

Differential Correlations among Allergy Tests According to Indoor Allergens in Allergic Rhinitis

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Abstract

Objectives: Several allergy tests are used for the diagnosis of allergic rhinitis; however, few studies have reported a direct comparison of the skin prick test (SPT), multiple allergen simultaneous test (MAST), and ImmunoCAP according to specific allergens. This study aimed to evaluate the correlations between each test and allergic rhinitis symptoms and to evaluate the correlations of the MAST and ImmunoCAP with the SPT for representative indoor allergens in Korea.

Methods: Electronic medical charts were retrospectively reviewed, and 698 patients with allergic rhinitis who had performed SPT, MAST, and ImmunoCAP were enrolled. Correlations between each allergy test for 4 representative indoor allergens and the symptoms of allergic rhinitis were analyzed. Agreements of the MAST and ImmunoCAP with the SPT were compared according to each allergen.

Results: The SPT showed higher correlations with allergic rhinitis symptoms for 4 indoor allergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat, and dog allergens) than the MAST or ImmunoCAP. In comparison between the MAST and SPT, the least correlation was observed for the dog allergen, whereas between the ImmunoCAP and SPT, the least correlation was observed for the cat allergen. The correlation between the ImmunoCAP and SPT was higher than that between the MAST and SPT for the dog allergen, whereas no significant differences were noted for other allergens.

Conclusions: Overall, the SPT showed a higher correlation with allergic rhinitis symptoms than the MAST or ImmunoCAP for 4 indoor allergens. ImmunoCAP showed similar reactivity to MAST; however, it showed better positivity with dog allergen in patients who were reactive to the allergen in the SPT. Care should be taken while evaluating dog allergen sensitization using the MAST.

Keywords

allergens, allergic rhinitis, skin prick tests, multiple allergen simultaneous test, ImmunoCAP

Introduction

The number of patients with allergic rhinitis, a common allergic disorder that induces recurrent sneezing, rhinorrhea, and nasal obstruction, has recently increased.^{1,2} The global prevalence of allergic rhinitis is 10% to 30% in adults and is as high as 40% in children.³ Allergic rhinitis is closely related to the patient's quality of life, and the identification of specific allergens is essential for the precise diagnosis of the disorder and for the determination of suitable treatment options. A diagnosis of allergic rhinitis is confirmed by allergen confirmation tests using either in vivo or in vitro methods. The determination of causative allergens using various test methods is important for precise diagnosis and for instituting avoidance therapy and allergen-specific immunotherapy.⁴ Among various allergens, house dust mites, animal dander, and microorganisms

are important indoor pollutants, and approximately 60% of the Korean population is estimated to be sensitized to house dust mites.⁵ In addition, animal dander comprises an

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important class of inhaled indoor allergens. The prevalence of animal sensitization has increased worldwide,⁶ and consequently, enhanced the burden of perennial allergic rhinitis.⁷ The identification of animal allergen is critical in patients sensitized to animal dander as it can lead to upper and lower airway disease aggravation.⁸ Therefore, we focused on the effect of house dust mite extracts and popular indoor animal dander—cat and dog—by comparing the results of different allergy tests.

The most widely used methods for the diagnosis of allergic rhinitis include the skin prick test (SPT) and serum-specific immunoglobulin E (IgE) tests. The SPT, a simple and minimally invasive method, is the gold standard for the diagnosis and screening of allergic rhinitis. Its sensitivity and specificity range from 68% to 100% and 70% to 91%, respectively.⁹ However, the results of SPTs are affected by seasonal changes, body region tested, age, skin condition, and use of medications such as antihistamines and beta-blockers.¹⁰

