Correlation analysis of two serum-specific Immunoglobulin E test systems and skin-prick test in allergic rhinitis patients from northeast China

Xiao-Dan Jiang, Ph.D., Guang-Yu Li, M.D., Zhen Dong, M.D., and Dong-Dong Zhu, Ph.D.

ABSTRACT

Background: *Skin-prick testing (SPT) is the most common screening method for allergy evaluation. The detection of serum-specific immunoglobulin E (sIgE) is also commonly used. The sensitivity and specificity of these testing methods may vary due to type of causative allergen and type of allergic manifestation. The purpose of this study was to evaluate the correlation between two methods of measuring sIgE (AllergyScreen [Mediwiss Analytic GmbH, Moers, Germany] and ImmunoCAP [Pharmacia, Uppsala, Sweden]) and SPT for the diagnosis of allergic rhinitis (AR).*

Methods: *All 216 patients who were referred to the allergist for suspected AR from June to October 2009 had SPT and the two serological tests. One hundred fifty-eight patients had a positive clinical history and a related positive SPT. The SPT was used as reference standard, and we selected three allergens (*Dermatophagoides pteronyssinus*, mugwort, and ragweed), which were common in fall in northeast China, to analyze the correlation of the two serum tests and SPT.*

Results: *Compared with the SPT, the diagnostic indexes (accuracy, sensitivity and specificity) of the AllergyScreen system and the ImmunoCAP system were 0.819 versus 0.810, 0.780 versus 0.872, and 0.862 versus 0.741, respectively. The accuracy was similar between the two systems ($p > 0.05$). The ImmunoCAP system method had a higher sensitivity ($p < 0.01$). The AllergyScreen system had a higher specificity ($p < 0.01$).*

Conclusion: *These data support that the AllergyScreen system and ImmunoCAP system can identify potentially significant allergens in the diagnosis of AR in patients from northeastern China.*

(Am J Rhinol Allergy 25, 116–119, 2011; doi: 10.2500/ajra.2011.25.3572)

Allergic rhinitis (AR) is a symptomatic disorder of the nose induced after allergen exposure *via* an immunoglobulin E (IgE)–mediated inflammation of the membranes lining the nose. The diagnosis of AR is based on the concordance between a typical history of allergic symptoms and diagnostic tests, which shows the presence of allergen-specific IgE, either in the skin (skin tests) or the blood (serum-specific IgE [sIgE]).[1] Inhalation provocation testing would be the most reliable for respiratory allergies, but its clinical practice is limited.[1–3]

Both skin-prick testing (SPT) and sIgE antibody measurement are commonly used in allergy evaluation. SPT is the most common screening method.[1,4,5] As with SPT, the detection of serum sIgE is thought to be an indicator of the degree of IgE-mediated sensitivity to a specific allergen. Measurement of serum sIgE by the ImmunoCAP system (Pharmacia, Uppsala, Sweden) is widely used.[6,7] A large number of studies have been performed to evaluate the performance of ImmunoCAP sIgE tests in the diagnosis of allergy, and it is generally thought that this method has a better sensitivity and specificity.[8–10] The ImmunoCAP system uses an enzyme-linked immunosorbent assay analytical method, with high sensitivity for single allergens, which are assayed individually. The AllergyScreen system (Mediwiss Analytic GmbH, Moers, Germany) is a screening test that uses a Western blot method to detect multiallergen combinations at one time to facilitate the clarification of a wide range of allergens in the serum. As such, it provides results that are faster and cheaper. In clinical practice, it is importance to know the reliability of these two serum sIgE test systems. Therefore, the primary purpose of this study was to compare the two serum sIgE test systems with SPT for three inhalant allergens in patients with AR from northeast China.

From the Department of Otorhinolaryngology, Head and Neck Surgery, China–Japan Union Hospital of Jilin University, Changchun, China
Funded by Key Clinical Program of the Ministry of Health, Grant NSC 07090138
The authors have no conflicts to declare pertaining to this article
Address correspondence and reprint requests to Dong-Dong Zhu, Ph.D., Department of Otorhinolaryngology, Head and Neck Surgery, China–Japan Union Hospital of Jilin University, Changchun 130033, China
E-mail address: zhudd@jlu.edu.cn

MATERIALS AND METHODS

Patients

Two hundred sixteen subjects who were referred to the allergist for a suspected AR from June to October in 2009 were recruited at China-Japan Union Hospital of Jilin University. A questionnaire was administered to assess the history and symptoms. Patients were asked to check any possible triggers that aggravated their symptoms, including house-dust mites (especially when touching pillows and bedclothes or books or papers), animal fur (especially dog and cat), seasonal grass pollens (ragweed, mugwort, humulus, chenopodium album, *etc.*), molds (indoor and outdoor mustiness or horticultural environment), and cockroaches. All of the subjects had SPT and serum sIgE tests performed. A physician diagnosis of AR was obtained from the presence of symptoms when exposed to the allergen in question in conjunction with a positive skin reading test response to the same allergen.[10] Before study enrollment, each patient provided written, informed consent. The study protocol was approved by our Institutional Ethics Committee. Nasal symptoms experienced by the patients were assessed by visual analog scales[12] to reflect the degree of severity of the disease.

