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The critical role of allergen-specific IgE, IgG4 and IgA antibodies in the tolerance of IgE-mediated food sensitisation in primary school children

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Primary objective. There are about 6% of children who are either intolerant to or lose their ability to tolerate food allergens, resulting in the development of food hypersensitivity. The hypothesis that increase in food allergen-specific IgE antibody level is associated with the decrease in the levels of food allergen-specific IgG4 and IgA antibodies was used as a biomarker of food tolerance.

Methods & Procedures. The Modified International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire (added gastrointestinal allergy questions) and Phadiatop infant test were used to screen one hundred 6–8-year-old allergic school children. Food allergen-specific IgE, IgG and IgA antibodies were measured by using the Phadia ImmunoCAP system radioabsorbent test (RAST). Immunoglobulin E antibodies to common aeroallergens, were also detected by enzyme-linked immunosorbent assay. **Main outcome.** The level of analysed food specific-IgE antibody was obviously higher in the study population. Sensitivity to dust mites among the children was nearly 90%, and that to cockroach was 47%. Egg white-, cow's milk-, α -lactoalbumin-, β -lactoglobulin- and casein-specific IgG4/IgE and IgA/IgE ratios were lower in the atopic school children but not in the tropomyosin-, mango- and kiwi-sensitive participants.

Conclusion. The level of cow's milk- and egg white-specific IgE antibody still remained high along with a decrease in the specific IgG4/IgE and IgA/IgE ratios in our study population. Therefore, allergen-specific IgG4 and IgA antibodies are important biomarkers of tolerance establishment, and failure to establish tolerance to food allergens may be related to the regulation of the inhalant allergens encountered in late childhood stages.

Keywords: allergen; allergy; foods; immunoglobulin; sensitivity; food allergen; aeroallergen; tolerance; asthma

Introduction

Food allergy (FA) can be clinically expressed as a condition characterised by a variety of immunoglobulin (Ig)E- and non-IgE-mediated respiratory symptoms, and food and inhalant allergens play an important role in the induction and exacerbation of respiratory allergic diseases (Eigenmann et al., 2008; Jesenak et al., 2008)

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Aeroallergen sensitisation and family history of asthma are known predictors of a significant association between FA and asthma. This association was found to be even stronger in subjects with multiple food allergies or severe FA (Schroeder et al., 2009). Moreover, self-reported FA is an independent risk factor for potentially fatal childhood asthma. Asthmatic children or adolescents with FA require highly aggressive asthma management (Vogel et al., 2008). FA is more frequently noted in children with asthma who also have skin and gastrointestinal disorders than in those only with asthma. Hence, the determination of the possible concomitant conditions with FA has been recommended in children with asthma (Krogulska, Wasowska-Krolikowska, & Trzezwinska, 2007). However, the foods responsible for producing allergic reactions vary with age. The clinical presentation also changes with the variation in food allergens, although the skin is the most frequently affected organ (Fernandez Rivas, 2009). In a survey on common allergens among 6–8-year-old grade 1 and 2 primary school children in Taipei that was conducted in 2009, we found that the sensitivity to aeroallergens, including dust mites (df, dp and bt), and German cockroaches, was high, with a prevalence of about 90 and 47%, respectively. Cow's milk and egg white sensitisation were also common among school children (prevalence: 22.85 and 24.23%, respectively) (Wan, Yang, & Wu, 2010). Literature review revealed that FA gradually decreases with age, and the level of specific IgE antibodies against antigens in the tolerant group was found to be lower than that in the intolerant group. Children develop tolerance to cow's milk, egg white and wheat usually by the age of 6 years (Imai et al., 2007). The gastrointestinal tract is generally exposed on a daily basis to an array of dietary proteins, but the majority of proteins are tolerated orally. However, in about 6% of children and 4% of adults, tolerance to a given dietary antigen is either not established or the ability to establish tolerance is lost, resulting in food hypersensitivity (Burks, Laubach, & Jones, 2008). We hypothesise that failure to establish food tolerance may upregulate the formation of aeroallergens and increase the risk of respiratory allergic diseases. Therefore, to identify the biomarkers of allergen tolerance and to induce tolerance in allergic individuals is one of the important objectives of asthma control.

Material and methods

One hundred 6–8-year-old primary school children were randomly selected to screen for allergy by using the modified International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire and the Phadiatop infant test. In each allergic individual, the levels of IgE, IgG and IgA antibodies against the most common food allergens, including egg white, cow's milk, α -lactoalbumin, β -lactoglobulin, casein, tropomyosin, kiwi and mango, were measured by using the Phadia ImmunoCAP system radioabsorbent test (RAST). The levels of IgE antibody against dust mites, including dp, df and bt, and cockroach were also measured by RAST. The ratios of IgG4/IgE, IgA/IgE and IgA/IgG4 for the different food allergens were analysed and compared.

