

How does the pattern of aeroallergen sensitization change over time across all ages?

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Background: Identification of aeroallergen sensitization is important for diagnosis and management of allergic diseases. Immunoglobulin E (IgE) sensitization status is known to change over time. However, few studies have explored changes in sensitization patterns across all age groups. The aim of the present study was to evaluate the changing patterns of in vitro IgE sensitization tests in allergic rhinitis patients across all age groups.

Methods: We recruited all patients who were diagnosed as having rhinitis and who underwent in vitro IgE sensitization testing from 2007 to 2016. Of these, we included 138 who underwent repeat testing. We analyzed epidemiological data and allergen sensitization patterns.

Results: Of all patients, 56.5% of exhibited changes in allergen sensitization patterns. The allergens to which all age groups were sensitive were most commonly mites, with the exception of patients aged 40 to 59 years. The age group in which “new sensitization,” composed of those with “newly developed sensitization” and “sensitization to more allergens,” was most frequent was the 2 to 12 years old group, followed by the 20 to 39 years old group. The age group

in which “desensitization,” composed of those with “negative conversion” and “desensitization to fewer allergens,” was most prevalent was the 20 to 39 years old group followed by the 13 to 19 years old group. Grass pollen was the most common newly-sensitized allergen and also the most common desensitized allergen.

Conclusion: IgE sensitization to aeroallergens can change in individuals with allergy. These changes may be different according to the patient's age. If rhinitis symptoms or treatment efficacy changes, repeat IgE sensitization testing is needed to find changes in allergen sensitization patterns. © 2017 ARS-AAOA, LLC.

Key Words:

allergic rhinitis; sensitization; specific IgE; aeroallergen; age; mite; change

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Allergic rhinitis (AR) is a common inflammatory disease of the nasal mucosa that is mediated by immunoglobulin E (IgE) against allergen(s). AR is characterized by rhinorrhea, nasal congestion, nasal itching, and sneezing.^{1,2} Non-allergic rhinitis (NAR) is a group of disorders featuring the symptoms of chronic rhinitis without allergic trigger.³ AR and NAR cannot be distinguished by symptoms alone because their symptoms are similar. Some features such as seasonality, sneezing, moderate/severe

symptoms, and response to antihistamines may differentiate AR from NAR.⁴ To distinguish AR and NAR, IgE sensitization tests are required, including skin-prick tests or in vitro tests for specific IgEs against aeroallergens.^{5,6} Thus, the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines recommend that diagnostic tools include allergy skin testing or measurement of allergen-specific IgE in serum.¹

However, the pattern of IgE reactivity to allergens changes over time in individuals. Patients with AR can become desensitized to allergens to which they were previously sensitized, while patients diagnosed as having NAR can be sensitized to allergens over time. In 1 Spanish study on adult NAR patients, 24% of those who were not sensitized to aeroallergens upon initial examination turned to be positive on IgE sensitization testing later.⁷ In a pediatric study performed in Thailand, 41% of children previously diagnosed as having NAR exhibited aeroallergen sensitization upon re-evaluation.⁸ One study

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TABLE 1. Classification of patients based on changing patterns of allergen sensitization as revealed by the MAST*

Group	Subgroup	Class
With change (A+B+C+D+E) (n = 78)	New sensitization (A+B+C) (n = 49)	Newly developed sensitization (A) (n = 15): When a patient lacking sensitization on the first test becomes sensitized to one or more allergens on the second test.
		Sensitization to more allergens (B+C) (n = 33): When a patient sensitized to one or more allergens on the first test becomes sensitized to new allergens on the second test.
	Desensitization (C+D+E) (n = 52)	Negative conversion (E) (n = 17): When a patient sensitized to one or more allergens on the first test becomes negative on the second test.
		Desensitization to some allergens (C+D) (n = 35): When a patient sensitized to one or more allergens on the first test becomes desensitized to one or more, but not all, allergens on the second test.
Without change (F) (n = 60)		No change in the pattern of sensitization (F) (n = 60): When a patient exhibits no change in sensitization pattern between the first and second tests.

