Accesed on: http://jkb.ub.ac.id/index.php/jkb/article/view/2727
Jurnal Kedokteran Brawijaya Vol. 31, No. 2, Agustus 2020, pp. 116-120
Article History: Received 27 Maret 2020, Accepted 16 Juli 2020

Research Article

Three Characterisctics of Atopy to Diagnose Allergy in Children with Respiratory Symptomps

Tiga Karakteristik Atopi untuk Mendiagnosis Alergi pada Anak dengan Gejala Saluran Pernapasan

Imanuel Far-Far[1], Anang Endaryanto[1], Retno Asih S[1], Gatot Soegiarto[2]

[1]Department of Pediatrics Faculty of Medicine Universitas Airlangga Surabaya

[2]Department of Internal Medicine Faculty of Medicine Universitas Airlangga Surabaya

ABSTRACT

The prevalence of allergic diseases has increased in the last decade. Therefore, precise and reliable in predicting allergy in children were needed. However, in daily practice, most misdiagnosis occurs because it is only based on a family history of allergy. This study aims to evaluate the chronicity, recurrence of symptoms with similar exposure, and family history of allergy to be used as a predictor of allergy in children with respiratory symptoms. Cross sectional study was conducted in children who referred to the Pediatric Allergy and Immunology Outpatient Clinic, Dr. Soetomo General Hospital, Surabaya from January 1st - July 31st 2019. Children with a suspected allergy who developed respiratory symptoms was included. The data was taken from standardized medical record. The sensitivity and specificity of the 3 characteristics of atopic with positive SPT were calculated. A total of 115 children were admitted and 109 children fulfill the inclusion criteria. Gender 60% male and 40% female. The most common group of age founded was age 5-<10 years 39.4%, followed by 1-<3 years (25.8%), 3-<5 years (22.9%), 10 years 8.3%, and <1 year (3.6%). Fifty-four patients (49.5%) fulfilled 3 characteristics of atopy and there were 64 patients (58.7%) with positive SPT results. The sensitivity, specificity, positive predictive value and negative predictive value were 81.3%, 95.6%, 96.3%, and 78.2%, respectively. The 3 characteristics of atopy have good sensitivity and specificity to predict allergy in children.

Keywords: *Allergy, atopy, respiratory symptoms, skin prick test*

ABSTRAK

Prevalensi penyakit alergi semakin meningkat dalam dekade terakhir sehingga diperlukan suatu metode yang cepat, tepat dan dapat dipercaya dalam prediktor risiko alergi seorang anak. Akan tetapi, dalam praktek sering penegakan diagnosis alergi tidak tepat sasaran karena pemeriksaan tes alergi hanya didasarkan pada riwayat alergi keluarga. Tujuan dari penelitian ini untuk mengevaluasi kronisitas dan keberulangan gejala dengan paparan yang sama dan riwayat alergi keluarga dapat digunakan sebagai prediktor risiko alergi pada anak yang mengalami gejala saluran pernapasan. Penelitian Cross sectional dengan sampel pasien anak suspek alergi yang mengalami gejala saluran pernapasan yang dikonsultasikan ke Poli Alergi Anak RSUD Dr. Soetomo Surabaya periode 1 Januari – 31 Juli 2019. Data diambil dari dokumen medis RSUD Dr. Soetomo yang sudah distandarisasi. Penelitian ini menganalisis kesesuaian 3 karakteristik atopi dengan skin prick test (SPT) menggunakan uji Mc Nemar dan Kappa. Dihitung sensitivitas dan spesifisitas 3 karakteristik atopi terhadap SPT positif. Jumlah sampel 115 anak, 109 anak memenuhi kriteria inklusi. Jenis kelamin laki-laki 60% dan perempuan 40%, distribusi usia <1 tahun 3,6%, usia 1-<3 tahun 25,8%, usia 3-<5 tahun 22,9%, usia 5-<10 tahun 39,4% dan >10 tahun 8,3%. Terdapat 54 pasien (49,5%) yang memenuhi 3 karakteristik atopi dan 64 pasien (58,7%) dengan hasil SPT positif. Sensitivitas, spesifisitas, nilai prediksi positif dan nilai prediksi negatif berturut-turut adalah sebesar 81,3%, 95,6%, 96,3% dan 78,2%. Tiga karakteristik atopi memenuhi sensitivitas dan spesifisitas yang baik untuk memprediksi alergi seorang anak.

