusively or partially breastfed for 6 months or more appeared to have lower level of serum IgE than those who were not, though this finding was not statistically significant. History of breastfeeding also influenced salivary IgE levels, as higher levels were found in formula-fed patients (34). This was thought to be the mechanism of how non-breastfed children had a higher tendency to develop allergic diseases (20,27-30). Kim et al. (5) showed that there was no correlation between duration of breastfeeding and IgE level, whilst

Husain et al. (35) showed no differences in IgE level between breastfed and non-breastfed children. Another study showed that maternal IgE level heavily influenced the level of IgE in breastfed children (36) thus making history of breastfeeding a highly potential confounding factor in this study. Our study did not find any significant differences in nutritional status and breastfeeding between the allergic case and control group.

A diagnosis of allergy can be made through history-taking by evaluating the symptoms, risk factors, and known allergens that may have caused the allergic symptoms, followed by a thorough physical examination. This can be further supported by performing diagnostic examinations. The gold standard for diagnosing allergy is performing a skin prick test, but this examination can cause discomfort in patients, particularly children, due to the local allergic reaction that it may cause (29). In this study, the subjects in the allergic case group were diagnosed as having allergic disease through a series of examinations, including the Early Detection for Allergy Score Card to assess the risk for allergy, ChAt questionnaire, and previous diagnosis of allergic disease by a paediatrician.

The risk for allergy was determined using the Early Detection for Allergy Score Card from the Allergy-Immunology Working Group of the Indonesian Paediatric Society. All subjects in the allergic case group showed a risk for allergies. This scoring system emphasizes on the genetic predisposition of allergic disease (30). The ChAt questionnaire, a 10-item questionnaire, looks for allergic symptoms and is aimed to identify children with allergies (11). The sensitivity and specificity of this tool is 92% and 90%, respectively. This novel questionnaire is a simple tool to detect any major allergic disease, allowing early identification and management of allergic disease in children (11). In this study, all subjects from the allergic case group had a positive score and from the control group had a negative score for allergies according to the ChAt questionnaire.

The specific IgE levels in the serum can be used to confirm the clinical suspicion of allergic disease in a child (2). This method is considered safe and highly sensitive for the diagnosis of allergy, but is an invasive procedure. A positive result in the specific serum IgE does not always result in a clinical manifestation of allergy, and therefore it is important to have a medical history and knowledge of disease characteristics in interpreting the results (23). Another tool to confirm allergies in children is using the basophil activation test (BAT) and allergen provocation test but it is high in cost (2).

This study showed higher levels of salivary IgE in the control group compared to allergic case group but the difference was not statistically significant . This finding is in accordance to that from Vernejoux et al.(37) which reported no significant differences in salivary IgE levels between the allergic and non-allergic groups. Although IgE is more easily detected in the saliva of atopic patients, its titration does not correlate with serum IgE, and the results are usually very low, at <2 IU/mL. Another study showed that detectable salivary IgE concentrations were higher in adults compared to children, where 68% of children showed undetectable salivary IgE concentration. This concentration is reported to increase with age (10).

This study found no difference in the median salivary IgE level between the allergic case group and control group, but the highest salivary IgE level was found in the allergic case group at 20.63 ng/mL, or 8.60 IU/mL. It is proposed that allergic symptoms may influence salivary IgE levels, as patients with pollen-induced allergy have been reported to demonstrate higher concentrations of salivary IgE during pollen season. Natural exposure to allergens at the time of examination can increase salivary IgE concentrations (37). The symptoms experienced by subjects during the time of examination were not recorded, and therefore we were unable to prove whether the subjects were having allergic symptoms that may correlate with the salivary IgE levels. This may cause the salivary IgE level in the case group not increase as expected. Genetic polymorphisms have also been related to the increase and decrease of IgE levels. For instance, IL-13 gene polymorphism has been identified to be correlated with both serum and salivary IgE concentrations (38).

This study aimed to find an alternative to serum IgE examination for identifying children with allergic disease, due to its invasive nature. The idea of collecting saliva for an alternative examination to detect allergic disease was thought to be promising. This study showed inconclusive results, which was attributed to the many factors that may have influenced salivary IgE concentration. Previous studies found that age affects salivary IgE levels, and its concentrations are usually very low in younger children, and IgE levels were low compared to IgA levels in saliva (20). The other study found that IgE levels would increase with age and demonstrated the cut off points of IgE levels in each age group (10).

Limitations in this study included the absence of specific serum IgE examinations in both groups, as well as stool examinations to rule out intestinal parasite infestations that may affect IgE levels. In our experience, it was difficult to obtain salivary samples from children under 6 years old when compared to collecting blood samples, because the subjects constantly swallow their saliva. Laboratory technicians had to wait longer to extract the desired volume of saliva, and this method was deemed to be impractical. Sampling of saliva through active extraction from the subject is preferable. It would have been better if children who are tested understood commands so they can actively provide specimens without being restrained. The advantages of this test are

the less time to receive the results, and a more simple method of examinaton. However, varying results from other studies also make salivary IgE not ideal to detect allergy in children alone (39).

CONCLUSION

Salivary IgE was the same level in both allergic case group and control group. Obtaining salivary sample from children under five years old is not ideal because of difficulty in following commands.

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