Skin-Prick Testing

SPTs were performed with the commercial standard inhalant allergen (ALK, Horsholm, Denmark) containing 10 allergens, including *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, mugwort, common ragweed, *Blattella germanica*, mold mix, grass mix, trees mix, cat dander, and dog dander. The patients took no antihistamines and other drugs that have antihistaminic effect at least 1 week before the test. SPT was performed on the patient's forearm. Positive and negative controls were included histamine (10 mg/mL) and saline solution, respectively. The test results were read at 20 minutes. We calculated the skin index (SI), which equals the wheal diameter ratio of allergen and histamine diameter. The SPT results were then divided into four categories from one to four[13]: class 1+, $SI < 0.5$; class 2+, $0.5 \leq SI < 1.0$; class 3+, $1.0 \leq SI < 2.0$; class 4+, $SI \geq 2.0$. A wheal diameter of at least 3 mm was considered positive.

Table 1 **Illustration of the calculation of outcome probabilities**

	SPT$^+$ and History Positive	SPT$^-$ and History Negative
sIgE$^+$	TP	FP
sIgE$^-$	FN	TN

Accuracy/concordance (%) = (TP + TN) × 100/TP + TN + FP + FN; sensitivity (%) = TP × 100/TP + FN; specificity (%) = TN × 100/FP + TN. FN = false negative; FP = false positive; TP = true positive; TN = true negative; sIgE = specific immunoglobulin E; SPT = skin-prick testing.

Specific IgE

Serum sIgE was quantified in all subjects with the AllergyScreen system and ImmunoCAP 100 system according to the manufacturer's directions. The AllergyScreen system was used to detect 20 kinds of allergens including *D. pteronyssinus*, mugwort, ragweed, German cockroach (*B. germanica*), cat epithelium and dander, dog dander, horse dander, mold mix, trees mix, *Humulus scandens*, cypress pollen, egg white, fish mixture, fruit mixture, rye pollen, wheat flour, walnut, milk, peanut, and soya bean. The AllergyScreen classification system divides results into seven categories from zero to six: class 0, <0.35 IU/mL; class 1, 0.35~0.70 IU/mL; class 2, 0.71~3.50 IU/mL; class 3, 3.51~17.5 IU/mL; class 4, 17.6~50 IU/ mL; class 5, 50.1~100 IU/mL; and class 6, >100 IU/mL. Subjects were considered sensitive to the allergens if the measurement of IgE was ≥0.35 IU/mL.

The ImmunoCAP system is a conventional single allergen system.[14] According to SPT and clinical history, we chose three common allergens (*D. pteronyssinus*, mugwort, and ragweed) in the late summer and fall in northeast China. The ImmunoCAP classification system also divides results into seven categories from zero to six: class 0, <0.35 kU/mL; class 1, 0.35~0.70 kU/L; class 2, 0.71~3.5 kU/L; class 3, 3.51~7.5 kU/L; class 4, 7.6~17.5 kU/L; class 5, 17.6~50 kU/L; and class 6, >50 kU/L. The units reported by ImmunoCAP are in accordance with the defined World Health Organization serum standard International Reference Preparation 75/520. Subjects were considered sensitive to the allergens if the measurement of IgE was ≥0.35 kU/L.

Diagnostic Criteria

All of the patients that we diagnosed with AR were confirmed by the presence of symptoms when exposed to the allergen in question in conjunction with a positive skin test response. The diagnostic value of a procedure is always defined by its accuracy, sensitivity, and specificity. Taking the result of SPT as the reference standard, we calculated the accuracy, sensitivity, and specificity of the AllergyScreen system and ImmunoCAP system (Table 1).

Statistics

The chi-square test was used for comparing frequencies. A value of $p < 0.05$ was considered statistically significant. Correlation analysis was realized by the Spearman's rank correlation method.