*The descriptors A-F are the same as those in Figure 1 and are defined as follows: A = patients with newly developed sensitization; B = patient with only sensitization to more allergens; C = patient with both sensitization to more allergens and desensitization to some allergens; D = patients with only desensitization to some allergens; E = patients with negative conversion; F = patient with no change.
MAST = multiple allergen simultaneous test.

in Italy found that the prevalence of positive skin-prick tests was 59% in asthmatic children at the age of 3 years but increased to 88% at the age of 11 years.⁹

Because the sensitization status for allergens can change over time and AR symptoms can also disappear without any specific reason, many clinicians recommend that repeated IgE sensitization tests may be necessary in order to detect the changing patterns of sensitizations, when symptoms change, or if new allergens are suspected. This is why it is important to evaluate the changing patterns of allergen sensitizations to better understand AR as well as NAR. However, there were few longitudinal studies that evaluated the changes seen in AR and NAR in Koreans across all age groups. We designed the study on the sensitization patterns across all age groups in Koreans. In this study, we hypothesized that the sensitization patterns of aeroallergens might change individually over time in children as well as adults. Our purpose was to evaluate the changing patterns of in vitro IgE sensitization tests in AR patients of different age groups.

Patients and methods

Patients

This was a retrospective, longitudinal panel study conducted in 1 university-based, secondary referral hospital. This study recruited all patients who were diagnosed with rhinitis by both authors and whose rhinitis was managed by both authors during the period 2007 to 2016. The inclusion criteria were as follows: (1) symptoms compatible with rhinitis; (2) physical findings on anterior rhinoscopy and/or nasal endoscopy compatible with rhinitis; and (3) repeated multiple allergen simultaneous tests (MASTs). Both authors set up critical pathways in clinical practice of

rhinitis on 2007, which states that MAST is repeated when a patient's symptoms change, AR symptoms disappear without any specific reason, or appearance of new allergens is suspected. The exclusion criteria were as follows: (1) history of immunotherapy; (2) use of biologicals including anti-IgE antibody during the follow-up period; (3) history of malignant or rheumatologic disease; and/or (4) residence of more than 1 month abroad.

We used the MAST (RoboScreenTM; Bee Robotics Ltd, North Wales, UK) for in vitro IgE sensitization testing; the panel includes 39 allergens including foods, tree/grass pollens, fungi, animal danders, cockroaches, and house dust mites. Class ≥ 2 was interpreted as positive.^{10,11}

Based on the ARIA guidelines, AR was diagnosed based on symptoms suggestive of AR and positive MAST results for at least 1 allergen (class 2 or higher). The symptoms included rhinorrhea, nasal obstruction, nasal itching, and sneezing, as documented in the ARIA guidelines.¹

Our classification of changes in sensitization patterns is shown in Table 1 and Figure 1. Based on age at first examination, patients were categorized into 5 age groups as follows: 2 to 12 years; 13 to 19 years; 20 to 39 years; 40 to 59 years; and 60 years and older.

Statistical analysis

All continuous variables are presented as means $\pm$ standard deviation and all categorical variables as percentages. The chi square and *t* test were used for between-group comparisons. All statistical analyses were performed using SPSS for Windows, version 15.0 (SPSS, Inc., Chicago, IL). All statistical tests were 2-tailed and the *p* value for statistical significance was defined to be *p* < 0.05.