As a method of IgE sensitization measurement, the multiple allergen simultaneous test (MAST) is commonly used to detect the presence of serum IgE against various allergens simultaneously. Compared with the SPT, MAST has the advantages of simplicity, reduced invasiveness, and consistency, as it is performed following standardized protocols.¹¹ However, the allergic disorder, age, race, and geographical aspects of the population should be considered during the selection of multiple allergen screening panels.¹² The ImmunoCAP system, introduced in 1989, is used for measuring specific IgE levels allowing the quantitative measurement of IgE antibody levels and shows better sensitivity than previous methods.¹³ Although the ImmunoCAP provides precise measurement of serum IgE levels against specific allergens, measuring the levels of a large number of antigens simultaneously is difficult and expensive.¹⁴

Due to differences in the sensitivity and specificity among test methods, test results could vary in the same patient depending on the method used, which could render the determination of the causative allergen difficult. While studies have compared the efficacy of these allergy tests in patients with allergic rhinitis,¹⁵ few have investigated the differences in positivity ratios among test methods, depending on the representative indoor allergens, in a large number of patients with allergic rhinitis. The present study was designed to determine the correlations of the MAST and ImmunoCAP with the SPT and to evaluate the differential detection rates according to specific allergens in patients with allergic rhinitis.

Materials and Methods

Study Design

This study was reviewed and approved by the Institutional Review Board of the Yonsei University Health System (IRB

4-2019-0338; Seoul, Republic of Korea) and was conducted in accordance with the principles embodied in the 1965 Declaration of Helsinki (as revised in Brazil in 2013). All patients provided written informed consent, and all attempts were made to ensure patient anonymity.

We retrospectively reviewed electronic medical charts from January 2015 to November 2017 and enrolled 698 patients with allergic rhinitis who had undergone SPT, MAST, and ImmunoCAP at the Department of Otorhinolaryngology of the Severance Hospital. The inclusion criteria were (i) adults over 18 years of age who were clinically diagnosed with allergic rhinitis with complaints of 1 or more of following symptoms: nasal congestion, rhinorrhea, sneezing, and itching sensations;¹⁶ and (ii) patients who underwent SPT, MAST, and ImmunoCAP for 4 representative allergens in Korea (*Dermatophagoides pteronyssinus* [Dp], *Dermatophagoides farinae* [Df], cat, and dog allergens). Patients who had taken anti-allergic rhinitis medications in the past 2 weeks as well as those with chronic diseases such as chronic renal failure and malignancies were excluded. Demographic data including data on age, sex, smoking, drinking status, body mass index, and medical history including asthma were evaluated. We also evaluated the scores of the Sino-Nasal Outcome Test (SNOT)-22 and scores of olfactory function as determined using the Korean version of the Sniffin' stick (KVSS) test,¹⁷ as well as total IgE levels and eosinophil percentages, in patients with allergic rhinitis.

Allergy Test Diagnostic Criteria

The SPT, MAST, and ImmunoCAP were routinely performed for patients with allergic rhinitis, and the test results were collected retrospectively from those who met the inclusion criteria. To perform the SPT, all patients were asked not to take any medication that would affect the result of SPT, and the same side of the forearm was chosen for the test. The patient's forearm was cleaned with a 70% isopropyl alcohol wipe before placing a drop each of a 26-allergen solution, negative control (0.9% normal saline), and positive control (1 mg/mL histamine in 50% glycerol and 0.4% phenol). A 23-gauge needle was used to lift the skin slightly to allow the penetration of the allergen into the epidermis. After 20 minutes, the wheal size was calculated as the mean of the longest diameter and the diameter at the midpoint perpendicular to the longest diameter. Wheal reactions corresponding to one-fourth of the diameter produced by the histamine reference (positive control) were graded as 1+, one-half of the diameter as 2+, equal to the diameter as 3+, and twice the diameter as 4+. Wheal sizes >3 mm or ≥3+ reactions (equal or greater than the wheal size of histamine reference) were considered as positive results in the SPT.^{18,19}