RESULTS

Patient Characteristics

There were 158 individuals diagnosed with AR (aged 8–68 years; mean, 28.4 years) based on the aforementioned criteria having a positive clinical history and a related positive SPT. There were slightly more men (58.9%) than women (41.1%) in the study. All of the patients had a positive SPT and a related clinical history. Approximately 25.9% (41/158) of individuals showed perennial nasal symptoms and 74.1% (117/158) reported seasonally related reactions. The main self-reported symptoms involved nasal itching, nasal obstruction, continuous sneezing, and watery rhinorrhea, estimated by the visual analog scale scores.

The Accuracy, Sensitivity, and Specificity of Serum sIgE Test with SPT

The accuracy, sensitivity, and specificity of two kinds of serum sIgE test system with SPT were presented in Table 2. The accuracy of AllergyScreen/SPT was 77.2–87.3% for the three allergens. The accuracy of ImmunoCAP/SPT was 72.8–87.3% for the three allergens. There was no statistical difference between these two tests (all, $p > 0.05$). The sensitivity of AllergyScreen/SPT was 65.9–89.1% across the three allergens. The sensitivity of ImmunoCAP /SPT was 87.0–87.8%. There was a significant difference ($p < 0.05$; besides ragweed). The specificity of AllergyScreen/SPT was 69.7–94.9%. The specificity of ImmunoCAP/SPT was 53.0–87.2%. There was a significant difference ($p < 0.05$; besides mugwort). There were five other allergens we tested both in AllergyScreen and in SPT, and the accuracy of AllergyScreen/SPT was 81.0–96.8% (presented in Table 3).

The Rank Correlation Analysis of Serum sIgE Test with SPT

Tables 4 and 5 show the concordance of individual SPT grade and sIgE classification, 474 detections (include the three allergens) coming from 158 patients. By Spearman's rank correlation analysis, there was positive correlation between AllergyScreen system and SPT ($rs = 0.617$; $p < 0.01$). There was also positive correlation between the ImmunoCAP system and SPT ($rs = 0.663$; $p < 0.01$). Table 6 shows that there was also positive correlation between the AllergyScreen system and ImmunoCAP system ($rs = 0.715$, $p < 0.01$).

DISCUSSION

The diagnosis of AR is based on a typical history of allergic symptoms and confirmatory diagnostic tests.[1] We performed this study to assess the value of the two serum sIgE detection systems' response to allergens in patients who were diagnosed with AR from the presence of symptoms when exposed to the allergen in question, in addition to a positive skin test response to the same allergen.

In our study, the 158 subjects (73.1%) had a positive clinical history and a related positive SPT. Using the result of SPT as the reference standard, the diagnostic indexes including accuracy or concordance, sensitivity, and specificity were measured. The total concordance of the AllergyScreen system and the ImmunoCAP system with SPT for *D. pteronyssinus*, mugwort, and ragweed were 0.819 versus 0.810, respectively. There was no significant difference. This result is in concordance with the reported results from Kersten[15] and Herzum[16] in other populations. The total concordance of AllergyScreen system with SPT for the other five allergens was 92.8%. We conclude that there was a good concordance of the two serum sIgE detection systems with SPT. Hence, we believe these methods would be useful in clinical practice in China and in other nations. In addition, we further compared the classification condition of the two systems with SPT. By Spearman's rank correlation analysis, there was a positive correlation between the AllergyScreen system and SPT grade. There was also a positive correlation between the ImmunoCAP system and SPT grade. Hence, we believe that these systems can be used quantitatively to grade allergy severity.

In our study, the sensitivity of the AllergyScreen system ranged from 65.9 to 89.1% and the specificity ranged from 69.7 to 94.9%. The sensitivity of the ImmunoCAP system ranged from 87.0 to 87.8%, and the specificity ranged from 53.0 to 87.2%. Different allergens lead to different sensitivities and specificities. For *D. pteronyssinus*, both of the systems have a high specificity, which was in accordance with King.[17] If the allergen shows negative results, we can exclude the possibility that the patient was hypersensitive to it by the two detection systems. The ImmunoCAP

Table 2 **Accuracy, sensitivity, and specificity between the AllergyScreen system or the ImmunoCAP system with skin-prick testing (SPT) as the reference standard in all patients tested for *Dermatophagoides pteronyssinus*, mugwort, and ragweed**