Kata Kunci: Alergi, atopi, *skin prick test,* gejala saluran pernapasan

Correspondence: Imanuel Far-Far. Department of Pediatrics Faculty of Medicine Universitas Airlangga Surabaya, Jl. Mayjen Prof. Dr. Moestopo No.47, Surabaya, East Java Tel. 081343479040 Email: imanuelfarfar@gmail.com

DOI: http://dx.doi.org/10.21776/ub.jkb.2020.031.02.9

INTRODUCTION

Allergic diseases prevalence has increased and varies based on the population study in the last decade (1,2). Previous study regarding the predictors of uncontrolled respiratory symptoms in children, one of which was caused by any atopic comorbidities (1). Moreover, according to Pacific Partnership 2015, the top two pediatric diagnosis belongs to 25% of respiratory disorders (2). A study in German included MAS birth cohort declare family history with allergies is not only a strong predictor to develop allergy, but also increases the risk of developing allergy multimorbidity (3). A fast, precise and reliable diagnostic method to confirm the diagnosis must be performed. However, in daily practice, there are a lot of misdiagnosis case occurs, because it is only based on a family history of allergy. This could be prevented if there is a high quality, high sensitivity and specificity, and simple methods that can be used by physicians to confirm skin tests quickly and accurately. There are 3 symptoms about someone tendency to have allergy, i.e. chronicity of symptoms, recurrence of symptoms with similar exposure and family history of allergy (4). This study aims to evaluate the chronicity, recurrence of symptoms with similar exposure, and family history of allergy as a predictor of allergy in children with respiratory symptoms.

METHOD

A cross-sectional study study was conducted based on the medical history of patients who referred to the Pediatric Allergy and Immunology Outpatient Clinic, Dr. Soetomo General Hospital, Surabaya from January 1st until July 31st, 2019. There were 109 patients with allergy suspected throughout the period. The inclusion criteria were patients aged 0-18 years old, had respiratory symptoms, and underwent a Skin Prick Test (SPT) in Pediatric Allergy and Immunology Outpatient Clinic during the period. Data were collected by consecutive sampling. We used three questionnaires, to predict allergy in children with respiratory symptoms (sneezing, runny nose, cough, wheezing and shortness of breath). Those three questionnaires were used to measure the chronicity of respiratory symptoms occurring more than 2 weeks, recurrence of respiratory symptoms with similar exposure (host dust mite, pet dander or food allergen)) and family history (father, mother and/or siblings) of allergy. These questionnaires have been validated and used by Dr. Soetomo General Hospital in Surabaya, Indonesia (Supplemental files) (5).

The patient's age, sex, and allergy symptoms were also collected from medical records. Skin prick test results were performed with sterile lancets and commercial allergens extract in the volar area the forearm, on columns which had been drawn. Nine allergens were tested, including HDM, cat, fruit, seafood, saltwater fish, cow's milk, chocolate, chicken, and egg. Control specimen used was normal saline (negative) and histamine (positive). Reactions were observed after 20 minutes. The wheal-and-flare reactions were measured with a ruler in millimeters (1mm=0.001m). The vertical and horizontal diameters of the wheal-and-flare were added and divided by 2, resulting in mean diameter, which was recorded. Skin prick test results were considered to be positive if the diameter was >3 mm than the negative control. The diagnose of allergy was established by Pediatric Allergy and Immunology consultant.

Data Analysis

The distribution pattern was shown in a descriptive table. The data analysis performed by using Microsoft Excel and IBM SPSS Statistic Ver. 21. The compatibility between the 3 characteristics of atopy with SPT was analyzed using McNemar test and Kappa test. The Mc Nemar test is a test for comparison. A p value <0.05 was considered statistically significant. The Kappa test is a compatibility test, if p <0.05, the compatibility is obtained. It is valid if there is a kappa association with p <0.05 and there is no difference between Mc Nemar with p ≥0.05. This study was approved by the Ethical Committee of Dr. Soetomo General Hospital, Surabaya No. 1145/KEPK/IV/2019.

RESULTS

A total of 109 children were enrolled in this study. The characteristics of respondents are presented in Table 1. They were consisted of 65 (60%) males and 44 (40%) females. The majority of respondents were aged 5 to 10 years (43 subjects, 39.4%).