The AdvanSure™ AlloScreen (LG Life Sciences, Korea) and ImmunoCAP (Thermo Fisher Scientific, Sweden) assays were used for serum IgE detection. Both tests were

performed according to standard instructions provided by the manufacturers using the 4 most common allergens (Dp, Df, cat, and dog allergens). Both assays used the same class determination range: class 0 (0.00-0.34 kU/L), class 1 (0.35-0.69 kU/L), class 2 (0.70-3.49 kU/L), class 3 (3.50-17.49 kU/L), class 4 (17.50-49.99 kU/L), class 5 (50.00-99.99 kU/L), and class 6 (>100 kU/L). MAST positivity was defined as a serum-specific IgE level ≥ 0.70 kU/L (class 2),²⁰ and ImmunoCAP positivity was defined as a serum-specific IgE level ≥ 0.35 kU/L (class 1),²¹ according to the definition of positive test results from a previous study that reported significant correlation between the 2 allergy test devices.²²

Statistical Analyses

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) to assess the validity and reliability of all tests. Accuracy, sensitivity, and specificity were considered as the diagnostic evaluation values for each test method. The McNemar's test was used to examine the significance of the positive ratio of each test method. The agreements between tests were evaluated by the comparison of positive or negative test results, and Cohen's kappa analysis was used to quantify the adjusted amount of agreement between the allergy tests. The kappa values were categorized as almost perfect (0.8-1.0), substantial (0.6-0.8), moderate (0.4-0.6), fair (0.2-0.4), and poor (<0.2).²³

Steiger's *z*-test was used to analyze the comparisons between correlations (correlations between the SPT and MAST vs correlations between the SPT and ImmunoCAP). A *P*-value $<.05$ was considered statistically significant.

Results

Demographics

The demographic data of 698 patients with clinically diagnosed allergic rhinitis are summarized in Table 1. Patients who underwent all 3 tests were included. The mean age of the participants was 45.2 ± 16.7 years, and 66.8% were male. In total, 33 (4.7%) patients had asthma, and the mean IgE level was 197.5 ± 340.5 IU/mL. The mean SNOT-22 score was 33.6 (moderate) ± 21.3 and the mean KVSS test score was 23.8 (hyposmia) ± 11.7 .

Correlation of Allergy Test Results with the Clinical Diagnosis of Allergic Rhinitis

The positivity ratios of the 3 tests with the clinical diagnosis of allergic rhinitis for the 4 representative allergens are shown in Figure 1. In general, the positivity ratios of the SPT for all 4 allergens were significantly higher than those of the MAST and ImmunoCAP ($P < .001$). The positivity

Table 1. Demographics of Patients with Allergic Rhinitis.

Characteristics	n (%)
Total patients	698 (100)
Age, years	45.2 ± 16.7
Males	466 (66.8)
Smoking	224 (32.1)
Alcohol	372 (53.3)
Body mass index, kg/m ²	24.404 ± 4.205
Hypertension	120 (17.2)
Diabetes mellitus	61 (8.7)
Asthma	33 (4.7)
SNOT-22	33.610 ± 21.330
KVSS	23.808 ± 11.681
Total IgE	197.520 ± 340.473
Eosinophil, %	3.128 ± 2.614

Abbreviations: SNOT-22, Sino-Nasal Outcome Test-22; KVSS, Korean version of the Sniffin' stick.

ratios for Dp and Df were relatively higher than those for cat and dog allergens in the SPTs ($P < .001$). The positivity ratio observed for the dog allergen in the MAST (3.7%) was significantly lower than those in the SPT and ImmunoCAP ($P < .001$). Except for that for the dog allergen, the values for other allergens were not significantly different between the MAST and ImmunoCAP. Taken together, the least correlation with the clinical diagnosis of allergic rhinitis was seen for the dog allergen in the MAST and the cat allergen in the ImmunoCAP.

