The Role of Phadiatop Test and Total Immunoglobulin E in Screening Aeroallergens: A Hospital-based Cohort Study

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Research

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Abstract

Background: To screen the existence of aeroallergens in patients with possible allergic rhinitis by venous blood becomes more popular, with advantages of more convenient and less consumption of time. The aim of this study is to investigate the sensitivity and specificity of Phadiatop test and total immunoglobulin E (IgE) level examination in both adults and children groups.

Methods: This study was conducted prospectively in a tertiary center. The process of recruitment took place from Jan 2015 to Dec 2019, and patients with clinical symptoms suggesting of persistent allergic rhinitis were recruited and their serum samples were collected. The results of total IgE levels, Phadiatop tests, and the positive items in the ImmunoCAP assay were recorded and analyzed.

Results: Total 9174 cases with complete data were enrolled, including 576 children and 8598 adults. A positive result in the ImmunoCAP assay was defined to confirm a positive atopic status towards aeroallergens. While using the total IgE level to predict positive aeroallergens, the sensitivity and specificity were 65.7% and 85.7% for adults and 86.3% and 77.4% for children, respectively. If we applied Phadiatop test for allergy screening, the sensitivity and specificity was 94.5%, 98.2% and 98.5%, 96.8% for the adult and the pediatric group, respectively.

Conclusions: Phadiatop test had a better diagnostic power for aeroallergen detection than the serum total IgE level, or even the dual test, for both the adult and pediatric groups in this hospital-based study. We suggest that the Phadiatop test is more cost-effective in aeroallergen screening for patients suspected of atopic airway diseases.

Background

The prevalence of allergic rhinitis (AR) in the United States is approximately 15% based on physician diagnoses and 30% based on self-reported nasal symptoms.¹ Studies have shown that the prevalence rate is even higher in Asian countries², with 27% reported in Korea³, 18.8% in Malaysia⁴ and up to 50.1% reported in elementary school children in Taiwan.⁵ AR contributes to missed or unproductive time at work and school, sleep problems, decreased involvement in outdoor activities, and a burden to our health and economy.^{6,7} The socioeconomic burden of AR is significant, including the cost of treatment, reduced productivity, and the use of inappropriate therapies.⁸ When it comes to children with uncontrolled AR, learning problems occur during school hours either by direct interference or indirectly through nocturnal sleep loss and secondary daytime fatigue.⁹ Children with AR tend to be shy, depressed, anxious, or fearful.¹⁰ The Pediatric Allergies in America survey emphasizes that congestion is the most impactful symptom in children.¹¹ Except for socioeconomic burdens, AR in pediatric groups is associated with several other comorbid conditions, including conjunctivitis, otitis media, pharyngitis, asthma, and obstructive sleep apnea.¹²

The diagnosis of AR is generally based on a history of symptoms that correspond with exposure to sensitizing allergens and physical examination.¹ However, the result can be ambiguous because of an arbitrary identification. Laboratory examination would be helpful and based on evidence of sensitization to common allergens, measured either by the presence of allergen-specific immunoglobulin E (IgE) in the serum or by positive epicutaneous skin tests.¹ However, skin tests take too much time, and patients have to undergo the risks of anaphylactic shock and other complications. Currently, the confirmation of allergy by single venous blood puncture has become more popular, with the advantages of more convenience and less time requirements.

Total IgE and Phadiatop (ThermoFisher Scientific, Uppsala, Sweden) are two serum examinations that could be first-line screening tools for atopic status, with characteristics of cost-effectiveness, efficiency, and convenience. A higher total IgE serum level (> 100 and 77 IU/mL for adults and children, respectively) or Phadiatop level > 0.35 KU/L was defined as positive.^{13–15} The Taiwanese health insurance system stipulates that specific IgE could be further checked if only the serum total IgE level was more than 100 IU/mL. However, Tu et al. have revealed an insufficient diagnostic accuracy of serum total IgE alone for detecting allergic diseases in the pediatric population in Taiwan.¹⁶ To the best of our knowledge, there is no recent large-scale sensitivity report for this particular issue to date for the Asian population. This study aimed to investigate the sensitivity and specificity of each blood test to predict the existence of hypersensitivity to aeroallergens in adult and child cohorts.