Table 1. Characteristic of respondents

Characteristics	n (%)
Gender, n (%)	
Male	65 (60)
Female	44 (40)
Age, n (%)	
< 1 year	4 (3.6)
1 - <3 years	28 (28.8)
3 - <5 years	25 (22.9)
5 - <10 years	43 (40)
>10 years	9 (7.7)
Allergens with positive skin prick test, n*	
HDM	52
Pet	19
Food	57
Chronicity of symptoms, n (%)	
Yes	77 (70.6)
No	32 (29.4)
Recurrence of symptoms with similar exposure, n (%)	
Yes	79 (72.5)
No	30 (27.5)
Family history of allergy, n (%)	
Yes	85 (78)
No	24 (22)
Fulfill 3 characteristics of atopy, n (%) **	
Yes	54 (49.5)
No	55 (50.5)

Note:
*one child had more than 1 allergen
**Subjects that fulfill 3 characteristics of atopy are subjects who have chronicity and recurrence of symptoms with similar exposure and family history of allergy

From 109 respondents, 77 (70.6%) reported chronicity of respiratory symptoms. Of these 77 children, 64 (83.1%) had a positive skin prick test. A total of 32 children didn't show any sign of respiratory chronicity symptoms, and all of them had negative skin prick test. In total, there were 64 (58.7%) children who tested positive and 45 (41.3%) who tested negative (Table 2). The McNemar test revealed different between chronicity of symptom and skin prick test result (p=0.001), but Kappa coefficient revealed a

strong degree of agreement (0.743) and statistically significance (p=0.001).

Table 2. Conformity between chronicity of symptom and skin prick test results

Chronicity of symptom	Total, n (%)	Skin prick test result		McNemar	Kappa test	
		Positive	Negative	P value*	Kappa coefficient	P value*
Yes	77 (70.6)	64	13	0.001	0.743	0.001
No	32 (29.4)	0	32			
Total, n (%)	109 (100)	64 (58.7)	45 (41.3)			

Note: Sensitivity = 100%; Specificity = 71.11%; Positive predictive value = 83.12%; Negative predictive value = 100%; Accuracy = 88.07%; *a p value <0.05 was statistically significant

Seventy-nine (72.5%) children had recurrence symptoms with similar exposure. Of these 79 children, 64 (81%) tested were positive. In addition, of the 30 subjects didn't show any sign of respiratory chronicity symptoms with similar exposure, and all of them had a negative skin prick test. In total, 64 (58.7%) children tested positive, while 45 (41.3%) tested negative (Table 3). The McNemar test revealed different between recurrence of symptoms with similar exposure and skin prick test results (p=0.001), but Kappa coefficient showed a strong degree of agreement (0.701) and statistical significance (p=0.001).

Table 3. Conformity between recurrence of symptoms with similar exposure and skin prick test results

Recurrence of symptoms with similar exposure	Total, n (%)	Skin prick test result		McNemar	Kappa test	
		Positive	Negative	P value*	Kappa coefficient	P value*
Yes	79 (72.5)	64	15	0.001	0.701	0.001
No	30 (27.5)	0	30			
Total, n (%)	109 (100)	64 (58.7)	45 (41.3)			

Note: Sensitivity = 100%; Specificity = 66.67%; Positive predictive value = 81%; Negative predictive value = 100%; Accuracy = 86.24%; *a p value < 0.05 was statistically significant

Eighty-five (78%) respondents had family history of allergy. Of these 85 children, 52 (61.2%) had a positive skin prick test. Twenty-four children who were reported not have family history of allergy, 12 (50%) tested positive. In total, 64 (58.7%) respondents tested positive and 45 (41.3%) tested negative (Table 4). The McNemar test revealed different family history of allergy and skin prick test results (p=0.002), but Kappa coefficient revealed a very low degree of agreement (0.085) and no statistical significance (p=0.326).

Table 4. Conformity between family history of allergy and skin prick test results

Family history of allergy	Total, n (%)	Skin prick test result		McNemar	Kappa test	
		Positive	Negative	P value*	Kappa coefficient	P value*
Yes	85 (78)	52	33	0.002	0.085	0.326
No	24 (22)	12	12			
Total, n (%)	109 (100)	64 (58.7)	45 (41.3)			

Note: Sensitivity = 81.25%; Specificity = 26.67%; Positive predictive value = 61.18%; Negative predictive value = 50%; Accuracy = 58.72%; *a p value < 0.05 was statistically significant

The children who fulfill all three characteristics of atopy are indicated to have the chronicity, recurrence symptoms with similar exposure and family history of allergy. Fifty-four (49.5%) subjects had three characteristics of atopy. Of these 54 children, 52 (96.3%) had positive skin prick test. Of the 55 subjects who were not reported the characteristic of atopy, 12 (21.8%) tested were positive. In total, 64 (58.7%) subjects tested positive and 45 (41.3%) tested negative (Table 5). The McNemar test showed different three characteristics of atopy and skin prick test results (p=0.013), but Kappa coefficient revealed a strong degree of agreement (0.744) and statistical significance (p=0.001).