Agreement of SPT with MAST and ImmunoCAP in Four Indoor Allergens

Table 2 shows the comparisons of sensitivity, specificity, and kappa values between the SPT and MAST. The highest agreement between the SPT and MAST was seen for Dp among the 4 allergens ($\kappa = 0.62$). In contrast, the lowest agreement between the SPT and MAST was seen for the dog allergen ($\kappa = 0.39$), with a sensitivity and specificity of 84.6% and 91.7%, respectively. The comparisons for the SPT and ImmunoCAP are shown in Table 3. The highest agreement between the SPT and ImmunoCAP was seen for Dp among the 4 allergens ($\kappa = 0.67$), with a sensitivity and specificity of 89.9% and 79.8%, respectively. The lowest agreement between the ImmunoCAP and SPT was seen for the cat allergen among the 4 allergens ($\kappa = 0.50$).

Correlation of Two Groups between the SPT and MAST versus SPT and ImmunoCAP

The different correlations were compared for SPT and MAST versus SPT and ImmunoCAP (Table 4). The correlation between the SPT and ImmunoCAP for the dog allergen was significantly higher ($P < .01$) than those between the

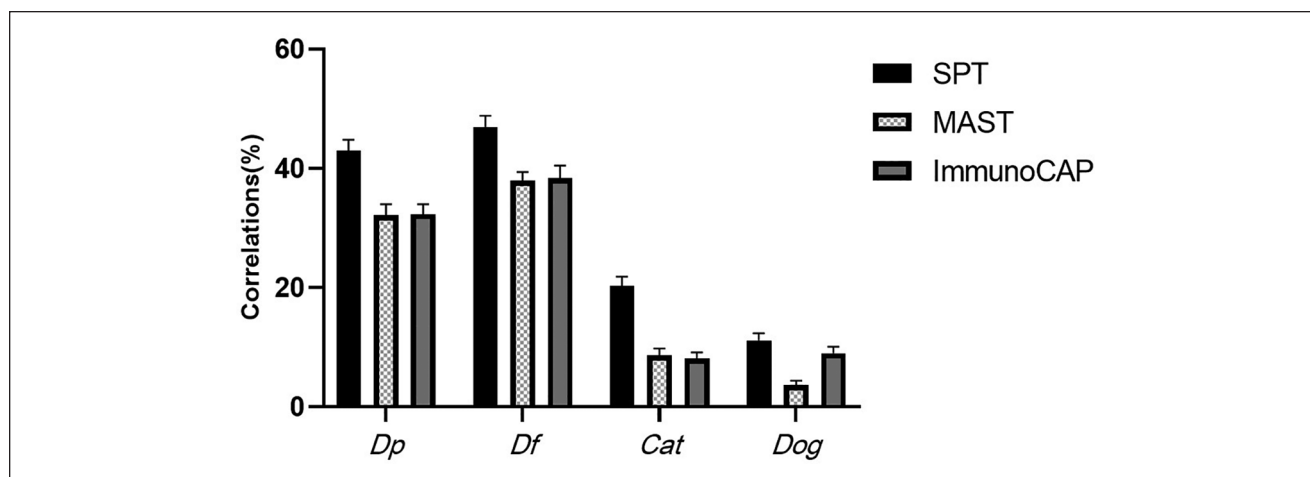


Figure 1. Correlations of allergy tests in relation to the clinical diagnosis of allergic rhinitis. Abbreviations: Dp, dermatophagoides pteronyssinus; Df, dermatophagoides farina.

Table 2. Agreement between the Results of the SPT and MAST (Positive or Negative).

Allergen	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	κ (95% CI)
Dp	88.9 (84.9-92.9)	78.9 (75.3-82.5)	83.9 (81.1-86.6)	0.62 (0.57-0.68)*
Df	86.8 (82.6-90.6)	77.4 (73.4-81.5)	82.1 (79.2-84.9)	0.61 (0.55-0.67)*
Cat	100 (100-100)	87.3 (84.8-89.8)	93.6 (92.3-94.9)	0.54 (0.46-0.63)**
Dog	84.6 (69.2-96.2)	91.7 (89.4-93.8)	88.1 (81-95.3)	0.39 (0.27-0.51)**

Abbreviations: SPT, skin-prick test; MAST, multiple allergen simultaneous test; CI, confidence interval; AUC, area under the curve; Dp, dermatophagoides pteronyssinus; Df, dermatophagoides farina.

