

The Role of Phadiatop Tests and Total Immunoglobulin E Levels in Screening Aeroallergens: A Hospital-Based Cohort Study

This article was published in the following Dove Press journal:
Journal of Asthma and Allergy

Yun-Chen Chang¹
Ta-Jen Lee¹
Chi-Che Huang^{1,2}
Po-Hung Chang^{1,2}
Yi-Wei Chen¹
Chia-Hsiang Fu^{1,2}

¹Department of Otolaryngology-Head and Neck Surgery, Linkou Chang Gung Memorial Hospital, Taoyuan City, 333, Taiwan; ²Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung University, Taoyuan City, 333, Taiwan

Background: Screening for the existence of aeroallergens in patients with possible allergic rhinitis using venous blood samples has become more popular, with advantages of increased convenience and less consumption of time.

Objective: The aim of this study was to investigate the sensitivities and specificities of Phadiatop tests and total immunoglobulin E (IgE) levels in both adults and children.

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 that suggested persistent allergic rhinitis were recruited and their serum samples collected. The results of the total IgE and Phadiatop tests as well as the positive items in the ImmunoCAP assay were recorded and analyzed.

Results: A total of 9174 cases with complete data were enrolled, including 576 children and 8598 adults. A positive result in the ImmunoCAP assay was considered a positive atopic status towards aeroallergens. While using the total IgE levels to predict positive aeroallergens, the sensitivities and specificities were 65.7% and 85.7%, respectively, for adults and 86.3% and 77.4%, respectively, for children. When we used Phadiatop tests for allergy screening, the sensitivities and specificities was 94.5% and 98.2%, respectively, for the adult group and 98.5% and 96.8%, respectively, for the pediatric group.

Conclusion: The Phadiatop test had better diagnostic power for aeroallergen detection than the serum total IgE levels, 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 with suspected atopic airway diseases.

Keywords: Phadiatop test, ImmunoCAP, total immunoglobulin E, IgE, aeroallergens

Introduction

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 countries,² 27% in Korea,³ 18.8% in Malaysia⁴ and up to 50.1% 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

Correspondence: Chia-Hsiang Fu
Division of Rhinology, Department of Otolaryngology-Head and Neck Surgery, Linkou Chang Gung Memorial Hospital and Chang Gung University, No. 5 Fu-Shin Street, Guishan District, Taoyuan City, 333, Taiwan
Tel +886-3-3281200, ext.: 8465
Fax +886-3-3979361
Email fufamily@adm.cgmh.org.tw

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 Beside the socioeconomic burdens, AR in the pediatric groups is also 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 to exposure to sensitizing allergens and physical examinations.¹ However, the results can be ambiguous due to the arbitrary nature of the identification. Laboratory tests for levels of the allergen-specific immunoglobulin E (IgE) in the serum or by positive epicutaneous skin tests are based on the evidence of sensitization to common allergens can be helpful.¹ However, skin tests take too long, and patients have to undergo the risks of anaphylactic shock and other complications. The confirmation of an allergy using a single venous blood puncture has the advantages of greater convenience and reduced time requirements. This technique is currently, thus, popular.

Total IgE and Phadiatop (ThermoFisher Scientific, Uppsala, Sweden) are two cost-effective, efficient, and convenient serum tests that can be used as first-line screening tools for atopic status. 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 testing for a specific IgE can only be performed if the total serum IgE level was more than 100 IU/mL. However, Tu et al have shown that use of the total serum IgE levels alone did not provide sufficient diagnostic accuracy in the detection of allergic diseases in the pediatric population in Taiwan.¹⁶ To the best of our knowledge, to date, there has been no recent large-scale sensitivity studies on this issue in the Asian population. Therefore, this study aimed to investigate the sensitivity and specificity of the total IgE and Phadiatop tests as predictors for hypersensitivities to aeroallergens in adult and child cohorts.

Methods

This study was approved by the Institutional Review Board (201902084B0, 201802254B0) of the Chang Gung Memorial Hospital. 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. Patients and the parents or legal guardians of patients under 18 years of age provided informed consent. This study was conducted in accordance with the Declaration of Helsinki. 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 tested 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 that a positive result for the detection of aeroallergen detection was a confirmation of AR. The Phadiatop test consisted of a solid-phase immunoassay for serum-specific IgEs, using a balanced mixture of the allergens that cause common inhalant allergies, coupled to the ImmunoCAP.¹⁷ The calculations of the results were performed automatically, according to the fluorescence responses. The results obtained for patient samples were then compared to the reference serum. In this study, according to previous studies, a positive value for the serum total IgE level was defined as being more than 100 IU/mL and 77 IU/mL in the adult and the pediatric groups, respectively.^{18–20}

All statistical analyses were performed using MedCalc software version 19.3 (MedCalc Software bv, Ostend, Belgium). Clinical outcomes, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), were calculated using diagnostic test evaluations. Receiver operating characteristic (ROC) curve tests were used to calculate best cutoff values of total IgE level for each group.