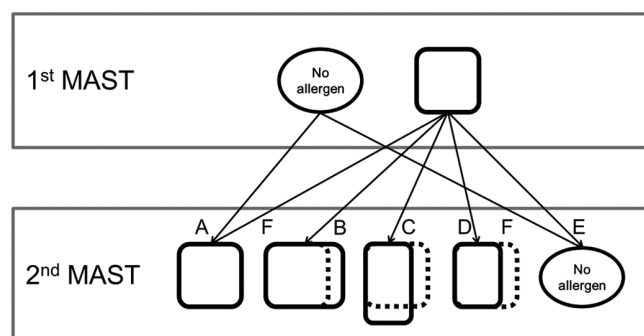


FIGURE 1. Diagram showing the changing patterns of allergen sensitization as revealed by the MAST (multiple allergen simultaneous test). The descriptors A to F are the same as those used in Table 1. The areas of the boxes reflect the numbers of allergens. The descriptors are defined as follows: A = patients with newly developed sensitization; B = patient with only sensitization to more allergens; C = patient with both sensitization to more allergens and desensitization to some allergens; D = patients with only desensitization to some allergens; E = patients with negative conversion; F = patient with no change. MAST = multiple allergen simultaneous test.

Ethics statement

Written informed consent was not obtained because of the retrospective nature of the study. However, the study protocol was approved by the Institutional Review Board of Uijeongbu St. Mary's Hospital (IRB policy No. UC16RISI0136).

Results

We finally included 138 patients (93 males [67.4%] and 45 females [32.4%]). The mean patient age was 26.7 ± 17.9 years at the time of the first MAST and 29.3 ± 18.2 years at the time of the second MAST. The follow-up period in total subjects was 31.7 ± 33.1 months. The follow-up periods according to the age group were as follows: 2 to 12 years old, 24.7 ± 28.4 months; 13 to 19 years old, 29.6 ± 29.1 months; 20 to 39 years old, 28.9 ± 33.5 months; 40 to 59 years old, 35.7 ± 36.0 months; and 60 years and older, 55.6 ± 38.9 months.

Allergen sensitization by age groups

On both the first and second MASTs, most frequently-sensitized allergens were mites (31.9% and 32.6%, respectively). On the first MAST, mites were the most common allergens in those aged 2 to 12 years, 13 to 19 years, and 20 to 39 years; grass pollens were the most common allergens in those aged 40 to 59 years. The second MAST yielded similar data (Table 2).

The sensitization rates to allergens of those aged 60 to 79 years (20.0% in the first MAST and 22.2% in the second) were much lower than those of other age groups (range, 48.6% to 69.7%). However, unlike the other age groups, the sensitization rates to tree, grass, and weed pollens remained very high in those aged 60 to 79 years, in whom sensitization to molds, animal dander, cockroaches, and house dust had disappeared (Fig. 2).

Figure 3 shows the changing patterns of allergen sensitization by age group. The “no changes” pattern was most common across all age groups, except for those aged 20 to 39 years, in which the “desensitization to fewer allergens” pattern was the most common. The “newly developed sensitization” pattern was most common in the youngest age group (2 to 12 years). Although newly developed sensitization and negative conversion was rare, fluctuation in the number of allergens (the “sensitization to more allergens” and “desensitization to fewer allergens” patterns) was most common in those aged 20 to 39 years. The “no changes” pattern was especially common in the oldest age group (60 to 79 years).

Comparison between groups with and without changes in allergen sensitization

The sensitized allergens were changed in 78 (56.5%) of 138 patients. We found no significant differences in age or sex between the “with changes” and “without changes” groups. During follow-up, 4 patients in the “with changes” group were diagnosed as having asthma (Table 3). These patients with newly developed asthma were members of the “new sensitization” subgroup. The new sensitized allergens in the individual patients were to *Dermatophagoides farina*, *Dermatophagoides pteronyssinus*, cat and dog dander, and *Cladosporium*.

Analysis of new allergens in the “new sensitization” group by age

To identify allergens to which patients were not sensitized on the first MAST, but were on the second, we analyzed a “new sensitization” group, composed of those with “newly developed sensitization” and “sensitization to more allergens.” The age group in which “new sensitization” was most frequent was the 2 to 12 year old group (40.0%), followed by the 20 to 39 years old group (39.4%) (Table 4). However, there were some differences between the groups; “newly developed sensitization” and “sensitization to more allergens” were equally common in those aged 2 to 12 years, but “sensitization to more allergens” was more prevalent than “newly developed sensitization” in those aged 20 to 39 years (Fig. 3).

