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ORIGINAL RESEARCH

Aeroallergen Sensitization and Its Changes in Adult Asthmatics Managed by Primary Care in the Western Yokohama, Japan

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Background: Knowledge of aeroallergen sensitizations is important for environmental adjustment in asthma management. We investigated the allergen sensitization status of adult asthmatics managed by primary care physicians.

Methods: We recruited 119 patients who measured "IgE-CAP16 allergic asthma (LSI medience)" three times in 2 years from patients who visited St. Marianna University Yokohama Seibu Hospital, between January 2009 and May 2018, and managed by primary care physicians.

Results: Sensitization rates (IgE Class ≧ 1) were high for house dust (33.6%), Japanese cedar (54.6%), mite (34.4%), and moth (24.3%) at baseline. Frequent associations were found at baseline between house dust and mite and, between Japanese cedar and cypress, as well as among insects and among fungi. Cluster analysis classified the IgE responses into seven categories. Allergens for which 10% of subjects changed to Class ≧1 over the 2 years were house dust (20.1%), mite (12.6%), Japanese cedar (31.1%), cypress (24.3%), ragweed (10.9%), moth (18.5%), *Candida* (21.8%), and *Aspergillus* (16.8%). Thirty-five subjects (29.4%) had no changes in any sensitization levels. Allergens with a correlation coefficient (R) of ≧0.3 between Δspecific IgE and Δtotal IgE were with ΔIgE were Δ*Alternaria* (0.366), Δmoth (0.307), and Δalder (0.302). The degree of asthma control was not associated with changes in the ImmunoCAP IgE class.

Conclusion: Aeroallergens were classified into seven clusters. Even in stable asthma managed by primary care physicians, allergen sensitization can change, so that these changes should be checked over time.

Keywords: asthma, primary care, aeroallergen, IgE, clinical remission

Introduction

Asthma is characterized by clinical symptoms such as wheezing, dyspnea, chest tightness, and coughing due to variable airway narrowing resulting from chronic inflammation.[1] This inflammation involves inflammatory cells such as eosinophils and Th2 lymphocytes, type 2 cytokines, and airway constituents such as airway epithelial cells and airway smooth muscle cells. In Japan, the prevalence of bronchial asthma is reported to be 11–14% in children and 6–10% in adults.[1] It is a disease with a high prevalence, and primary care physicians often have to manage it. As an allergic disease, asthma is affected by sensitization to inhaled allergens.

In Japan, the main aeroallergens are mite, house dust, pollen, fungi, proteins from animals or insects. In clinical practice, specific IgE tests are often used to screen for possible allergens. Antigen sensitization has regional specificity. Japan is a long country spanning 3500 km from north to south. It has a warm and humid climate with distinct seasons, and different conditions between the Pacific side and the Sea of Japan side, meaning that there are large regional differences in vegetation and insect distribution, and regional differences have also been found in allergens. In the previous study of adults and children throughout Japan,[2] the positivity rates were low for Japanese cedar in Hokkaido and Okinawa, for alder in Hokkaido, and for insects in Okinawa and Kyushu. In addition, Tanaka et al[3] found clear regional differences in Japanese cedar and alder allergy among adults in Sapporo, Tokyo, Osaka, Fukuoka, and Okinawa. Similar allergens cross-react; among the inhaled allergens with high

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positivity rates in Japan, similar ones such as Japanese cedar and cypress, mite and house dust, and various types of insect proteins are known to cross-react, and a survey in Japan found relationships within groups of pollen-derived, microbe-derived, and animal-derived antigens.[4] However, there are no reports on the time course of aeroallergen sensitization in mild adult asthma managed by primary care.

Asthma is often managed by primary care physicians owing to its high prevalence, but detailed examinations are difficult to perform outside of specialized facilities, so it must often be diagnosed and treated in a restricted environment. As a result, little knowledge has been accumulated. In the western area of Yokohama, St. Marianna University Yokohama Seibu Hospital and primary care physicians have cooperated to establish a hospital-clinic collaboration system. Stable asthmatics are managed by primary care physicians and undergo regular detailed examinations once a year, that reflect the status of their asthma under primary care management.[5] In the previous studies about this management system, we reported on the frequency and duration of exacerbations,[5] the progress of spirometry and oscillometry,[6] and the progress of fungal allergy.[7]

Therefore, on the basis of the hypotheses that (1) aerosensitization changes over time even in stable asthma under primary care management, and (2) patients with worsening sensitization tend to show worsening of their asthma, we investigated the changes in serum specific IgE over time in asthma patients managed by the collaboration.