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). Of the 25 children with total IgE levels >77 IU/mL and negative Phadiatop tests, none (0%) presented with positive results for aeroallergens, as verified by ImmunoCAP assay. Meanwhile, of the 56 children with total IgE levels

Table 1 The Percentage of Subjects with a Positive ImmunoCAP Test in Each Subgroup of Adult and Pediatric Patients

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

Abbreviations: tlgE, total immunoglobulin E; CAP, ImmunoCAP test.

<77 IU/mL and positive Phadiatop tests, 55 (98.2%) presented positive results for aeroallergens, 1 (1.8%) presented negative result for aeroallergens. There were 393 children with total IgE levels >77 IU/mL and positive Phadiatop tests, 390 (99.2%) presented with positive aeroallergen results, and 3 (0.8%) presented with negative aeroallergen results. Meanwhile, of the 102 children with total IgE levels <77 IU/mL and negative Phadiatop tests, only 7 (6.9%) were positive in the ImmunoCAP assay results (Table 1).

Of the adult subjects, there were 568 patients with total IgE levels >100 IU/mL and negative Phadiatop tests, and 102 (18.0%) presented with positive aeroallergens tests (Table 1). Furthermore, 1597 adults had total IgE levels <100 IU/mL and positive Phadiatop tests, and 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 confirmed positive aeroallergen results. 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 results.

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) who 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 sensitivities and specificities of the total IgE and Phadiatop tests to identify allergies. At least one positive result for the aeroallergen tests in the ImmunoCAP assay was defined as confirmation of the inhalant allergy. When only the total IgE levels were taken into consideration to detect allergies, the sensitivity rates were 65.7% and 86.3% and specificity rates 85.7% and 77.4% for the adult and pediatric groups, respectively. Alternatively, when we used the Phadiatop tests, the sensitivity rates were 94.5% and 98.5% and specificity rates were 98.2% and 96.8% for the adult and pediatric groups, respectively. While the total IgE levels and the Phadiatop tests were both taken into account to confirm allergy statuses, the sensitivity rates were 96.5% and 98.5%, and specificity rates were 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 Adult and Pediatric Groups

		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

Abbreviation: IgE, immunoglobulin E.

Table 3 The Positive and Negative Predictive Value of Each Blood Test to Detect Positive Aeroallergens in Adult and Pediatric Groups

		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

Abbreviations: IgE, immunoglobulin E; PPV, positive predictive value; NPV, negative predictive value.

Analysis of Positive and Negative Prediction Values

According to our study, when we used only the total IgE level to screen for allergic status, the PPV was 87.0% for the adult group and 93.3% for the pediatric group. In comparison, the NPV was 63.2% and 60.8%, for the adult and pediatric groups, respectively. When we used only the Phadiatop test instead, the PPV was 98.7% for the adult group and 99.1% for the pediatric group, while the NPV was 92.5% and 94.5%, for the adult and pediatric groups, respectively. When we used both tests for allergy screening, we found that PPV was 90.3% for the adult group and 93.9% for the children's group, while the NPV was 96.5% and 93.1%, for the adult and pediatric groups respectively (Table 3).

Furthermore, through the 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 showed that 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, $P < 0.001$) (Figure 1A). In the pediatric group, the ROC curve for total IgE level showed that 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, $P < 0.001$) (Figure 1B).

From statistical results, we found that even when we used 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 satisfactory as those for the Phadiatop test. In the adult group, sensitivity rates were 95.5% and 77.1% and specificity rates were 90.8% and 78.6% for the Phadiatop test and the adjusted total IgE level, respectively. In the pediatric group, sensitivity rates were 99.3% and 79.1% and the specificity rates were 100% and 87.0% for the Phadiatop test and the adjusted total IgE level, respectively.