Grass pollen was the most common allergen to which patients became newly sensitized in all age groups, except those aged 13 to 19 years and 60 to 79 years. The second most common allergen differed by age group, being house dust in those aged 2 to 12 years; foods, tree pollens, and molds in those aged 13 to 19 years; foods, tree pollens, and mites in those aged 20 to 39 years; and tree pollens and molds in those aged 40 to 59 years. Patients became sensitized to indoor allergens, including animal danders, house dust, and mites, early in life, especially between 2 and 12 years of age (Table 4).

TABLE 2. Summary of allergen sensitization data by age group*

Sensitized allergens	All ages (n1 = 138; n2 = 138)	Age 2–12 years (n1 = 35; n2 = 25)	Age 13–19 years (n1 = 30; n2 = 32)	Age 20–39 years (n1 = 33; n2 = 38)	Age 40–59 years (n1 = 35; n2 = 34)	Age 60–79 years (n1 = 5; n2 = 9)
Any allergen						
1st MAST	59.4	48.6	66.7	69.7	60.0	20.0
2nd MAST	57.2	52.0	62.5	63.2	58.8	22.2
Foods						
1st MAST	17 (12.3)	2 (5.7)	3 (10.0)	6 (18.2)	5 (14.3)	1 (20.0)
2nd MAST	15 (10.9)	0 (0)	3 (9.4)	7 (18.4)	4 (11.8)	1 (11.1)
Tree pollen						
1st MAST	19 (13.8)	4 (11.4)	1 (3.3)	7 (21.2)	6 (17.1)	1 (20.0)
2nd MAST	19 (13.8)	3 (12.0)	2 (6.3)	4 (10.5)	8 (23.5)	2 (22.2)
Grass pollen						
1st MAST	35 (25.4)	5 (14.3)	4 (13.3)	12 (36.4)	13 (37.1)	1 (20.0)
2nd MAST	28 (20.3)	3 (12.0)	4 (12.5)	8 (21.1)	11 (32.4)	2 (22.2)
Weed pollen						
1st MAST	23 (16.7)	1 (2.9)	4 (13.3)	8 (24.2)	9 (25.7)	1 (20.0)
2nd MAST	18 (13.0)	0 (0)	3 (9.4)	4 (10.5)	9 (26.5)	2 (22.2)
Molds						
1st MAST	15 (10.9)	5 (14.3)	4 (13.3)	2 (6.1)	4 (11.4)	0 (0)
2nd MAST	14 (10.1)	1 (4.0)	3 (9.4)	6 (15.8)	4 (11.8)	0 (0)
Animal danders						
1st MAST	17 (12.3)	5 (14.3)	6 (20.0)	6 (18.2)	0 (0)	0 (0)
2nd MAST	13 (9.4)	2 (8.0)	3 (9.4)	7 (18.4)	1 (2.9)	0 (0)
Cockroaches						
1st MAST	12 (8.7)	1 (2.9)	0 (0)	7 (21.2)	3 (8.6)	1 (20.0)
2nd MAST	9 (6.5)	0 (0)	1 (3.1)	4 (10.5)	4 (11.8)	0 (0)
House dust						
1st MAST	27 (19.6)	6 (17.1)	8 (26.7)	10 (30.3)	3 (8.6)	0 (0)
2nd MAST	18 (13.0)	3 (12.0)	6 (18.8)	8 (21.1)	1 (2.9)	0 (0)
Mites						
1st MAST	44 (31.9)	10 (28.6)	12 (40.0)	14 (42.4)	8 (22.9)	0 (0)
2nd MAST	45 (32.6)	6 (24.0)	12 (37.5)	16 (42.1)	9 (26.5)	2 (22.2)

*Values are n (%).

MAST = multiple allergen simultaneous test; 1st MAST = first MAST performed on the same individual; 2nd MAST = second MAST performed on the same individual; n1 = number of 1st MAST patients; n2 = number of 2nd MAST patients.