	Allergen	AS-SPT	CAP-SPT
Accuracy/concordance	*D. pteronyssinus*	138/158 (87.3%)	138/158 (87.3%)
	Mugwort	122/158 (77.2%)	131/158 (82.9%)
	Ragweed	128/158 (81.0%)	115/158 (72.8%)
	Total	388/474 (81.9%)	384/474 (81.0%)
Sensitivity	*D. pteronyssinus*	27/41 (65.9%)*	36/41 (87.8%)*
	Mugwort	86/117 (73.5%)**	102/117 (87.2%)**
	Ragweed	82/92 (89.1%)	80/92 (87.0%)
	Total	195/250 (78.0%)**	218/250 (87.2%)**
Specificity	*D. pteronyssinus*	111/117 (94.9%)*	102/117 (87.2%)*
	Mugwort	36/41 (87.8%)	29/41 (70.7%)
	Ragweed	46/66 (69.7%)*	35/66 (53.0%)*
	Total	193/224 (86.2%)**	166/224 (74.1%)**

*$p < 0.05$; **$p < 0.01$.
AS = AllergyScreen system; CAP = ImmunoCAP system.

Table 3 **Accuracy between AllergyScreen system with skin-prick testing (SPT) in all patients tested for *Blattella germanica*, cat dander, dog dander, mould mix, and trees mix**

	Allergen	AS-SPT
Accuracy/concordance	*B. germanica*	151/158 (95.6%)
	Cat dander	149/158 (94.3%)
	Dog dander	153/158 (96.8%)
	Mould mix	152/158 (96.2%)
	Trees mix	128/158 (81.0%)
	Total	733/790 (92.8%)

AS = AllergyScreen system.

Table 4 **The rank correlation of the AllergyScreen system serum sIgE test class with skin-prick testing (SPT) grade**

SPT Grade	AllergyScreen System Class						
	0	1	2	3	4	5	6
−−−	190	9	11	6	4	3	1
+	4	1	1	2	0	0	0
++	15	4	18	15	5	1	1
+++	26	7	18	28	20	10	9
++++	13	4	4	18	6	10	10

sIgE = specific immunoglobulin E.

Table 5 **The rank correlation of ImmunoCAP system serum sIgE test class with skin-prick testing (SPT) grade**

SPT Grade	ImmunoCAP System Class						
	0	1	2	3	4	5	6
−−−	166	14	24	13	4	2	1
+	3	0	1	1	1	2	0
++	11	5	15	13	10	2	3
+++	13	7	23	14	28	21	12
++++	5	0	14	9	12	13	12

sIgE = specific immunoglobulin E.

Table 6 **The rank correlation of the AllergyScreen system serum sIgE test class with the ImmunoCAP system**

ImmunoCAP System Class	AllergyScreen System Class						
	0	1	2	3	4	5	6
0	179	2	6	5	3	1	2
1	15	3	6	1	1	0	0
2	30	7	21	14	3	2	0
3	11	8	10	13	5	3	0
4	7	3	8	19	7	6	4
5	5	0	1	13	9	2	10
6	1	1	0	4	7	10	5

sIgE = specific immunoglobulin E.

system has a higher sensitivity than the AllergyScreen system (87.8% versus 65.9%). Therefore, in our clinical practice, if the patients have a positive clinical history for *D. pteronyssinus*, but the SPT is negative, we can use the serum sIgE test using ImmunoCAP. For the mugwort, the ImmunoCAP system has a higher sensitivity and the AllergyScreen system has a higher specificity. For ragweed, the AllergyScreen system is superior to the ImmunoCAP system in every diagnostic value; however, in the specificity, the two systems have lower values (69.7 and 53.0%). This illustrates that the two systems may yield false positive results in the diagnosis of ragweed. Liu *et al.*[18] studied 35 patients with AR to compare the two *in vitro* test methods. Four allergens (*D. pteronyssinus*, mugwort, animal hair, and cockroach) were studied. The sensitivity, specificity, and accuracy of the AllergyScreen system and the CAP system were 89% versus 96%, 75% versus 84%, and 80% versus 89%, respectively. These were a little different from our results. We considered that the sample size, the different types of allergens, and the different region in China may compose the possible reasons.

The ImmunoCAP system is a well-established method for the diagnosis of AR. It was thought to have a higher sensitivity and specificity than the IMMULITE System (Siemens Medical Solutions, Germany) and Enzyme Allergo-Sorbent Test (Allergopharma, Reinbek, Germany).[19,20] The ImmunoCAP system is used for the serum sIgE detection for a single allergen. In our study, the ImmunoCAP system has a higher sensitivity and correlated well with the SPT. Therefore, in our clinical practice, we could identify the relevant allergens combining it with SPT when the results of SPT disagreed with the clinical history. In addition, we could observe the concentration change of serum sIgE before and after immunotherapy by this detection system. The AllergyScreen system is a simple analysis of a whole range of allergens possible in one test, and only 250 μL serum is required. It

has a higher specificity than the ImmunoCAP system and correlates well with the SPT. Importantly, it has a lower cost. In our clinical practice, it is helpful in equivocal situations and also can be used for screening large samples and epidemiological research.