Table 5. Conformity between 3 characteristics of atopy and skin prick test results

Three characteristics of atopy	Total, n (%)	Skin prick test result		McNemar	Kappa test	
		Positive	Negative	P value*	Kappa coefficient	P value*
Yes	54 (49.5)	52	2	0.013	0.744	0.001
No	55 (50.5)	12	43			
Total, n (%)	109 (100)	64 (58.7)	45 (41.3)			

Note: Sensitivity = 81.25%; Specificity = 95.56%; Positive predictive value = 96.30%; Negative predictive value = 78.18%; Accuracy = 87.16%; *a p value < 0.05 was statistically significant

DISCUSSION

According to a multicenter study in China, the prevalence of childhood allergic disease was common in male than female, with ratio 1.1-1.5:1 (6). The result of our study was accordance with the theory above that the largest group of age founded between 5 to 10 years old and male and male was more common than female (1.48:1). Similar to previous report recorded by Ebert and Pillsbury in 2011 (7), boys also tend to have asthma or another atopic disease more than girls, with ratio 1.8:1.

However, parents tend to incorrectly deduce the probable causing allergy manifestation with food allergy. There are several components to make a specific allergy diagnosis. First, a subject must be had a corresponding symptom to an allergic disease. Second, physician must be had enough knowledge about allergic disorders and specific allergy tests. Third, a quality allergy testing instruments, and finally, a physician must be capable for interpreting the test results in patient with minimal symptoms (8).

There were 13 subjects with chronicity of respiratory symptoms with negative SPT results. Negative SPT results might be happen due to chronicity of respiratory symptoms not only due to allergies but also other causes such as tuberculosis infection, rhinosinusitis infection, laryngotrakeobroncomalasia, pertussis, atypical pneumonia and GERD (9). In our study, the chronicity symptoms obtained high sensitivity and low specificity. So if there is no chronicity of symptoms, it means that the SPT is likely to get negative results. However, if there is a chronicity symptoms, the SPT will not necessarily get a positive result. Statistically, the McNemar test showed different results between chronicity symptoms and SPT results, but the Kappa coefficient revealed a strong degree of agreement and statistical significance. This means that chronicity symptoms alone is not strong enough to diagnose allergy that needs to be strengthened by other facts that support an allergy and must be continued with

SPT as a gold standard for allergy diagnostics.

Researches in several countries shows house-dust mites (HDM) are the most common cause of sensitization and bronchial asthma (10-13). Atopy is the major predisposing factor for asthma identified up to now, and allergen exposure, particularly indoor allergens, is considered as a causal factor for asthma. Food allergy is frequently underestimated in association with asthma however food allergy has been shown to trigger or exacerbate broncho-obstruction in 2 to 8.5% of children with asthma. There is also evidence that double-blind placebo-controlled oral challenge is able to increase unspecific bronchial hyper responsiveness. Sensitization to food can occur early in life involving T cell response, mainly of the Th2 phenotype, but also IgE-mediated hypersensitivity (14,15).

There were 15 subjects with recurrence of symptoms with similar exposure but negative SPT results. Negative SPT results may be caused by complaints of recurrent respiratory symptoms with similar exposure not only because of allergies but also other causes such as recurrent respiratory infections (16). In our study, the recurrence of symptoms with similar exposure obtained high sensitivity and low specificity. So if there are no recurrence of symptoms with similar exposure, it means that the SPT is most likely to get a negative result. However, if there are recurrence of symptoms with similar exposure, the SPT will not necessarily get positive results. Another study that assessed the recurrence of clinical symptoms of allergic rhinitis in predicting positive SPT allergic showed quite high sensitivity (86%) but low specificity (20%) (17). In this study, the McNemar test revealed different results between recurrence symptoms with similar exposure and SPT result, but Kappa coefficient revealed a strong degree of agreement and statistical significance. This means that recurrence symptoms with similar exposure alone were not strong enough to diagnose allergy, and need to be strengthened by other facts that support an allergy, also must be continued with the SPT as a gold standard for allergy diagnostics.