Methods

The protocol of this study was approved by the institutional review board. The recruitment process took place from January 2015 to December 2019, during which a total of 9174 consecutive patients with clinical symptoms suggestive of persistent AR were recruited. We enrolled patients with at least one typical symptom associated with AR (runny nose, nasal obstruction, itchy nose, or sneezing) that persisted for at least four consecutive weeks. The serum samples collected from the enrolled patients were sent for total IgE levels and six common aeroallergens using the ImmunoCAP 1000 system (ThermoFisher Scientific, Uppsala, Sweden), including *Dermatophagoides pteronyssinus* (d1), *Dermatophagoides farinae* (d2), cat dander (e1), dog dander (e5), cockroach (i6), and grass mix (Bermuda grass, Rye grass, Bahia grass, Common Ragweed, English Plantain, Goosefoot Lamb's quarters) (rx3). We proposed a positive result of aeroallergen detection as a confirmation of AR. The Phadiatop test consists of a solid-phase immunoassay for serum-specific IgE using a balanced mixture of relevant allergens causing common inhalant allergies coupled to ImmunoCAP.¹⁷ The calculation of results was performed automatically according to the fluorescence response obtained for patient samples compared to the response obtained for the reference serum supplied. According to previous studies, a positive value of the serum total IgE level in the present study was defined to be more than 100 IU/mL and 77 IU/mL in the adult and the pediatric group, respectively.^{18–20}

Results

Distribution of serum tests in the two groups

A total of 9174 patients with complete serum data were enrolled during the four years of the study, including 576 children (age range, 2–17 years) and 8598 adults (age ≥ 18 years). Among the 25 children with total IgE levels > 77 IU/mL but negative in Phadiatop tests, none (0%) presented with positive aeroallergens, as verified by ImmunoCAP assay. Meanwhile, among 56 children with total IgE levels < 77 IU/mL but positive in the Phadiatop test, 55 (98.2%) presented positive results for aeroallergens. There were 393 children with total IgE levels > 77 IU/mL and positive Phadiatop tests, and 390 (99.2%) presented with positive aeroallergen results. Meanwhile, among 102 children with total IgE levels < 77 IU/mL and negative Phadiatop tests, only seven (6.9%) were positive in the ImmunoCAP assay results (Table 1).

Table 1

The percentage of subjects with a positive ImmunoCAP test in each subgroup of adult and pediatric patients. tIgE, total immunoglobulin E; CAP, ImmunoCAP test

Adult group			Pediatric group	
	Subgroup number	Number (%) of CAP (+)	Subgroup number	Number (%) of CAP (+)
tIgE (+), Phadiatop (+)	3285	3251 (99.0)	393	390 (99.2)
tIgE (+), Phadiatop (-)	568	102 (18.0)	25	0 (0)
tIgE (-), Phadiatop (+)	1597	1569 (98.2)	56	55 (98.2)
tIgE (-), Phadiatop (-)	3148	178 (5.7)	102	7 (6.9)
Total cases	8598		576	

Among the adult subjects, there were 568 patients with total IgE levels > 100 IU/mL but negative Phadiatop tests, and 102 (18.0%) presented with positive aeroallergens tests (Table 1). Furthermore, 1597 adults had total IgE levels < 100 IU/mL but positive Phadiatop tests, 1569 (98.2%) of them had a positive aeroallergen test. There were 3285 adult subjects with total IgE levels > 100 IU/mL and positive Phadiatop tests, and 3251 (99.0%) of them had positive aeroallergen results confirmed. Meanwhile, there were 3148 adult subjects with total IgE levels < 100 KU/L and negative Phadiatop tests, and only 178 (5.7%) of them had positive aeroallergen analyses.

For the patients with negative total IgE levels but positive Phadiatop results, the majority (91.4% and 96.4% for the adult and pediatric groups, respectively) presented with positive ImmunoCAP assay results were allergic to dust mites (*D. pteronyssinus*). On the other hand, for those with negative total IgE levels

and negative Phadiatop tests, the most common aeroallergen with positive results was the cockroach (41.2% and 42.9% for the adult and pediatric groups, respectively).