Allergens to which patients in the “desensitization” group were not sensitized on the second MAST, by age group

We defined “desensitization” to include “negative conversion” and “desensitization to fewer allergens.” The age group in which “desensitization” was most prevalent was

the 20 to 39 years old group (48.6%) followed by the 13 to 19 years old group (40.0%) (Table 5).

Grass pollen was the most common allergen to which desensitization was apparent, especially in those aged 2 to 12 years, 20 to 39 years, and 40 to 59 years. In the 2 to 12 years old group, tree and grass pollens were the most

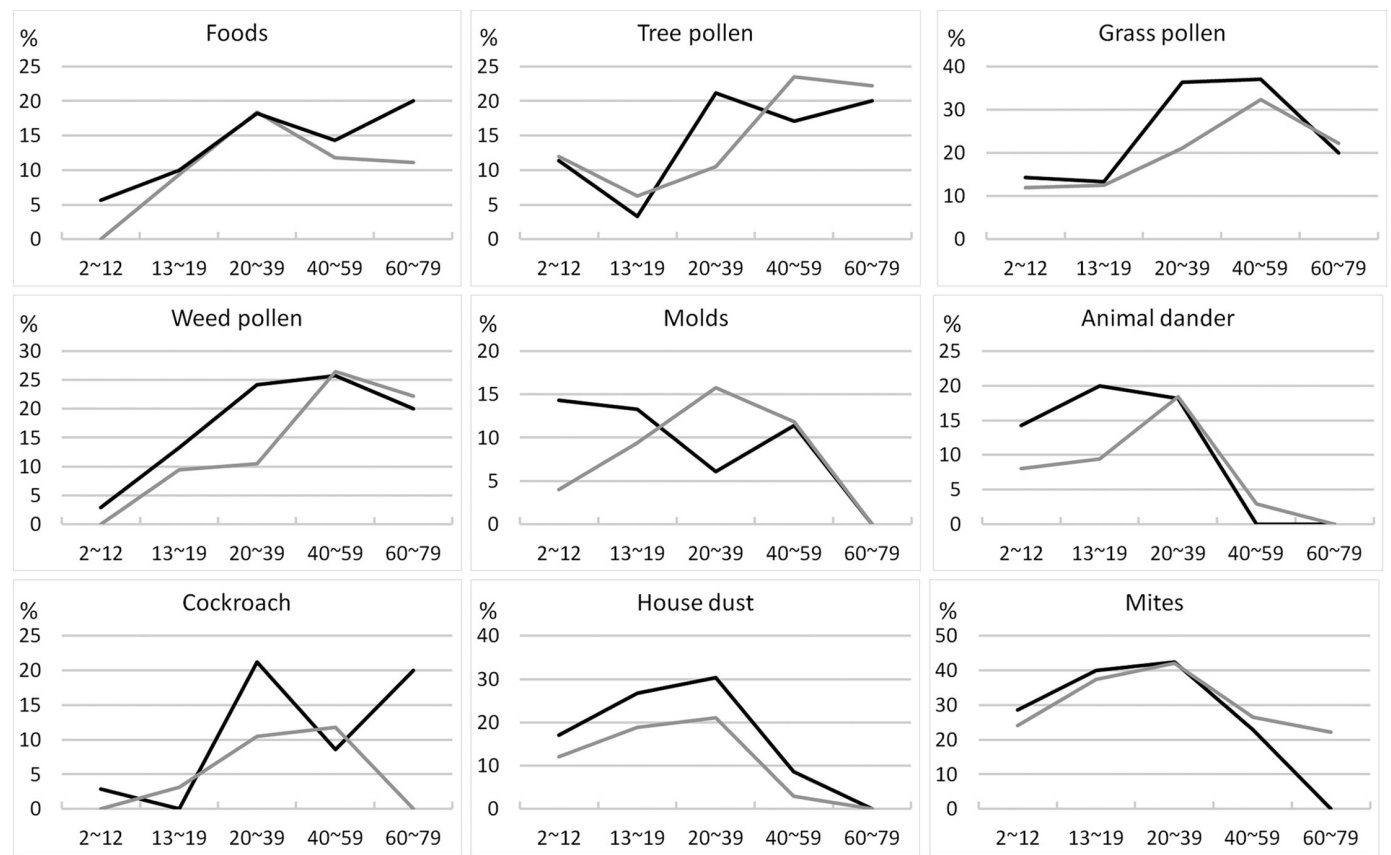


FIGURE 2. Distribution of allergen sensitization in different age groups. The black lines represent data from the first MAST and the gray lines represent those from the second MAST. MAST = multiple allergen simultaneous test.