* $P < .001$. ** $P < .05$.

Table 3. Agreement between the Results of the SPT and ImmunoCAP (Positive or Negative).

Allergen	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	κ (95% CI)
Dp	92 (88.5-95.6)	80.5 (76.9-84.1)	86.3 (83.8-88.8)	0.67 (0.61-0.72)*
Df	89.9 (86.2-93.3)	79.8 (76-83.5)	84.8 (82.2-87.5)	0.67 (0.61-0.72)*
Cat	96.5 (91.2-100)	86.4 (83.6-88.9)	91.5 (88.7-94.2)	0.50 (0.41-0.58)**
Dog	73 (61.9-84.1)	95 (93.2-96.5)	84 (78.4-89.6)	0.61 (0.52-0.71)**

Abbreviations: SPT, skin-prick test; CI, confidence interval; AUC, area under the curve; Dp, Dermatophagoides pteronyssinus; Df, Dermatophagoides farina.

* $P < .001$. ** $P < .05$.

SPT and MAST, whereas the correlation for Dp, Df, and cat allergens did not differ significantly between the 2 groups. Taken together, ImmunoCAP presented a higher correlation with SPT for the dog allergen.

Discussion

The SPT and serum allergen-specific IgE tests are commonly used to detect type 1 IgE-mediated immediate hypersensitivity reactions, with the former being the standard method for non-invasive diagnosis of allergic rhinitis.¹⁹ The present study compared allergy tests in parallel in a large

number of patients with allergic rhinitis and compared their correlations according to representative indoor allergens in Korea. The SPT demonstrated a higher correlation with the clinical symptoms of allergic rhinitis than the MAST or ImmunoCAP. Among the 4 indoor allergens, the correlation between the ImmunoCAP and SPT was higher than that between the MAST and SPT only for the dog allergen; comparable correlations were seen for the other allergens.

Among the indoor allergens selected for this study, Dp and Df are the most common allergens acting through the inhalational route and inducing allergic rhinitis, and most patients with allergic rhinitis show positive reactions to

Table 4. Correlation between the SPT and MAST and between the SPT and ImmunoCAP.

Allergen	SPT and MAST	SPT and ImmunoCAP	P-value
	κ (95% CI)	κ (95% CI)	
Dp	0.623 (0.565-0.681)	0.668 (0.613-0.724)	.157
Df	0.613 (0.555-0.671)	0.669 (0.614-0.724)	.105
Cat	0.545 (0.462-0.628)	0.494 (0.408-0.579)	.210
Dog	0.389 (0.27-0.508)	0.614 (0.515-0.713)	.004**

Abbreviations: SPT, skin-prick test; MAST, multiple allergen simultaneous test; CI, confidence interval; Dp, dermatophagoides pteronyssinus; Df, dermatophagoides farina.

** $P < .05$.

house dust mites.²⁴ Dog and cat allergens were also investigated because allergies to dogs and cats is a major risk factor for the development of allergic rhinitis and asthma.²⁵ Previous studies have reported an increased prevalence of sensitization to animals in the United States,²⁶ Europe,²⁷ and Asian countries.²⁸

Recently, various diagnostic allergy tests have been developed for the diagnosis of different allergic diseases. Studies have shown that the detection rates of allergy tests differ depending on the type of allergy. The detection rates of the SPT and ImmunoCAP for the diagnosis of nut allergy were 53% and 66%, respectively, indicating the higher efficacy of the ImmunoCAP test. The single most useful test for the diagnosis of oral allergy syndrome is the Immuno-solid Phase Allergen Chip test, whereas the SPT is the preferred test for diagnosing latex allergy.²⁹