This study was inspired by many findings in daily practice to diagnose allergy only based on family history of allergy. Von Mutius and Nicolai's research shows the sensitivity and specificity of a family history of allergy to predicting allergy are 85% and 13.8% (18). Similarly, a study by Weninggalih, *et al.,* in 2007, the sensitivity and specificity of history family allergy in predicting allergy in children are 70% and 55.6% (19). In this study, the family history of allergy showed high sensitivity and low specificity. So if there is no family history of allergy means the SPT is most likely to get a negative results. But if there is a family history of allergy, the SPT will not necessarily get a positive result. Statistically, by the McNemar test revealed different family history of allergy and SPT results, but Kappa coefficient revealed a very low degree of agreement and no statistical significance. This means that a family history of allergy alone needs to be strengthened by other facts that support an allergy and must be continued with the SPT as a gold standard for allergy diagnostics.

In this study, the 3 facts about detecting the characteristic of atopy when examined separately do not provide maximum results as illustrated in table 2-4 so that simple quality methods (sensitive and specific) are needed so that practicing physicians can confirm skin tests quickly and accurately. In this study, three characteristics of atopy showed high sensitivity and high specificity. Therefore, if there are no three characteristics of atopy, the SPT is most likely to get a negative result and vice versa. Statistically, this study showed a different result between the three characteristics of atopy with SPT results, but on the other hand, Kappa coefficient revealed strong degree of agreement and statistical significance. This means that the 3 characteristics of atopy are a simple quality detection method (sensitive and specific) and must be followed by the SPT as a gold standard for allergy diagnostics.

There were only 2 children who showed three atopy characteristics with a negative SPT result. This result might be caused by a non-IgE mediated reaction, so it doesn't trigger wheal on the SPT. A Study of Zuidmeer showed certain fruits such as strawberries, oranges, and tomatoes that thought to directly stimulate mast cells to release histamine. Clinical symptoms of allergies with non-IgE mediated usually appear on mucocutaneous and gastrointestinal (19). The study also noted that there were 12 children whose SPT results were positive but did not meet 3 characteristics of atopy. Sensitization of the skin to allergens such as seafood allergens can be caused by cross-reactivity. However, skin sensitization to food allergens is not always the same as cross-reactivity. One allergen in seafood, tropomyosin, is also found in house dust (HDM) which is responsible for high sensitization (20).

This study has a high positive and negative predictive value of 96.3% and 78.18%. Similarly, a previous study found combination of several variables including clinical symptoms, triggering season, family history of allergy and treatment history in predicting positive skin test results showing a high PPV and NPV (84% and 74%) (4,21). The clinical benefit of using 3 characteristics of atopy which were reducing referral error for SPT, early identification, and management may provide opportunities to prevent the development of clinical symptom. Hence, a better allergy prevention programs will be reach since the natural course of allergic diseases can be suppressed. Finding of this study need to be carefully interpreted due to some limitation in this study as a result of retrospective in design and was recall bias in this study because data of 3 characteristics of atopy were obtained from the history taking.

Result of this study confirming that the chronicity, recurrence of symptoms with similar exposure, and family history of allergy can be used as strong predictors of allergy in children to improve the quality of early detection of allergy. Further studies with prospective methods and a larger number of subjects are needed to analyzed the chronicity and recurrence of symptoms with similar exposure and family history of allergy as a predictor of allergy in children with respiratory symptoms.