Sensitivity and specificity analyses

We further analyzed the sensitivity and specificity of the total IgE level and the Phadiatop test to identify an allergy. At least one positive result among the aeroallergen tests in the ImmunoCAP assay was defined as confirmation of the inhalant allergy. When only the total IgE level was taken into consideration to detect allergy, the sensitivity rates were 65.7% and 86.3% and specificity was 85.7% and 77.4% for the adult and pediatric groups, respectively. Alternatively, when we applied the Phadiatop test, the sensitivity rate was 94.5% and 98.5% and specificity was 98.2% and 96.8% for the adult and pediatric groups, respectively. While the total IgE level and the Phadiatop test were both taken into account to confirm allergy status, the sensitivity was 96.5% and 98.5%, and specificity was 84.9% and 77.9% for the adult and pediatric groups, respectively (Table 2).

Table 2
The sensitivity and specificity of each blood test to detect positive
aeroallergens in two groups. IgE, immunoglobulin E

		Adult group	Pediatric group
Total IgE level	Sensitivity (%)	65.7	86.3
	Specificity (%)	85.7	77.4
Phadiatop test	Sensitivity (%)	94.5	98.5
	Specificity (%)	98.2	96.8
Combined both tests	Sensitivity (%)	96.5	98.5
	Specificity (%)	84.9	77.9

Analysis of positive and negative prediction values

According to our study, if we only applied total IgE level to screen for allergic status, the positive predictive value (PPV) would be 87.0% for the adult group and 93.3% for the pediatric group. In comparison, the negative predictive value (NPV) would be 63.2% and 60.8%, respectively. If we only applied the Phadiatop test instead, the PPV would be 98.7% for the adult group and 99.1% for the pediatric group, while the NPV would be 92.5% and 94.5%, respectively. If we applied both tests for allergy screening, we found that PPV would be 90.3% for the adult group and 93.9% for the children’s group, while the NPV would be 96.5% and 93.1%, respectively (Table 3).

Table 3

The PPV and NPV of each blood test to detect positive aeroallergens in two groups. IgE, immunoglobulin E; PPV, positive predictive value; NPV, negative predictive value

		Adult group	Pediatric group
Total IgE level	PPV (%)	87.0	93.3
	NPV (%)	63.2	60.8
Phadiatop test	PPV (%)	98.7	99.1
	NPV (%)	92.5	94.5
Combined both tests	PPV (%)	90.3	93.9
	NPV (%)	96.5	93.1

Furthermore, through the receiver operating characteristic (ROC) curve, we found the best cut-off value of total IgE level to detect AR according to Youden's index. Among the adult group, it revealed the optimal cut-off value to detect a positive aeroallergen result was 73.8 IU/mL, with a sensitivity rate of 77.1% and specificity rate of 78.6% (area under curve, AUC = 0.87, $p < 0.001$) (Fig. 1a). In the pediatric group, the ROC curve for total IgE level revealed the optimal cut-off value to detect a positive aeroallergen result was 122.0 IU/mL, with a sensitivity rate of 79.1% and specificity rate of 87.0% (AUC = 0.85, $p < 0.001$) (Fig. 1b).

According to the statistical results, we found that even when we applied the adjusted total IgE level obtained from the ROC curve (73.8 IU/mL and 122.0 IU/mL for the adult and pediatric groups, respectively), the sensitivity and specificity rates to screen for AR were not as satisfying as the Phadiatop test. In the adult group, sensitivity rates were 95.5% versus 77.1%, and specificity rates were 90.8% and 78.6% for the Phadiatop test and the adjusted total IgE level. In the pediatric group, sensitivity rates were 99.3% and 79.1%, and the specificity rates were 100% versus 87.0% for the Phadiatop test and the adjusted total IgE level.

Discussion

The estimated prevalence of AR is 20–30% for adults and up to 40% for children in both the United States and Europe.¹ The serum total IgE level plays an important role in assessing patients with suspected allergic disease for many years. However, there is still a lack of adequate sensitivity reported to date. In our study, we presented the largest number of patients in the English literature to date. It is the first study about allergy screening aimed at patients presenting with persistent rhinitis regardless of age. The role of serum total IgE or Phadiatop as a first-line screening and diagnosis for allergy has been discussed.