In previous reports, in vitro serum IgE detection test results showed 85% to 95% concordance with the results of SPTs according to the allergens being tested and the test method utilized to identify serum IgE.^{30,31} The MAST and ImmunoCAP assays exhibited similar diagnostic performances;¹⁴ however, studies have reported that the sensitivity, specificity, and efficacy of the MAST were not adequately high to replace the SPT in detecting causative allergens.²⁰ A study of 78 patients with allergic rhinitis showed an overall sensitivity and specificity of 73.4% and 95.3% for the MAST and of 81.4% and 94.5% for the ImmunoCAP, respectively. The specificity of the ImmunoCAP was higher than its sensitivity, with an overall agreement of 80.6% between the SPT and ImmunoCAP.³² The recently developed MAST immunoblot method that simplified the testing procedure has a reported assay sensitivity and specificity of 78% and 86.2%, respectively.¹⁵

In this study, Dp and Df showed relatively higher positivity ratios than cat and dog allergens in the 3 allergy tests; however, the agreement between test methods for cat and dog allergens differed from those reported previously.³³ In a previous study that compared SPT and MAST, the degree of agreement for cat allergen was higher than that for dog allergen, which was confirmed by the result of this study. However, the agreement for Dp and Df was lower than cat,

which was different than that observed in this study.²⁰ In another study that compared between SPT and ImmunoCAP, Dp, and Df showed higher agreement than cat and dog, and the degree of agreement for dog was higher than that for cat, which was consistent with our study results.³² In a previous report that compared ImmunoCAP and MAST, the results of both tests correlated well for cat allergens; however, a relatively low agreement was shown for dog allergen. However, the correlation between SPT was not investigated for the allergens tested in the study.³⁴

In our result, the comparisons of allergy tests, including SPT, ImmunoCAP, and MAST were performed together. Cat allergen showed similar agreement between the allergy tests, as reported previously, while dog allergen showed higher agreement between SPT and ImmunoCAP than that between SPT and MAST. The differences in the test results are likely due to the difference in the allergen materials used in the studies. The manufacturing methods of allergy test devices and the regional differences may also have contributed to the discrepancies between the results of different studies. In addition, the positive criteria for an allergy test and the time taken for an investigation could affect the agreements between the different allergy tests.

To summarize, this study showed that the SPT had higher correlation with the clinical diagnosis of allergic rhinitis compared with the MAST or ImmunoCAP for 4 representative allergens. The agreement between the SPT and ImmunoCAP for the dog allergen were significantly higher than those between the SPT and MAST, whereas comparable agreements were observed for the other allergens.

This study was limited because of its retrospective design. Moreover, the false positivity and false negativity of the AlloScreen and ImmunoCAP assays were discriminated based on the SPT results, and the possible selection bias and recall bias of study participants can affect the result of the correlations between the allergy tests. In addition, the cut-off value for sIgE positivity can differ between allergens. Although SPT is used to demonstrate an immediate IgE-mediated allergic reaction and represent a major diagnostic tool in the field of allergy,^{18,35} nasal provocation testing has been widely used as a reference standard in

scientific investigations involving the pathogenesis of allergic rhinitis.³⁶ Nevertheless, previous studies suggested that skin-prick testing is reasonably accurate in identifying patients with suspected symptoms of allergic rhinitis using meta-analysis⁹ and in patients with asthma.³⁷ Among the patients with allergic rhinitis, the olfactory function score was below average and the patients with chronic rhinosinusitis might have been involved in the patient group.³⁸ In addition, the effect of smokers in the prevalence of allergic rhinitis were not able to be considered in this analysis.³⁹ Further studies with larger study populations are needed to compare the efficacy of allergy tests in allergic rhinitis patients and the agreement with the nasal provocation test considering various confounding factors.

Based on the results of the present study, ImmunoCAP showed similar reactivity to MAST; however, it showed better positivity with Dog allergen in those who were reactive to the allergen in the SPT. Different correlations of allergy tests according to other allergens should be further evaluated. The result of this study may help in the appropriate interpretation of allergy test results according to specific indoor allergens in patients with allergic rhinitis.

Declaration of Conflicting Interests

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