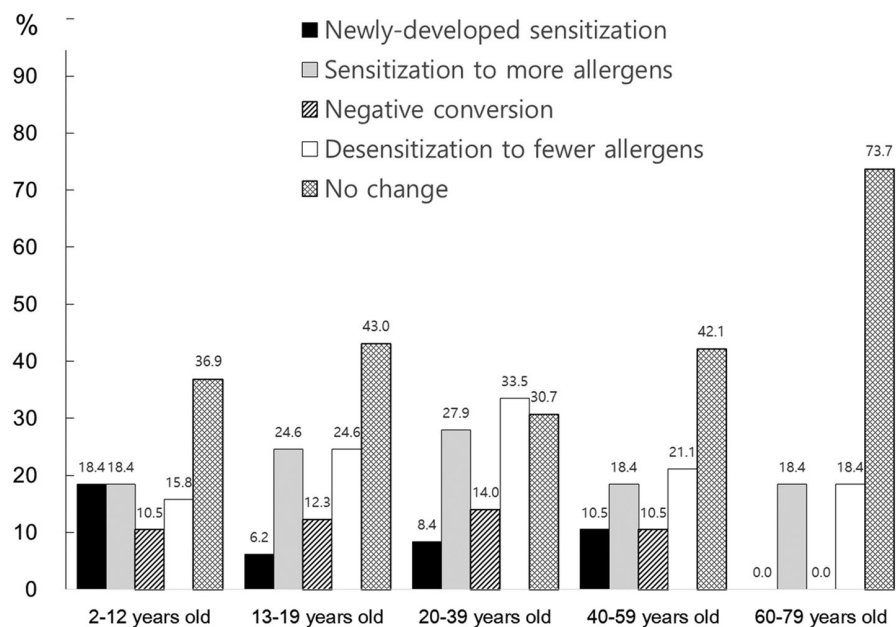


FIGURE 3. Changing patterns of allergen sensitization by age group.

TABLE 3. Comparison between the two groups exhibiting changes, or not, to allergen sensitization

	With changes (n = 78) (56.5%)	Without changes (n = 60) (43.5%)	p
Age (years), mean $\pm$ SD [range]			
1st MAST	26.0 $\pm$ 17.1 [2–70]	27.7 $\pm$ 19.1 [3–74]	0.597
2nd MAST	29.1 $\pm$ 17.2 [2–71]	29.6 $\pm$ 19.6 [3–77]	0.880
Gender, male:female (male %)	54:24 (69.2)	39:21 (65.0)	0.599
Newly developed comorbidities			
Asthma	4	0	
Atopic dermatitis	0	0	

MAST = multiple allergen simultaneous test; 1st MAST = first MAST on the same individual; 2nd MAST = second MAST on the same individual; SD = standard deviation.

TABLE 4. Summary of newly sensitized allergens in “new sensitization” patients by age group*