CONCLUSION

These data support the use of the AllergyScreen and ImmunoCAP systems to identify potentially significant individual allergens in the diagnosis of AR. The ImmunoCAP system method had a higher sensitivity. The AllergyScreen system had a higher specificity. As a simple, rapid turnaround time and low cost system, the AllergyScreen system can test multiallergens at one time. This test is complementary to the SPT and ImmunoCAP system, with low cost, rapid turnaround, and good test parameters as advantages for its use.

ACKNOWLEDGMENTS

The authors thank Dr. Jayant M. Pinto, Assistant Professor of the Department of Otolarynology, Head and Neck Surgery, the University of Chicago, for his excellent contributions to the experiments described in this article.

REFERENCES

1. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update. Allergy 63:S8–S160, 2008.
2. Sharma HP, Wood RA, Bravo AR, et al. A comparison of skin prick tests, intradermal skin tests, and specific IgE in the diagnosis of mouse allergy. J Allergy Clin Immunol 121:933–939, 2008.
3. Khan DA. Allergic rhinitis with negative skin tests: Does it exist? Allergy Asthma Proc 30:465–469, 2009.
4. Bousquet J, Cauwenberge P, Khaltaev N, et al. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 108:S147–S334, 2001.
5. Dolen WK. Skin testing and immunoassays for allergen-specific IgE. Clin Rev Allergy Immunol 21:229–239, 2001.
6. Söderström L, Kober A, Ahlstedt S, et al. A further evaluation of the clinical use of specific IgE antibody testing in allergic diseases. Allergy 58:921–928, 2003.
7. Williams PB, Barnes JH, Szeinbach SL, et al. Analytic precision and accuracy of commercial immunoassays for specific IgE: Establishing a standard. J Allergy Clin Immunol 105:1221–1230, 2000.
8. Paganelli R, Ansotegui IJ, Sastre J, et al. Specific IgE antibodies in the diagnosis of atopic disease. Clinical evaluation of a new in vitro test system, UniCAP, in six European allergy clinics. Allergy 53:763–768, 1998.
9. Williams PB, Siegel C, and Portnoy J. Efficacy of a single diagnostic test for sensitization to common inhalant allergens. Ann Allergy Asthma Immunol 86:196–202, 2001.
10. Calabria CW, Dietrich J, and Hagan L. Comparison of serum-specific IgE (ImmunoCAP) and skin-prick test results for 53 inhalant allergens in patients with chronic rhinitis. Allergy Asthma Proc 30:386–396, 2009.
11. Takwoingi Y, Akang E, Nwaorgu G, et al. Comparing nasal secretion eosinophil count with skin sensitivity test in allergic rhinitis in Ibadan, Nigeria. Acta Otolaryngol 123:1070–1074, 2003.
12. Linder A. Symptom scores as measures of the severity of rhinitis. Clin Allergy 18:29–37, 1988.
13. Dreborg S, and Frew A. Position Paper: Allergen standardization and skin tests. Allergy 47:S48–S82, 1993.
14. Ewan PW, and Coote D. Evaluation of a capsulated hydrophilic carrier polymer (the ImmunoCAP) for measurement of specific IgE antibodies. Allergy 45:22–29, 1990.
15. Kersten W. Comparison of the AllergyScreen (Mediwiss Analytic, Moers) with the skin test (HAL, Dusseldorf-in-vivo) and the CAP system (Pharmacia, Freiburg-in-vitro). Allergologie 25:203–208, 2002.
16. Herzum I, Blümer N, Kersten W, et al. Diagnostic and analytical performance of a screening panel for allergy. Clin Chem Lab Med 43:963–966, 2005.
17. King MJ, Tamulis T, and Lockey RF. Prick puncture skin tests and serum specific IgE as predictors of nasal challenge response to *Dermatophagoides pteronyssinus* in older adults. Ann Allergy Asthma Immunol 101:12–17, 2008.
18. Liu C, Han D, Zhang L, et al. Comparison of two specific immunoglobulin E test systems in the diagnosis of allergic rhinitis [in Chinese]. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 23:484–487, 2009.
19. Costongs GM, and Bas BM. The first fully automated allergy analyser UniCAP: comparison with IMMULITE for allergy panel testing. Eur J Clin Chem Clin Biochem 35:885–888, 1997.
20. Sander I, Kespohl S, Merget R, et al. A new method to bind allergens for the measurement of specific IgE antibodies. Int Arch Allergy Immunol 136:39–44, 2005. □