Methods

Patients' Data

We extracted data from the outpatient respiratory department of St. Marianna University Yokohama Seibu Hospital on 119 asthma patients. These patients had been assessed three times over a 2-year period between January 2009 and May 2018, by using the ImmunoCAP system for IgE-CAP16 allergic asthma (LSI Medience, Tokyo) (CAP16) managed via asthma clinic-hospital collaboration system. We measured IgE at baseline, one year later, and two years later, all in the same season.

An asthma diagnosis was confirmed by respirologists in Yokohama Seibu Hospital on the basis of the asthma prevention and management guidelines at the time.[1,8,9] Patients who did not show signs of asthma (as determined from their medical information records), and were thought to have other respiratory diseases, patients with unknown details because of the disposal of medical records, and patients in whom CAP16 could not be measured three times in 2 years were excluded.

Asthma Control

On the basis of this report and the Asthma Prevention and Management Guidelines 2021 in Japan,[1,10] the asthma control status was classified into three groups as well controlled (WC), inadequately controlled (IC), and poor controlled. The well-controlled (WC) group was defined as having no symptoms and using short acting beta agonist (SABA) less than once a month. The inadequately controlled (IC) group was defined as not meeting the criteria for WC because of symptom induction or the need for treatment in addition to SABA. In this study, there were no poor control asthmatics, and most were in the WC group. In recent years, the concept of clinical remission (CR) has been proposed for especially well-controlled asthma.[10] Therefore, we defined the CR group as having had no symptoms for 2 years and having maintained $\%FEV_1 \geqq 80\%$.

Allergic Sensitization

Aeroallergen-specific serum IgE was measured by using the ImmunoCAP system for IgE-CAP16 allergic asthma (LSI Medience, Tokyo). The CAP16 items are house dust, mite, Japanese cedar, cypress, alder, orchard grass, ragweed, mugwort, cat, dog, cockroach, midge, moth, *Candida, Alternaria*, and *Aspergillus*. Class ≧1 was considered to indicate sensitization, and if a patient's specific IgE level changed over the observation period to Class I or higher, change was considered significant. If the test was positive for one or more perennial antigens, the test was considered to indicate atopic asthma.

Fraction of Exhaled Nitric Oxide (FeNO)

The FeNO (fraction of exhaled nitric oxide) was measured with NIOX-VERO (Chest, Tokyo) in accordance with the instruction manual. With the measuring device attached, the subject exhaled at 50 mL/s after maximum inspiration, and the value at which it was judged that exhalation was suitable for measurement by NIOX-VERO was recorded.[11]

Spirometry

Spirometry was performed with CHESTAC-8800 (Chest, Tokyo).[12] Maximum inspiration and maximum expiration were performed, and FVC, FEV_1, and flow-volume curves were evaluated. The value when sufficient maximum forced expiration was achieved was recorded.

Statistical Analysis

Statistical analysis was performed in JMP Pro 16 (SAS Institute, Cary, NC, USA). Each index was shown as a frequency or mean and standard deviation or median and quartile, and the Mann–Whitney *U*-test was used to determine differences between groups, with $p < 0.05$ considered significant. Chi-square test or Fisher's test was performed to determine the association between the frequency of each index, with $p < 0.05$ considered significant. If the result was significant, the chi-square value and deviation for each category were calculated, and elements with high chi-square values were considered to have a significant relationship. To examine the associations among the specific IgE values for 16 inhaled allergens, a cluster analysis was performed and the items were classified into clusters with high associations by using Ward's method.

The Declaration

Our study complied with the Declaration of Helsinki and was approved by the St. Marianna University School of Medicine Ethics Committee (No. 6917). It was a survey of routine clinical examinations, so that patients' consent to review their medical records was not required by the Ethics Committee of St. Marianna University School of Medicine. The study plan was posted on the St. Marianna University School of Medicine's website and in the outpatient clinic using an opt-out system, and the study plan was made available for subjects to freely view. A system was established to respond to any questions or requests.