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

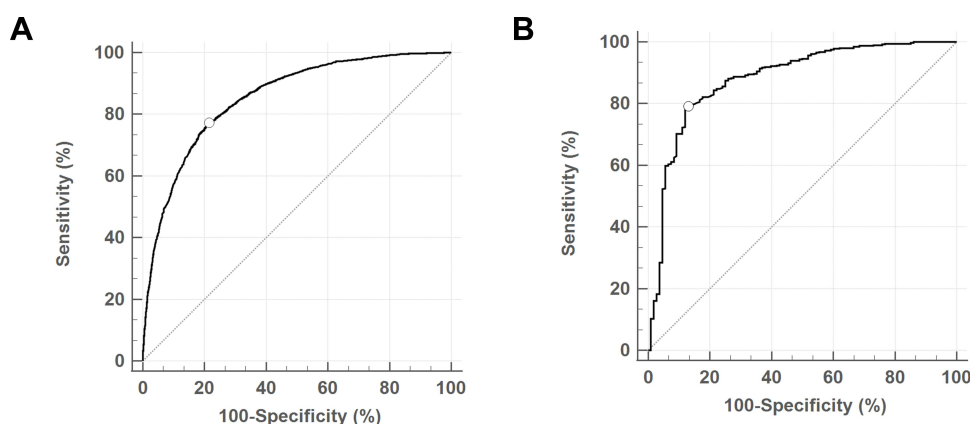


Figure 1 The ROC curve analysis for optimal cutoff value of serum total IgE level in (A) the adult group, with AUC = 0.85, $p < 0.001$, cutoff value = 73.8, and (B) the pediatric group, with AUC = 0.87, $p < 0.001$, cutoff value = 122.0.

Abbreviations: AUC, area under the curve; ROC, receiver operating characteristic; IgE, immunoglobulin E.

The serum total IgE level has played 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 analysed the data of the largest number of patients, to date. It was the first study on allergy screening aimed at patients presenting with persistent rhinitis regardless of age. Then, the roles of serum total IgE or Phadiatop as first-line tools for the screening and diagnoses of allergies were determined.

A panel of ImmunoCAP tests, which includes six common perennial aeroallergens for confirmation of AR, was used in this study. All of our patients presented with typical symptoms of AR for more than four weeks before undergoing the blood tests, and they were enrolled continuously, without seasonal differences. Thus, the ImmunoCAP panels that included food or other seasonal pollens were not used in this study.

Pierotti et al reported that the Phadiatop test had a sensitivity of 96% and a specificity of 92% for inhalant allergens from 220 tested samples.²¹ To the best of our knowledge, no recent large-scale study has reported the usefulness of total IgE and Phadiatop test in the same patient group. During clinical practice, we can use either serum total IgE levels or the Phadiatop test as a first-line screening for allergy. However, the Phadiatop test presented better sensitivity and specificity than the total IgE level in detecting a positive aeroallergy. The cost for the serum analysis is currently approximately three US dollars for each test. Furthermore, a dual analysis using both the total IgE level and the Phadiatop test did not show better sensitivity, specificity, PPV, and NPV than the Phadiatop test alone for aeroallergen screening in both the adult and pediatric groups. Thus, we can conclude that the Phadiatop test would be more efficient and cost-effective as a first-line allergy screening tool 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 included aeroallergens of dust mites, cat dander, dog dander, and tree pollen, but not cockroaches.

Our study limitations included its retrospective design and the lack of inclusion of a control group. In addition, the study population came from a single institution, a tertiary referral center in Northern Taiwan, with possible selection bias for disease severity and territoriality. It is recommended that future studies include more detailed

parameters such as seasonal allergies and associated comorbidities, as well as the inclusion of control groups with a prospective design. Nevertheless, the large number of patients in this study and the inclusion of subjects with different ages have shed light on the value of serum total IgE levels and Phadiatop tests as first-line screening tools for positive aeroallergens.