A panel of ImmunoCAP tests, which includes six common perennial aeroallergens for confirmation of AR, was applied in this study. All of our patients presented with typical symptoms of AR more than four

weeks before undergoing blood tests, and they were enrolled continuously without seasonal differences. Thus, ImmunoCAP panels that include food or other seasonal pollens were not applied in this study.

Pierotti et al. reported that the Phadiatop test had a sensitivity of 96% and a specificity of 92% in inhalant allergy from 220 tested samples.²¹ To the best of our knowledge, no recent large-scale study reported the usefulness of total IgE and Phadiatop test in the same patient group. During clinical practice, we may apply either serum total IgE levels or the Phadiatop test as a first-line screening for allergy. The cost for the serum exams is around three US dollars for each. However, the Phadiatop test presented better sensitivity and specificity than the total IgE level in detecting a positive aeroallergy. Furthermore, the dual exam, including total IgE level and the Phadiatop test, did not show a better sensitivity, specificity, PPV, and NPV than the Phadiatop test alone for aeroallergen screening in both the adult and pediatric groups. Thus, we may conclude that the Phadiatop test would be more efficient and cost-effective as a first-line allergy screening for those suspected of having atopic airway diseases.

In our study, patients with negative Phadiatop tests had the highest prevalence of allergies to cockroach, compared to other groups. The reason for this result may be that the content of the Phadiatop test has aeroallergens of dust mites, cat dander, dog dander, and tree pollen, but not cockroaches.

Limitations of our study include its retrospective design and the lack of design of the control group. In addition, the study population came from a single institution, a tertiary referral center in Northern Taiwan, with possible selection bias about disease severity and territoriality. Finally, we have no healthy control group in our study as a comparison. Future studies may set up more detailed parameters such as the tendency for allergic seasons, the associated comorbidities for more accurate analysis, and enrollment cases for normal control. Nevertheless, many patients among the various age groups in the present study shed light on the value of serum total IgE level and the Phadiatop test as first-line screening tools for positive aeroallergens.

Conclusions

In conclusion, we suggest that the Phadiatop test is more cost-effective in aeroallergen screening for patients suspected of atopic airway diseases. It had a better diagnostic power for aeroallergen detection than the serum total IgE level, or even the dual test, for both the adult and pediatric groups in this hospital-based study. This study may provide physicians with a reference for future clinical applications.

List Of Abbreviations

IgE, immunoglobulin E

AR, allergic rhinitis

Declarations

Ethics approval and consent to participate: This study was approved by the Institutional Review Board (201902084B0, 201802254B0) of Chang Gung Memorial Hospital.

Consent for publication: The authors confirmed that this manuscript is original and it, or any part of it, has not been previously published; nor is it under consideration for publication elsewhere.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare no competing interests.

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Author's contributions

YCC: discussed the design of the manuscript, screening of systematic search, reading of included articles, data extraction, tables, discussed the design of the manuscript, reviewed the manuscript. TJL: screening of systematic search, reading of included articles, reviewed the manuscript. CCH: reviewed the manuscript. PHC: reviewed the manuscript. YWC: reviewed the manuscript. CHF: discussed the design of the manuscript, reviewed and edited the article, reading of included articles, figures, tables. All authors provided critical review, read and approved the final manuscript.

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Figures

Figure 1

The receiver operating characteristic (ROC) curve analysis for optimal cutoff value of serum total IgE level in a) the adult group, with AUC = 0.85, $p < 0.001$, cutoff value = 73.8, and b) the pediatric group, with AUC = 0.87, $p < 0.001$, cutoff value = 122.0. AUC, area under the curve.

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The receiver operating characteristic (ROC) curve analysis for optimal cutoff value of serum total IgE level in a) the adult group, with AUC = 0.85, $p < 0.001$, cutoff value = 73.8, and b) the pediatric group, with AUC = 0.87, $p < 0.001$, cutoff value = 122.0. AUC, area under the curve.