Result

Table 1 shows the patients' background characteristics at the baseline. There were 119 patients (91 women). The median age was 64.9 years, and 59 had atopic asthma. In the analysis of asthma severity, three patients were in step 1, 37 in step 2, 38 in step 3, and 41 in step 4. There were 114 subjects in the CR or WC group. In addition, both peripheral eosinophils in blood and FeNO were stable No patients used any molecular targeted drugs during the 2-year follow up period.

Table 2 shows patients' comorbidities. The most common disease was allergic rhinitis, followed by sinusitis and Non-Steroid-Anti-Inflammatory-Drugs-Exacerbated Respiratory Disease (N-ERD). Other coexisting conditions included asthma-chronic obstructive pulmonary disease overlap syndrome (ACO), heart failure, sleep apnea syndrome, and bronchiectasis. None of the patients had comorbid allergic bronchopulmonary mycosis (ABPM) or eosinophilic granulomatosis with polyangiitis (EGPA). None of the patients showed any worsening of their comorbid conditions over the 2-year follow-up, and their condition remained stable. None of the patients was pregnant or breastfeeding.

Table 3 shows the relationship between the rate of sensitivity to each aeroallergen and the total serum IgE levels at baseline. The proportions of patients with Class ≧ 1 sensitization were, for house dust (33.6%), mite (34.4%), Japanese cedar (54.6%), cypress (33.6%), alder (10.1%), orchard grass (13.4%), ragweed (10.1%), mugwort (10.1%), cat (6.7%), dog (11.7%), cockroach (6.7%), midge (6.7%), moth (24.3%), *Candida* (23.5%), *Alternaria* (8.4%), and *Aspergillus* (16.8%); for all of these the specific IgE levels were significantly correlated with the total IgE levels (Table 3). Of these, the items with a correlation coefficient >0.6 were *Candida*, cockroach, and moth had $R > 0.6$.

Table 4 shows the relationships between the specific IgE levels for pairs of different allergens at baseline. House dust IgE levels were correlated with those against mite, moth, and *Aspergillus*. Japanese cedar IgE levels were significantly

Table 1 Patient Characteristics at Study Entry

Number	119
Sex (male/female)	28/91
Age (years)	64.9 ± 13.7
Atopy/no atopy	59/60
Asthma severity (1/2/3/4)	3/37/38/41
Smoking history (no/ex-smoker/current)	90/22/7
Asthma control (CR/WC/IC)	79/35/5
FEV_1 (L)	2.21±0.733
%FEV_1 (% of predicted)	120.4±19.8
FEV_1/FVC (%)	74.4±9.45
Peripheral eosinophils in blood (%)*	2.4 (1.27, 3.82)
Serum IgE (IU/mL)	100 (28, 417.5)
FeNO(ppb)+	19 (13.5, 31)

Notes: The data are presented as median 〈interquartile range〉 or means ± SD. The number of patients tested were 119 except in the case of *peripheral eosinophils in blood (n=114), +: FeNO (n=109). Asthma control: CR WC.
Abbreviations: CR, clinical remission; WC, well controlled; IC, insufficiently controlled; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; FeNO, fraction of exhaled nitric oxide.

Table 2 Patients' Comorbidities

Comorbidity	No. of Subjects (%)
N-ERD	6 (5.0%)
ABPM	0
EGPA	0
Allergic rhinitis	60 (50.4%)
Asthma-COPD overlap	5 (4.2%)
Sinusitis	12 (10.0%)
Heart failure	5 (4.2%)
Sleep apnea	5 (4.2%)
Bronchiectasis	5 (4.2%)

Note: Data are presented as numbers (percentages).
Abbreviations: N-ERD, NSAIDs-exacerbated respiratory disease; ABPM, allergic bronchopulmonary mycosis; EGPA, eosinophilic granulomatosis with polyangitis.

correlated with those against cypress, alder, orchard grass, ragweed, and mugwort, and ragweed IgE levels were significantly correlated with those against mugwort. *Candida* IgE levels were significantly correlated with those against *Aspergillus* and *Alternaria*, and those against *Aspergillus* and *Alternaria* were correlated each other. Significant correlations were also observed between the IgE levels against cat and those against dog, between moth IgE levels and those against midge and cockroach, and between those against cockroach and those against midge. Those combinations with particularly strong correlations ($R > 0.7$), were house dust-mite, house dust-*Aspergillus*, Japanese cedar-cypress, ragweed-mugwort, *Aspergillus-Alternaria*, cat-dog, and cockroach-midge.