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 dual testing, in both the adult and pediatric groups in this hospital-based study. This study provides physicians with a reference for future clinical applications.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Wheatley LM, Togias A. Clinical practice. Allergic rhinitis. *N Engl J Med*. 2015;372:456–463. doi:10.1056/NEJMcpr1412282
2. Chong SN, Chew FT. Epidemiology of allergic rhinitis and associated risk factors in Asia. *World Allergy Organ J*. 2018;11:17. doi:10.1186/s40413-018-0198-z
3. An SY, Choi HG, Kim SW, et al. Analysis of various risk factors predisposing subjects to allergic rhinitis. *Asian Pac J Allergy Immunol*. 2015;33:143–151. doi:10.12932/AP0554.33.2.2015
4. Norback D, Hashim JH, Markowicz P, et al. Endotoxin, ergosterol, muramic acid and fungal DNA in dust from schools in Johor Bahru, Malaysia—Associations with rhinitis and sick building syndrome (SBS) in junior high school students. *Sci Total Environ*. 2016;545–546:95–103. doi:10.1016/j.scitotenv.2015.12.072
5. Hsu SP, Lin KN, Tan CT, Lee FP, Huang HM. Prenatal risk factors and occurrence of allergic rhinitis among elementary school children in an urban city. *Int J Pediatr Otorhinolaryngol*. 2009;73:807–810. doi:10.1016/j.ijporl.2009.02.023
6. Meltzer EO, Blaiss MS, Derebery MJ, et al. Burden of allergic rhinitis: results from the Pediatric Allergies in America survey. *J Allergy Clin Immunol*. 2009;124:S43–70. doi:10.1016/j.jaci.2009.05.013
7. Kulthanan K, Chusakul S, Recto MT, et al. Economic burden of the inadequate management of allergic rhinitis and urticaria in asian countries based on the GA (2) LEN Model. *Allergy Asthma Immunol Res*. 2018;10:370–378. doi:10.4168/aaair.2018.10.4.370
8. Sardana N, Craig TJ. Congestion and sleep impairment in allergic rhinitis. *Asian Pac J Allergy Immunol*. 2011;29:297–306.
9. Bousquet J, Khaltav N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA (2) LEN and AllerGen). *Allergy*. 2008;63(Suppl 86):8–160.
10. Camelo-Nunes IC, Sole D. Allergic rhinitis: indicators of quality of life. *J Bras Pneumol*. 2010;36:124–133. doi:10.1590/S1806-37132010000100017
11. Walker S, Khan-Wasti S, Fletcher M, Cullinan P, Harris J, Sheikh A. Seasonal allergic rhinitis is associated with a detrimental effect on examination performance in United Kingdom teenagers: case-control study. *J Allergy Clin Immunol*. 2007;120:381–387. doi:10.1016/j.jaci.2007.03.034

12. Coste A. ENT diseases associated with allergic rhinitis: a review of the literature. *Ann Otolaryngol Chir Cervicofac.* **2000**;117:168–173.
13. Jansen DF, Rijcken B, Schouten JP, et al. The relationship of skin test positivity, high serum total IgE levels, and peripheral blood eosinophilia to symptomatic and asymptomatic airway hyperresponsiveness. *Am J Respir Crit Care Med.* **1999**;159:924–931. doi:10.1164/ajrccm.159.3.9804024
14. Kim EJ, Kwon JW, Lim YM, et al. Assessment of total/specific IgE levels against 7 inhalant allergens in children aged 3 to 6 Years in Seoul, Korea. *Allergy Asthma Immunol Res.* **2013**;5:162–169. doi:10.4168/aa.2013.5.3.162
15. Johansson SG, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: report of the nomenclature review committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol.* **2004**;113:832–836. doi:10.1016/j.jaci.2003.12.591
16. Tu YL, Chang SW, Tsai HJ, et al. Total serum IgE in a population-based study of Asian children in Taiwan: reference value and significance in the diagnosis of allergy. *PLoS One.* **2013**;8:e80996. doi:10.1371/journal.pone.0080996
17. Zeng G, Hu H, Zheng P, et al. The practical benefit of Phadiatop test as the first-line in vitro allergen-specific immunoglobulin E (sIgE) screening of aeroallergens among Chinese asthmatics: a validation study. *Ann Transl Med.* **2018**;6:151. doi:10.21037/atm.2018.04.06
18. Ringel KP, Dati F, Buchholz E. IgE-Normalwerte bei Kindern. *Laboratoriums Blätter.* **1982**;32:26–34.
19. Dati F, Ringel KP. Reference values for serum IgE in healthy non-atopic children and adults. *Clinical Chemistry.* **1982**;28:1556.
20. Horowitz GL, Altaie S, Boyd JC, et al. *Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory.* 3rd. Vol. 28. Clinical and laboratory standards institute; **1982**:30.
21. Pierotti FF, Aranda CS, Cocco RR, et al. Phadiatop, Phadiatop Infant and total IgE evaluated in allergic Brazilian children and adolescents. *Allergol Immunopathol.* **2019**;48:259–264. doi:10.1016/j.aller.2019.06.013

Journal of Asthma and Allergy

Dovepress

Publish your work in this journal

The Journal of Asthma and Allergy is an international, peer-reviewed open-access journal publishing original research, reports, editorials and commentaries on the following topics: Asthma; Pulmonary physiology; Asthma related clinical health; Clinical immunology and the immunological basis of disease; Pharmacological interventions and

new therapies. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/journal-of-asthma-and-allergy-journal>