The Statistical Package for Social Sciences (SPSS™ version 12 for Windows™; SPSS, Inc., Chicago, IL, USA) software was used for statistical analysis. A *P* value of <0.05 was considered as statistically significant.

Results

The rate of positive reaction against antigens in the 100 school children was 92.13% ($n = 82$); this rate was compared with the result of the ISAAC questionnaire allergy screening test. The positive rates of specific IgE antibodies against the inhalant allergens (dust mites, including dp, df and bt, and cockroach) and food allergens (egg white, milk, α -lactoglobulin, β -lactoalbumin, casein, tropomyosin, mango and kiwi) were 90%, 86%, 83% and 47%; and 29%, 16%, 42%, 12%, 11%, 28%, 4% and 9%, respectively. The allergen-specific IgG4 and IgA levels are shown in Table 1. The IgG4/IgE and IgA/IgE ratios were markedly lower in the allergen-specific IgE-positive school children than in allergen-specific IgE-negative school children (Figures 1 and 2). Allergen-specific IgA and IgG4 levels might possibly be the target biomarkers of food intolerance and food allergen hypersensitivity in 6–8-year-old school children.

Discussion

Food incompatibilities affect approximately 20% of the general population in Western countries. In about one-fourth of the affected children and one-tenth of the affected adults, the incompatibility is associated with an allergy, that is, on an immunologically generated incompatibility reaction (Bischoff, 2007). FA is defined as an immune system-mediated adverse reaction to food proteins. Some representative class 1 food allergens are peanut, egg white and cow's milk; they are heat- and acid-stable glycoproteins that induce allergic sensitisation via the gastrointestinal tract and cause a systemic reaction. Class 2 food allergens are homologous to proteins in birch tree pollen and pollen, and class 2 FA develops as a consequence of respiratory sensitisation to the cross-reactive pollen. Class 2 food allergens are very heat-labile and tend to induce reactions limited to oral allergic symptoms (Nowak-Węgrzyn, 2007). Although any food can provoke an allergic reaction, relatively few foods are responsible for the vast majority of significant food-induced allergic reactions, such as milk, egg white, peanuts, tree nuts, fish and shellfish (Sicherer & Sampson, 2006). Moreover, large, prospective population-based studies on clinical

Table 1. The positive rates of specific IgE antibodies and the mean value of specific IgG4, specific IgA against the food allergens.

	Spec.-IgE Positive rate (%)	Spec.-IgG4 Mean (mgA/L)	Spec.-IgA Mean (mgA/L)
f1, egg white	30	17.46	0.87
f2, Milk	17	32.53	52.39
f76, α -lactalbumin	13	16	1.11
f77, β -lactoglobulin	5	13.11	1.7
f78, casein	11	29.85	8.5
f351, tropomyosin, Shrimp	27	0.18	0.61
f91, mango	5	1.44	2.02
f84, kiwi	9	4.07	1.67

Note: 1. Specific IgE positive (+) ≥ 0.35 KUA/L.

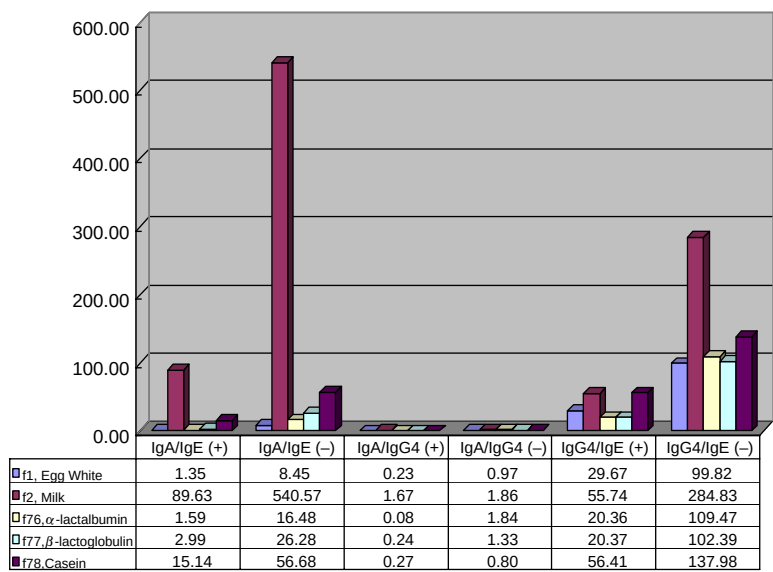


Figure 1. The IgG4/IgE and IgA/IgE ratios in the allergen-specific IgE-positive school children and in the allergen-specific IgE-negative school children.