Cluster analysis was performed to show the commonalities between specific IgE levels (Figure 1). Highly relevant items were classified into seven clusters: (1) house dust, mite, and *Candida*, (2) insects, (3) *Alternaria* and orchard grass, (4) pollen 1 (Japanese cedar and cypress), (5) *Aspergillus*, (6) animals, and (7) pollen 2 (ragweed, mugwort, and alder).

The proportions of patients who showed increases or decreases in sensitivity of at least one class in antigen specific IgE, levels during the observation period were, for house dust (20.1%), mite (12.6%), Japanese cedar (31.1%), cypress (24.3%), alder (5.8%), orchard grass (6.7%), ragweed (10.9%), cat (4.2%), dog (8.4%), cockroach (6.7%), midge (8.4%),

Table 3 Rates of Positivity (ImmunoCAP Class 1 or Higher) for Specific IgE at Baseline, and Relationships Between Serum-Specific IgE and Serum Total IgE Levels

	No. of Patients with ImmunoCAP ≧ Class1 (%)	Specific IgE vs Total IgE*	
		ρ	P
Mite	41 (34.4%)	0.517	<0.001
House dust	40 (33.6%)	0.507	<0.001
Japanese cedar	65 (54.6%)	0.474	<0.001
Cypress	40 (33.6%)	0.513	<0.001
Alder	12 (10.1%)	0.365	<0.001
Orchard grass	16 (13.4%)	0.376	<0.001
Ragweed	12 (10.1%)	0.455	<0.001
Mugwort	12 (10.1%)	0.486	<0.001
Candida	28 (23.5%)	0.692	<0.001
Aspergillus	20 (16.8%)	0.515	<0.001
Alternaria	10 (8.4%)	0.556	<0.001
Cat	8 (6.7%)	0.403	<0.001
Dog	14 (11.7%)	0.409	<0.001
Cockroach	8 (6.7%)	0.607	<0.001
Midge	8 (6.7%)	0.598	<0.001
Moth	19 (24.3%)	0.667	<0.001

Note: *Spearman's rank correction test.

Table 4 Relationships Among Specific IgE Levels in Response to Different Allergens at Baseline

Allergen Pair	Relationship Between IgE Levels*	
	ρ	P
House dust		
- Mite	0.974	<0.001
- Moth	0.631	<0.001
- *Aspergillus*	0.702	<0.001
Japanese cedar		
- Cypress	0.911	<0.001
- Alder	0.336	<0.001
- Orchard grass	0.409	<0.001
- Ragweed	0.436	<0.001
- Mugwort	0.451	<0.001
Ragweed-Mugwort	0.820	<0.001
Candida		
-Aspergillus	0.506	<0.001
-Alternaria	0.519	<0.001
Aspergillus-Alternaria	0.793	<0.001
Cat-Dog	0.775	<0.001
Moth		
- Cockroach	0.651	<0.001
- Midge	0.656	<0.001
Cockroach-Midge	0.796	<0.001

Note: *Spearman's rank correction test.

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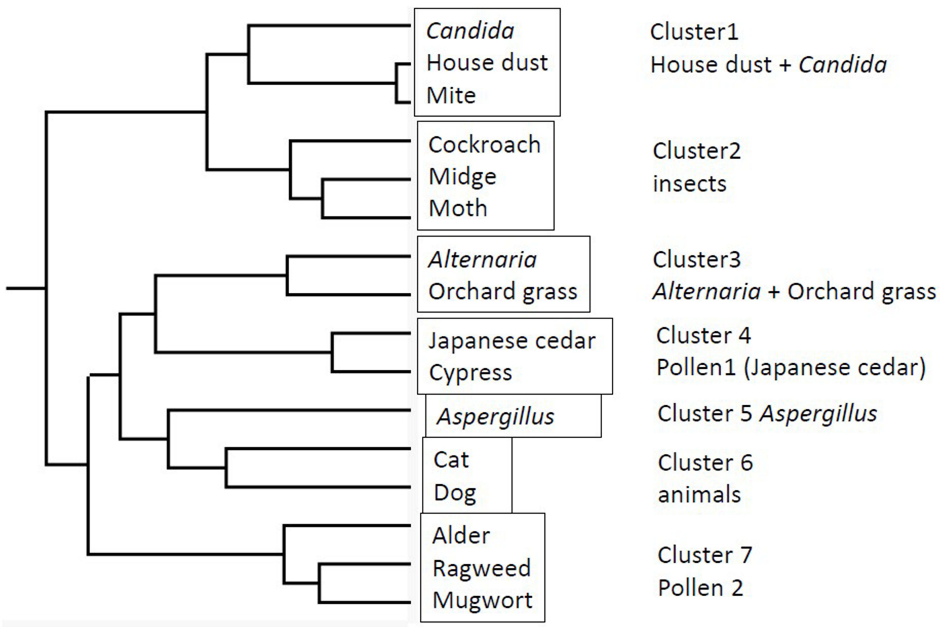

