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Age-dependent distribution of the atopic phenotype and allergen sensitization among asthmatic children in southern Taiwan

Yu-Tsun Su,[1] Yung-Ning Yang,[2] Ying-Chun Li,[3] Ching-Chung Tsai,[2] Li-Min Chen,[2] Yung-Cheng Lin,[1] Chen-Kuang Niu,[4] Yu-Cheng Tsai[1]

Abstract

Background: Asthma is divided into atopic and non-atopic phenotypes. The percentages of atopic asthma and allergen sensitization in patients of different ages have not been well studied.

Objective: To determine the percentage distribution of atopic and non-atopic phenotypes in different age groups of asthmatic children, and investigate the distribution of specific IgE to different allergens when stratified by age group in southern Taiwan.

Method: We conducted this hospital-based, retrospective, cross-sectional study in southern Taiwan between 2004 and 2006. Asthmatic children aged 3 to 18 years who were diagnosed according to the Global Initiative for Asthma guidelines were enrolled. The MAST-CLA system was used to detect 36 allergen-specific IgEs.

Results: A total of 620 asthmatic children were divided into three groups: preschool (3-6 years old, n=360), school-aged (7-12 years old, n=213), and adolescent (13-18 years old, n=41) children. The atopic and non-atopic phenotypes were observed in 54.8% and 45.2% of the asthmatic children, respectively. The atopic phenotype was observed in 45.6%, 65.7%, and 80.5% of the preschool, school-aged and adolescent groups, respectively. The percentages of the atopic phenotype were significantly different when stratified by age group (p<0.001), and there was a positive trend of percentage distribution. The percentages of sensitization to aeroallergens were significantly different and observed in 44.0%, 65.7%, and 80.5% of the preschool, school-aged and adolescent groups, respectively (p<0.001). There were positive trends between age groups and prevalence rates of sensitization to the main aeroallergen and other aeroallergen groups, but not to each allergen of the seafood or other food allergen group.

Conclusions: A trend of an increasing percentage of the atopic phenotype when stratified by age group was found in asthmatic children in southern Taiwan. Aeroallergens contributed more to pediatric asthma than food allergens. The prevalence of sensitization to aeroallergens increased with increasing age when stratified by age group.

Keywords: atopy, allergen, asthma, pediatrics, phenotype

From:
[1] Division of Pediatric Pulmonology and Allergy-Immunology, Department of Pediatrics, E-Da Hospital/I-Shou University, Kaohsiung City, Taiwan
[2] Department of Pediatrics, E-Da Hospital/I-Shou University, Kaohsiung City, Taiwan
[3] Institute of Health Care Management, National Sun Yat-Sen University, Kaohsiung City, Taiwan
[4] Division of Pediatric Pulmonology and Allergy-Immunology, Department of Pediatrics, Chang-Gung Memorial Hospital, Kaohsiung City, Taiwan

Corresponding author:
Yu-Cheng Tsai
Division of Pediatric Allergy-Immunology, Department of Pediatrics, E-Da Hospital/I-Shou University
#1, Yida Road, Jiaosu Village, Yanchao District, Kaohsiung City 82445, Taiwan
E-mail: suyutsun@gmail.com; ed100616@edah.org.tw

Abbreviations:
Der p: Dermatophagoides pteronyssinus
Der f: Dermatophagoides farinae
MAST-CLA: multiple allergosorbent chemiluminescent assay

Introduction

Asthma is the most common chronic disease among children. The global burden of asthma has continued to rise over the past few decades, including Taiwan.[1,2] Asthma is divided into atopic and non-atopic phenotypes. These phenotypes have different pathophysiological findings, and therefore have different prognoses and treatment policies.[3-5]

Aeroallergens and food allergens have specific importance in different entities of allergic diseases, and the former is usually more important than the latter in a hyper-reactive airway. Although food allergens have a greater impact on skin allergies than on a hyper-reactive airway,[6] they still play a role in pediatric asthma.[7-10]

The atopic phenotype is predominant among pediatric patients compared to adults;[11] however, studies on the importance of aeroallergens and food allergens in asthmatic children stratified by age group are relatively limited. We therefore conducted this hospital-based study to determine the percentage distributions of atopic and non-atopic phenotypes in different age groups of asthmatic children, and evaluate the distribution of allergen-specific IgEs of aeroallergens and food allergens when stratified by age in southern Taiwan.