	All ages (n = 138)	Age 2–12 years (n = 35)	Age 13–19 years (n = 30)	Age 20–39 years (n = 33)	Age 40–59 years (n = 35)	Age 60–79 years (n = 5)
Number of “new sensitizations”	49 (35.5)	14 (40.0)	10 (33.3)	13 (39.4)	11 (31.4)	1 (20.0)
Foods	10 (7.4)	1 (2.9)	3 (10.0)	3 (9.1)	2 (5.7)	1 (20.0)
Tree pollen	11 (8.0)	2 (5.7)	3 (10.0)	3 (9.1)	3 (8.6)	0 (0)
Grass pollen	20 (14.5)	6 (17.1)	2 (6.7)	5 (15.2)	7 (20.0)	0 (0)
Weed pollen	2 (1.4)	1 (2.9)	0 (0)	0 (0)	1 (2.9)	0 (0)
Molds	10 (7.4)	2 (5.7)	3 (10.0)	2 (6.1)	3 (8.6)	0 (0)
Animal danders	4 (2.9)	2 (5.7)	0 (0)	1 (3.0)	1 (2.9)	0 (0)
Cockroaches	2 (1.4)	0 (0)	1 (3.3)	0 (0)	1 (2.9)	0 (0)
House dust	6 (4.3)	4 (11.4)	1 (3.3)	1 (3.0)	0 (0)	0 (0)
Mites	8 (5.8)	3 (8.6)	0 (0)	3 (9.1)	2 (5.7)	0 (0)

*Values are n (%).

common allergens to which sensitization had been lost on the second test. However, molds and house dust were the most common such allergens in those aged 13 to 19 years (Table 5).

Discussion

Identification of aeroallergen sensitization is important for diagnosis and treatment such as allergen avoidance and immunotherapy.^{2,12} Additionally, sensitization to a specific allergen is the most important risk factor for development of allergic symptoms and disease.^{13,14} IgE sensitization status is known to change over time. Veskitkul et al.⁸ found that 41% of children with NAR developed new aeroallergen sensitization; periodical re-evaluation of NAR children with certain risk factors was required. In a study on adults with NAR, Rondón et al.⁷ found that 24% became newly sensitized to aeroallergens several years after initial negative testing. Westman et al.¹⁵ performed a large birth-cohort

study on the natural course of rhinitis in children. The proportion with AR increased between 4 and 8 years of age, whereas the proportion with NAR fell slightly; 12% of children with AR and 73% of those with NAR entered remission. In our present study, 56.5% of patients exhibited changes in their sensitization patterns during follow-up. Additionally, 26.8% of patients with NAR became newly sensitized to aeroallergens, whereas 20.7% of patients with AR became desensitized to allergens to which they had been previously sensitized. The age group in which “new sensitization” was most frequent was the 2 to 12 years old group (40.0%), followed by the 20 to 39 years old group (39.4%). The age group in which “desensitization” was most prevalent was the 20 to 39 years old group (48.6%) followed by the 13 to 19 years old group (40.0%).

Many studies suggest that changes in sensitization to pollens are induced by changes in allergen exposure. Ariano et al.¹⁶ reported that increased pollen loading caused by progressive climate change increased the

TABLE 5. Summary of allergens “lost” on the second test in “desensitization” patients by age group*

	All ages (n = 138)	Age 2–12 years (n = 35)	Age 13–19 years (n = 30)	Age 20–39 years (n = 33)	Age 40–59 years (n = 35)	Age 60–79 years (n = 5)
Number of “desensitizations”	52 (37.7)	10 (28.6)	12 (40.0)	17 (48.6)	12 (34.3)	1 (20.0)
Foods	13 (9.4)	2 (5.7)	3 (10.0)	5 (15.2)	2 (5.7)	1 (20.0)
Tree pollen	15 (10.9)	5 (14.3)	1 (3.3)	6 (18.2)	2 (5.7)	1 (20.0)
Grass pollen	24 (17.4)	5 (14.3)	1 (3.3)	10 (30.3)	7 (20.0)	1 (20.0)
Weed pollen	11 (8.0)	1 (2.9)	0 (0)	6 (18.2)	4 (11.4)	0 (0)
Molds	12 (8.7)	4 (11.4)	4 (13.3)	1 (3.0)	3 (8.6)	0 (0)
Animal danders	6 (4.3)	4 (11.4)	1 (3.3)	1 (3.0)	0 (0)	0 (0)
Cockroaches	6 (4.3)	1 (2.9)	0 (0)	3 (9.1)	1 (2.9)	1 (20.0)
House dust	14 (10.1)	4 (11.4)	4 (13.3)	4 (12.1)	2 (5.7)	0 (0)
Mites	11 (8.0)	1 (2.9)	5 (16.7)	4 (12.1)	1 (2.9)	0 (0)