Figure 1 Cluster analysis of aeroallergen specific IgE levels at baseline.

moth (18.5%), *Candida* (21.8%), *Alternaria* (5.8%), and *Aspergillus* (16.8%). Thirty-five patients (29.4%) had no changes in ImmunoCAP class for any of the allergens over the observation period.

The relationship between changes in antigen-specific IgE and in total IgE is shown in Table 5. Allergens for which the changes in specific IgE were significantly correlated with the change in total IgE were Japanese cedar, cypress, alder,

Table 5 Relationships Between Changes in Serum-Specific IgE Levels and Changes in Serum Total IgE Levels Over the 2-Year Observation Period

Allergen	ΔSpecific IgE vs ΔIgE*	
	ρ	*P*
ΔMite	0.0774	0.411
ΔHouse dust	0.0736	0.434
ΔJapanese cedar	**0.284**	**0.002**
ΔCypress	0.167	0.07
ΔAlder	**0.302**	**0.010**
ΔOrchard grass	0.166	0.076
ΔRagweed	**0.271**	**0.003**
ΔMugwort	0.156	0.09
Δ*Candida*	0.050	0.594
Δ*Aspergillus*	**0.262**	**0.004**
Δ*Alternaria*	**0.366**	**<0.001**
ΔCat	−0.0239	0.797
ΔDog	0.143	0.124
ΔCockroach	**0.188**	**0.043**
ΔMidge	**0.207**	**0.026**
ΔMoth	**0.307**	**<0.001**

Note: *Spearman's rank correction test.

Table 6 Relationships Between Asthma Control Group (Clinical Remission, Well Controlled, and Insufficiently Controlled) and Proportion of Subjects with ImmunoCAP-Specific IgE Changes to Class 1 or Higher Over the 2-Year Observation Period

Allergen	No. (%) of Subjects with ImmunoCAP Changes to ≥ Class 1 (%)			
	Clinical Remission (n=79)	Well Controlled (n=35)	Insufficiently Controlled (n=5)	*P value**
Mite	12 (15%)	3 (8.5%)	0	0.72
House dust	16 (20%)	7 (20%)	1 (20%)	1.00
Japanese cedar	23 (29%)	10 (28%)	4 (80%)	0.096
Cypress	19 (24%)	8 (23%)	2 (40%)	0.79
Alder	4 (5.0%)	3 (8.5%)	0	0.60
Orchard grass	6 (7.5%)	2 (5.7%)	0	1.00
Ragweed	10 (12%)	3 (8.5%)	0	0.87
Mugwort	6 (7.5%)	2 (5.7%)	0	1.00
Candida	21 (26.5%)	5 (14.2%)	0	0.38
Aspergillus	12 (15%)	7 (20%)	1 (20%)	1.00
Alternaria	5 (6.3%)	2 (5.7%)	0	0.67
Cat	3 (3.8%)	2 (5.7%)	0	0.72
Dog	8 (10%)	2 (5.7%)	0	0.83
Cockroach	5 (6.3%)	3 (8.5%)	0	0.80
Midge	8 (10%)	2 (5.7%)	0	0.83
Moth	15 (19%)	5 (14%)	2 (40%)	0.49

Note: **P* values were determined by $\chi 2$ test or Fisher's test.

ragweed, Aspergillus, Alternaria, cockroach, midge, and moth, with particularly strong correlation in the case of Δalder, ΔAlternaria, and Δmoth.

Table 6 shows proportions of subjects in each asthma control group with increases or decreases in serum specific IgE levels of at least ≧1 class over the 2 year observation period. There were no significant correlations between the changes in specific IgE level and the asthma control status by chi square test. Changes in the specific IgE level in response to Japanese cedar were seen in four of five subjects (80%) in the IC group, but there was no significant correlation and the class decreased in all patients.