Methods

This study was undertaken at E-Da Hospital/I-Shou University in southern Taiwan between June 1, 2004 and November 31, 2006. Patients diagnosed with asthma by a pediatric pulmonologist/immunologist who received allergen-specific IgE tests were enrolled. The asthmatic children aged 3-18 years were divided into three groups: preschool (3-6 years old), school-aged (7-12 years old), and adolescent (13-18 years old). Asthma was diagnosed according to the Global Initiative for Asthma (GINA) guidelines,[12] and was based on the patients' documented clinical symptoms, rescue medicine used, activity limitation, and pulmonary function tests. The study protocol was approved by the hospital's institutional review board.

Allergen-specific IgE

Total IgE is influenced by age, genetic predisposition and other factors. Specific IgE reflects individual sensitization to a specific allergen and is more useful than total IgE in clinical use.[13-15] We used specific IgE to define the atopic and non-atopic phenotypes and study the percentage of sensitization to different allergens in asthmatic children in southern Taiwan. All children received specific allergen tests via MAST-CLA (Hitachi Chemical Diagnostics, Inc., Mountain View, CA) to detect allergen-specific IgEs.[14,16-21] The MAST report was graded from 0-4. A grade of specific IgE to a specific allergen equal to or greater than 2 indicated that the child had sensitization to that specific allergen;[19,22] otherwise, the child did not have sensitization to that specific allergen. We selected 36 allergens specific to the Asian region and divided them into four groups (**Table 1**). If the asthmatic children had sensitization to any of these allergens, they were defined as having the atopic phenotype and sensitization to that allergen group; otherwise, they were defined as having the non-atopic phenotype.

Statistical analysis

We compared the percentage of the atopic and the non-atopic phenotype in the different age groups, and the prevalence rates of specific IgEs to different allergen groups in the three age groups using descriptive analysis and the chi-square test. Statistical analysis was performed using the Statistical Package for Social Sciences software package (version 15 for Windows®, SPSS Inc., Chicago, IL).

Results

Demographic characteristic of the subjects

A total of 620 asthmatic children aged 3-18 years were enrolled. There were 388 boys and 232 girls, with an average age of 6.6±3.2 years. The children were divided into three groups: preschool (3-6 years old, n=366), school-aged (7-12 years old, n=213), and adolescent (13-18 years old, n=41). Male predominance was noted in all three age groups (**Table 2**). The rate of comorbid allergic rhinitis was significantly different among the different age groups (p<0.001), with a higher rate reported in the older age groups.

Percentage distribution of atopic and non-atopic phenotypes when stratified by age group in the asthmatic children

The atopic phenotype was observed in 54.8% of all cases. The percentages of atopic asthma in the preschool, school-aged, and adolescent groups were 45.6%, 65.7%, and 80.5%, respectively. In both genders, the percentage distributions of the atopic phenotype and non-atopic phenotype were significantly different with age (p<0.001, **Table 2**), and the percentage of atopic phenotype was higher in the older age groups. We further divided the children into more detailed age groups, and found that the atopic phenotype occurred in 40.2% of 3-year-old asthmatic children and 86.2% of those aged 14-18 years (p<0.001, **Figure 1**). There was a positive trend of an increasing percentage of atopic phenotype with an increasing age.

Table 1. The different allergens in the four allergen groups

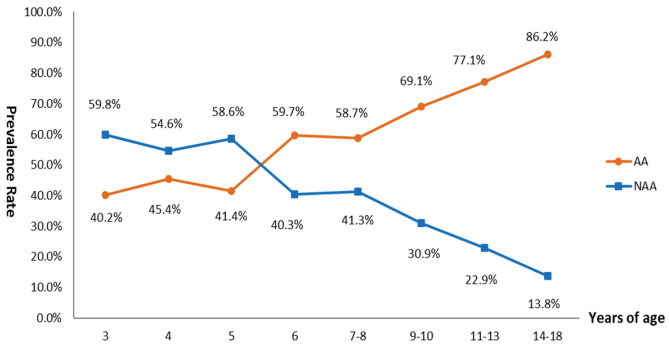
Allergen groups	Allergens included
Main aeroallergen group	Dermatophagoides pteronyssinus, Dermatophagoides farinae, House dust, Cockroach Mix, Dog, Cat
Other aeroallergen group	Feather Mix, Pine Mix, Cottonwood/Willow, Eucalyptus, Mulberry Mix, Grass Mix, Bermuda Grass, Ragweed Mix 1, Pigweed Mix, Alternaria, Aspergillus, Candida, Cladosporium, and Penicillum
Seafood group	Crab, Shellfish, Shrimp, Codfish
Other food allergen group	Citrus Mix, Corn, Wheat, Vegetable Mix, Pork, Beef, Milk, Yeast (Brewer), Soybean, Peanut, Egg Yolk, and Egg White