*Values are n (%).

proportions of patients sensitized to pollens. Park et al.¹⁷ reported that skin reactivity to tree pollens increased significantly in Korea over 3 decades; but skin reactivity to grass and weed pollens, dog dander, and cockroaches fell. They suggested that such changes might be caused by variations in outdoor environmental factors such as pollen load, global warming, and plant distribution. However, neither of these studies was longitudinal; they were both cross-sectional in nature.

There were only 2 longitudinal studies that evaluated the changes seen in AR and NAR in Koreans. Lee et al.¹⁸ analyzed the data of children at the age of 7 years using skin-prick test for 5 inhalant allergens and specific IgE for 2 dust mites and concluded that the status of allergen sensitization is ever-changing. Lee et al.¹⁹ evaluated the changes of allergen sensitization in children using skin-prick test for 26 common aeroallergens and found that children who became newly sensitized to allergens tended to exhibit significant increases in body mass index (BMI). However, to date no studies have focused on Korean adults.

In our longitudinal study, changes in sensitization to grass pollens were most prominent; such pollens were both the most common new-sensitization allergens (14.5%) and the most common desensitization allergens (17.4%). The rate of sensitization to mites increased slightly up to the third decade of life, while rates of sensitization to foods, grass and weed pollens, molds, animal danders, cockroaches, and house dust decreased with age up to the second decade. The rate of sensitization to tree pollens was constant among all age groups.

We found that IgE sensitization to mites decreased with age but sensitization to pollen, especially grass pollen, increased. Our findings are similar to those of Jarvis et al.,²⁰ who found that the prevalence of sensitization to house dust mites and cats clearly decreased with age, but

this was not the case for grass pollen. We found that the prevalence of allergic sensitization decreased with age. We suggest that sensitization to perennial AR-related allergens may decrease with time; desensitization is triggered by repeated exposure over many years. However, sensitization to seasonal AR allergens may increase over time, because repeated re-exposure may enhance the immune response. Further studies are required.

One strength of our study is its design: it was a longitudinal panel study, which is useful to determine the trend or changing patterns efficiently because of the collection of data in long periods of time. It also has more power than cross-sectional studies when it comes to excluding time-invariants and unobserved individual bias, as it uses repeated observations at individual levels. Second, the MAST evaluated a lot of allergens (39 in the present study); other similar studies evaluated only 5 to 18 allergens.^{7,8,16,18} Third, we included patients of all ages, from children to older adults; Rondón et al.⁷ studied only adults, and other studies included only children.^{8,16,18}

However, our study also had certain limitations. First, the sample size of each age group, especially the 60 to 79 years old group, was too small to allow detailed generalizations. Second, follow-up periods of repeated in vitro IgE sensitization tests differed among patients. This was because MAST was repeated when a patient's symptoms changed, AR symptom disappeared without any specific reason, or appearances of new allergens were suspected. Third, some allergens to which patients were positive may not have contributed to their clinical symptoms or disease; allergens were identified using an in vitro IgE sensitization test. Fourth, we used the MAST rather than the skin-prick test. Although in vitro tests of serum allergen-specific IgEs yield values similar to those of the skin-prick test, the latter test remains a major diagnostic

tool in the field of allergy. However, the MAST has the advantage that many more allergens can be simultaneously tested. Also, the MAST results correlate well with skin-prick test data from rhinitis patients and can be an alternative to skin testing.^{21,22} Finally, our study featured retrospective chart review; further prospective studies with larger sample sizes are required to confirm our general conclusions.

Conclusions

Allergen sensitization patterns changed constantly over time in all age groups, not only in younger children. Therefore, regular follow-up and re-evaluation of IgE sensitization is essential to document changes in allergen sensitization patterns when rhinitis symptoms or treatment efficacy changes, or when considerable time has elapsed since the last IgE sensitization test. 

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