ACKNOWLEDGEMENT

We would like to thank the staffs of the Department of Pediatrics in Dr. Soetomo General Hospital/ Faculty of Medicine, Universitas Airlangga, Surabaya for their assistance in data collection. We also appreciate the help of Kinanti Ayu Ratnasari for editing this manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Kansen HM, Le TM, Uiterwaal CSPM, *et al. Prevalence and Predictors of Uncontrolled Asthma in Children Referred for Asthma and Other Atopic Diseases*. Journal of Asthma and Allergy. 2020; 13: 67–75.
2. Dorey HF, Dorey JM, Burman NJ, *et al*. *Observations of Pediatric Disease Prevalence from Pacific Partnership 2015.* Military Medicine. 2018; 183(1): 530–537.
3. Gough H, Grabenhenrich L, Reich A, *et al. Allergic Multimorbidity of Asthma, Rhinitis and Eczema Over 20 Years in the German Birth Cohort MAS.* Pediatric Allergy and Immunology. 2015; 26(5): 431–437.
4. Endaryanto A. *Implikasi Klinis Imunologi Alergi*. 1st edition. Surabaya: Airlangga University Press (AUP); 2015.
5. Far-Far I, Endaryanto A, and Setyoningrum RA. *Instrumen-Poli Alergi RSUD Dr. Soetomo.Docx. Figshare. Preprint*. (Online) 2020. https://doi.org/10.6084/m9.figshare.12022488.v1
6. Zhao J, Bai J, Shen K, *et al. Self-Reported Prevalence of Childhood Allergic Diseases in three Cities of China: A Multicenter Study.* BMC Public Health. 2010; 10(551): 1-7.
7. Ebert CS and Pillsbury HC. *Epidemiology of Allergy.* Otolaryngologic Clinics of North America. 2011; 44(3): 537–548.
8. Larenas-Linnemann D, Luna-Pech JA, and Mösges R. *Debates In Allergy Medicine: Allergy Skin Testing Cannot Be Replaced By Molecular Diagnosis In The Near Future*. The World Allergy Organization Journal. 2017; 10(1): 1–7.
9. Rahajoe N, Kartasasmita CB, Supriyatno B, and Setyanto DB. *Pedoman Nasional Asma Anak*. 2nd edition Volume 2. Surabaya: UKK Respirologi PP Ikatan Dokter Anak Indonesia; 2016: p. 5.
10. Platts-Mills TA, Thomas WR, Aalberse RC, Vervloet D, and Champman MD. *Dust Mite Allergens and Asthma: Report of a Second International Workshop.* The Journal of Allergy and Clinical Immunology. 1992; 89(5): 1046–1060.
11. Squillace SP, Sporik RB, Rakes G, *et al. Sensitization to Dust Mites as a Dominant Risk Factor for Asthma Among Adolescents Living in Central Virginia: Multiple Regression Analysis of a Population-Based Study*. American Journal of Respiratory and Critical Care Medicine. 1997; 156(6): 1760–1764.
12. Gøtzsche PC and Johansen HK. *House Dust Mite Control Measures for Asthma: Systematic Review*. Allergy. 2008; 63(6): 646–659.
13. Schei MA, Hessen JO, and Lund E. *House-Dust Mites and Mattresses.* Allergy. 2002; 57(6): 538–542.
14. Baena-Cagnani CE and Teijeiro A. *Role of Food Allergy in Asthma in Childhood.* Current Opinion in Allergy and Clinical Immunology. 2001; 1(2): 145–149.
15. Wistiani HN. *Hubungan Pajanan Alergen terhadap Kejadian Alergi pada Anak.* Sari Pediatri. 2011; 13(3): 185–190.
16. Kaswandani N, Mirtha L, Soegiharto B, *et al. Tata Laksana Anak dengan ISPA Berulang: Mencegah Terus Berulang.* In: Oswari H, Djer MM, Dewi R, and HArijadi (Eds). Kiat Membuat Anak Sehat, Tinggi, dan Cerdas. Jakarta: Ikatan Dokter Anak Indonesia Cabang DKI Jakarta; 2016: p. 71–78.
17. Mathur AK, Stern DA, Daines MO, Wright AL, Martinez FD, and Carr TF. *Sensitivity and Specificity of a Clinical Diagnosis of Allergic Rhinitis in Childhood.* Journal of Allergy and Clinical Immunology. 2016; 137(2): AB163.
18. Mutius E and Nicolai T. *Familial Aggregation of Asthma in a South Bavarian Population*. American Journal of Respiratory and Critical Care Medicine. 1996; 153(4 Pt1): 1266–1272.
19. Zuidmeer L, Goldhahn K, Rona RJ, *et al. The Prevalence of Plant Food Allergies: A Systematic Review*. The Journal of Allergy and Clinical Immunollogy. 2008; 121(5): 1210–1218.
20. Turner P, Ng I, Kemp A, and Campbell D. *Seafood Allergy in Children: A Descriptive Study*. Annals of Allergy, Asthma & Immunology. 2011; 106(6): 494–501.
21. Annesi-Maesano I, Didier A, Klossek M, Chanal I, Moreau D, and Bousquet J. *The Score for Allergic Rhinitis (SFAR): A Simple and Valid Assessment Method in Population Studies.* Allergy. 2002; 57(2): 107–114.