Discussion

We investigated changes in allergic sensitization in 119 adult asthma patients managed by primary care physicians. Correlations were observed among specific IgE levels, and the patients' response was classified into seven clusters. Aeroallergens for which the specific IgE levels had high correlation coefficients with total IgE at the start of observation were *Candida*, cockroach, and moth. The specific IgE responses to most allergens showed changes to Class ≧ 1 during the observation period, but 35 subjects showed no changes. Strong correlations were observed between changes in antigen-specific IgE and changes in total IgE, particularly for alder, *Alternaria*, and moth. Changes in allergen-specific IgE did not significantly correlate with asthma control status in any patient.

IgE cluster 1 was composed of house dust, *Candida*, and mite, and was considered to be related to indoor dust. Cluster 2 was composed of insects such as cockroach, midge, and moth. Cluster 3 was composed of *Alternaria* and orchard grass. A common feature of *Alternaria* and orchard grass is that they are all dispersed by thunder. Cluster 4 was classified as Japanese cedar and cypress, pollens derived from conifers in spring. Cluster 5 was *Aspergillus*. Cluster 6 was composed of animals such as dog and cat. Cluster 7 as alder, ragweed, and mugwort, derived from grass pollen. The seven cluster classifications in this study are very similar to those reported by Kitahara et al,[4] but cluster 3 differed. The fact that thunder can disperse the pollen suggests a relationship with thunderstorm asthma, but the details are unknown and further investigation is required. Furthermore, the possibility that individual results are being overestimated due to the small number of subjects cannot be ruled out, and a significant association does not necessarily indicate cross-reactivity or immunogenicity.

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The proportion of sensitized individuals was similar to that of adults in southern Kanto.[2] However, we found that the proportion of fungi was higher, and the proportion of insects was lower than southern Kanto in Minami et al's report. This may reflect the regional specificity of the location of Yokohama Western area (in Southern Kanto, Yokohama is an urban area near the sea).

At the start of observation, the allergens for which the specific IgE values were highly correlated with the total IgE values were *Candida*, moth, and cockroach, whereas the allergens with $R > 0.3$ between Δtotal IgE and changes in antigen-specific IgE were *Alternaria*, moth, and alder, which did not match the initial results. We considered the possibility that this difference may have been related to high rates of sensitization to these allergens or to new allergy induction. However, a report by Agarwal et al[13] stated that a reversal phenomenon occurs between specific IgE and total IgE in ABPA, and the mechanism of total IgE and specific IgE changes has not yet been fully elucidated. And also, due to the number of aeroallergens, it cannot be ruled out that there are accidental associations due to multiple testing. Therefore, it is difficult to clarify the reason at this time, and additional research is required.

No significant relationships were observed between the changes in specific IgE according to asthma control status over the observation period. A worsening of sensitization was expected in patients with asthma exacerbation, but we found no such disease-associated worsening. The reasons for this may be that our study subjects were managed by primary care; many of them had good outcomes and were in the CR or WC, with their allergic reactions suppressed by treatment intervention in cases of exacerbation. In addition, although no significant difference between in the changes in specific IgE with asthma control status was observed, the fact that for many of the allergens there were relatively large percentage changes in IgE sensitivity class in the CR group suggests that there was a time lag between the degree of exacerbation and sensitization during the observation period, or that the changes in the two are unrelated.

In regard to hypothesis (1) that sensitization changes over time, even in stable asthma managed by primary care, 29.4% of patients showed no change of ImmunoCAP Class $\geqq 1$ in any of the allergen specific IgE levels. Therefore, about 70% of patients had a change of at least class $\geqq 1$. As most of our study subjects were stable asthmatics, it can be said that "sensitization doses change over time, even in stable asthma managed by primary care".

In regard to hypothesis (2) that worsening sensitization between specific IgE changes and control status during the course of the disease. The number of patients in the IC group was small, and it did not include patients with poorly controlled asthma, making verification difficult in this study. The risk of future exacerbations is thought to be due to long-term allergen exposure. As a basis for asthma management, avoiding exacerbating factors is very important.[1] Although investigating antigen sensitization can be useful for asthma management because it leads to allergen avoidance,[1] there is little motivation to test for stable asthma managed by primary care, and no similar investigations were found within the scope of our search. We found that sensitization changes over time, even in stable asthma, so it is useful to regularly investigate allergen-specific IgE, even in stable asthmatics. However, measuring many allergen-specific IgE every year occurs costs. In the case of allergens that appear to have high cross reactivity and for which the specific IgE levels were classified into seven clusters, it may be possible to predict changes in IgE levels for the other allergens in a cluster by testing one of them. However, the appropriate allergens, frequency of judgment, changes during long-term observation, and effects of therapeutic intervention are unknown, and further research is required.