course, development of tolerance and risk for other atopy in children with IgE-positive cow's milk allergy (CMA) have shown that the tendency of developing allergic reaction is higher in children who have asthma (31%), rhinoconjunctivitis (66%), atopic eczema (81%) and sensitisation to any allergen (88%) than control subjects. Thus, IgE-mediated CMA often persists during childhood and is a risk factor for other atopy (Saarinen et al., 2005). According to our current study in 2009, the percentage of cow's milk and egg white sensitisation remained high even in 6–8-year-old school children instead of decreasing and inducing tolerance (Wan et al.,

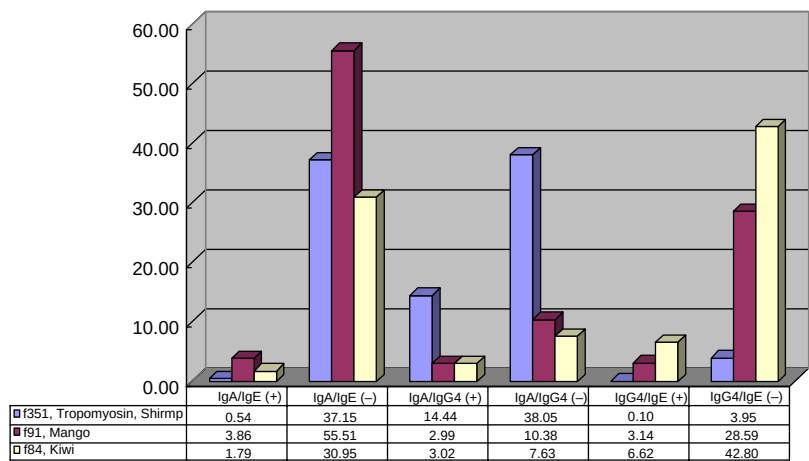


Figure 2. The IgG4/IgE and IgA/IgE ratios in the allergen-specific IgE-positive school children and in the allergen-specific IgE-negative school children.

2010). Therefore, determining the reasons and identifying the biomarkers responsible for the persistence of food intolerance with increasing aeroallergen sensitivity in late childhood is important.

The development of tolerance in IgE-mediated allergies has been associated with lower cow's milk-specific IgE level, higher IgG4 level and constant IgA level (Ruiter et al., 2007; Savilahti, Saarinen, & Savilahti, 2010). Thus, high cow's milk-specific IgE level is predictive of the persistence of CMA, and development of tolerance is associated with elevated levels of β -lactoglobulin-specific serum IgA and subsequent increased levels of β -lactoglobulin- and α -casein-specific IgG4 (Savilahti, Saarinen, & Savilahti, 2010). Moreover, eczematous food-sensitised infants with high levels of IgG4 and high ratios of IgG4/IgE antibodies to food allergens are more likely to consume these foods at 4(1/2) year than infants with low levels and ratios (Tomicic et al., 2008). In the food-allergic children in whom oral-specific desensitisation was successful, food allergen-specific IgE level showed a significant decrease, whereas food allergen-specific IgG4 level showed a significant increase (Patriarea et al., 2007). Sletten reported a tolerance-induced inhibition of the Th2-type of immune response with significant increase in IgA dominance in CMA patients. This was because in the tolerant patients, there was an apparent shift in the humoral immune response from a β -lactoglobulin-specific IgE- and/or IgG4-dominated immune response to an IgA-dominated immune response with a 90- and 15-fold increase in the IgA/IgE or IgA/IgG4 ratios in the tolerant IgE- and non-IgE-mediated CMA patients, respectively (Sletten et al., 2006). However, the European Academy of Allergology and Clinical Immunology (EAACI) task force report showed that testing of IgG4 responses to foods is irrelevant for the laboratory report-based confirmation of FA or intolerance and should not be performed in the cases of food-related disorders (Stapel et al., 2008). In our current study, we found that food allergen-specific IgG4/IgE and IgA/IgE ratios were markedly decreased in the IgE-mediated allergic school children but not in the non-IgE-mediated allergic school children. The current prevalence of any atopic disease is 20% at 1.5 years of age, declining to 14% at 5 years of age, followed by an increase to 25% at 10 years of age. Sensitisation to inhalant allergens and/or food allergens showed a lower rate of sensitisation among asymptomatic (3, 10 and 12%) than in symptomatic (8, 39 and 30%) atopic patients at 1.5, 5 and 10 years of age, respectively. Moreover, the highest rate of sensitisation (53%) was found among children with persistent asthma at 10 years of age (Host et al., 2002).

In conclusion, failure to establish tolerance to food allergens might upregulate sensitisation to inhalant allergens. Thus, there is a need to understand the mechanisms underlying allergen intolerance and identify biomarkers for food intolerance to devise treatment and prevention methods to control asthma by inducing tolerance in hypersensitive individuals.

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