The limitations of our study were as follows. First, it was a single-center retrospective study, and the small number of patients may have influenced the cluster classification. In addition, the results may reflect the regional specificity of Yokohama Western area. While regional characteristics are likely to be evident, the sample size is too small for universal analysis. Furthermore, the small number of patients limits the statistical accuracy of stratified analysis. In particular, the large number of items and repeated testing presents a problem of false positives due to multiple testing. Secondly, in previous studies where patients have been accumulated, some patients who have dropped out of the hospital-clinic collaboration owing to worsening asthma or treatment for other diseases, including comorbidities, have been excluded.[5] Therefore, the data on only those patients who continued to be managed stably may have been extracted, and data on patients with poor control would therefore have been scarce. There are not enough insufficiently controlled patients to test hypothesis 2), so it cannot be inferred from this study. Thirdly, because the evaluation is retrospective, the causal relationship is unclear. Further research is needed to determine how IgE assessment should be applied to asthma management. For example, allergen immunotherapy directly involves aeroallergen sensitization, our study did not include education on active allergen avoidance based on the results of allergen specific IgE, and nor did it include allergen immunotherapy. Allergen immunotherapy is a fundamental treatment for allergies that suppresses the reaction to allergens to which the patients' airways may be have become sensitized.[1] Allergen immunotherapy for childhood asthma (aged 2–6 years) prevented new sensitization 3 years later and reduced symptoms in the treatment group by more than half.[14] Novembre et al[15] reported that sublingual pollen immunotherapy for in 5- to 14-year-olds halved symptoms and asthma onset 3 years later after the end of immunotherapy, suggesting that allergen immunotherapy can suppress new sensitization. Further prospective intervention studies are needed to investigate the results of interventions such as education on antigen avoidance and treatments including allergen immunotherapy. Fourthly, our study included patients who were registered with the Asthma Hospital-Clinic Collaboration system between 2009 and 2018, and in none of them were molecular targeted drugs were used. Further research is needed to investigate the changes in immune responses in patients in whom such drugs are used.

Conclusions

In a group of patients in the Asthma clinic collaboration who were stably managed by primary care physicians, the rates of positivity rate for inhaled allergens and related allergens were similar to those in existing reports, and clusters of IgE responses were classified into seven types on the basis of their cross-reactivity. The status of aeroallergen sensitization changed over time in many patients. When we consider making environmental adjustments in the form of allergen avoidance in asthma management, we should check for changes in sensitization over time by regularly investigating allergen IgE responses. However, further research is needed to determine what interventions are appropriate and whether these results are universal.

Abbreviation

ABPM, allergic bronchopulmonary mycosis; CR, Clinical remission; EGPA, eosinophilic granulomatosis with polyangiitis; FEV_1, forced expiratory volume in 1 s; FeNO, fraction of exhaled nitric oxide; FVC, forced vital capacity; IC, insufficiently controlled; N-ERD, NSAIDs-exacerbated respiratory disease; WC, well controlled.

Ethical Statement

Our study complied with the Declaration of Helsinki and was approved by the St. Marianna University School of Medicine Ethics Committee (No. 6917). It was a survey of routine clinical examinations, so that patients' consent to review their medical records was not required by the Ethics Committee of St. Marianna University School of Medicine. After collecting the patients' data, our information manager anonymized it. Therefore, the personal information of the patients in this study cannot be identified from published data. This study plan was posted on the St. Marianna University Medical School website and in the outpatient consultation room by using the put-out method to accumulate clinical indicators of usual care, and the subjects were given free access to the study plan. A system was set up to respond immediately to any questions or requests.

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Author Contributions

All authors made substantial contributions to the reported work in terms of conception, study design, conduct, acquisition, analysis, and/or interpretation of data, participated in drafting, revising, or critical review of the paper, gave final approval of the version to be published, agreed to the journal to which the paper will be submitted, and agreed to be accountable for all aspects of the work.

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Authors other than MM have no conflicts of interest to disclose.

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