Table 2. Demographics of the subjects, and the percentages of atopic and non-atopic phenotypes in the three age groups

Age group (years old)	Total	3-6	7-12	13-18	*p* value#
Patient	620(100)	366(59)	213(34.4)	41(6.6)	
Age, mean±SD, y	6.6±3.2	4.4±1.1	8.8±1.5	14.6±1.7	
Gender					0.895
female	232(37.4)	137(37.4)	81(38.0)	14(34.1)	
male	388(62.6)	229(62.6)	132(62.0)	27(65.9)	
Phenotype					<0.001**
AA type	340(54.8)	167(45.6)	140(65.7)	33(80.5)	
NAA type	320(45.2)	199(54.4)	73(34.3)	8(19.5)	
Female					0.023*
AA type	129(55.6)	66(48.2)	54(66.7)	9(64.3)	
NAA type	103(44.4)	71(51.8)	27(33.3)	5(35.7)	
Male					<0.001**
AA type	211(54.4)	101(44.1)	86(65.2)	24(88.9)	
NAA type	177(45.6)	128(55.9)	46(34.8)	3(11.1)	
Allergic rhinitis					<0.001**
Yes	465(75.0)	248(67.8%)	179(84.0)	38(92.7)	
No	155(25.0)	118(32.2%)	34(16.0)	3(7.3)	
Location					<0.001**
Rural	210(33.9)	129(35.2)	67(31.5)	14(34.1)	
Urban	410(66.1)	237(64.8)	146(68.5)	27(65.9)	

Data are numbers (percentages) unless specified otherwise.
AA: atopic asthma phenotype, NAA: non-atopic asthma phenotype
p value for chi-square test of phenotype distributions across age groups
* *p* value < 0.05., ** *p* value < 0.001.

Figure1. The distribution of atopic and non-atopic phenotypes in different age groups (*p value<0.001).



AA: atopic asthma phenotype, NAA: non-atopic asthma phenotype
* *p* value for the chi-square test of percentages of allergen sensitization across age groups.

Allergen-specific IgE of aeroallergens and food allergens in asthmatic children and in different age groups

The rates of sensitization to main aeroallergens, other aeroallergens, seafood, and other food allergens were 52.9%, 4.8%, 7.7%, and 6.1%, respectively (**Table 3**). In total, 54.8% of the asthmatic children had sensitization to aeroallergens or food allergens, 53.9% to aeroallergens, 12.9% to food allergens, and 11.9% to both aeroallergens and food allergens. We compared the specific IgEs in the four different allergen groups among the three age groups. Sensitization to aeroallergens was observed in 44.0%, 65.7%, and 80.5% of the preschool, school-aged and adolescent groups, respectively. There were significant differences between age and sensitization to the main aeroallergen ($p<0.001$) and other aeroallergen ($p=0.013$) groups, and positive trends were noted. However, the percentage distributions between age and sensitization to each allergen of the seafood or other food groups were not significantly different.

Discussion

In the present study, the prevalence rates of sensitization to aeroallergens and food allergens were analyzed by different age groups of asthmatic children. The percentage of atopic phenotype was found to increase with age, and there were positive trends between age and prevalence rates of sensitization to the main aeroallergen and other aeroallergen

Table 3. Prevalence rates of specific IgEs to different allergens in the different age groups

Age group (years old)	Total N=620	3-6 N=366	7-12 N=213	13-18 N=41	*p* value#
Aeroallergens or food allergens	340(54.8)	167(45.6)	140(65.7)	33(80.5)	<0.001**
Both aeroallergens and food allergens	74(11.9)	42(11.5)	29(13.6)	3(7.3)	0.478
Aeroallergens	334(53.9)	161(44.0)	140(65.7)	33(80.5)	<0.001**
Main aero-allergens	328(52.9)	158(43.2)	137(64.3)	33(80.5)	<0.001**
Dermatophagoides pteronyssinus	284(45.8)	131(35.8)	122(57.3)	31(75.6)	<0.001**
Dermatophagoides farinae	315(50.8)	150(41.0)	162(62.0)	33(80.5)	<0.001**
House dust	143(23.1)	61(16.7)	64(30.0)	18(43.9)	<0.001**
Cockroach Mix	29(4.7)	7(1.9)	17(8.0)	5(12.2)	<0.001**
Dog	40(6.5)	17(4.6)	18(8.5)	5(12.2)	0.06
Cat	24(3.9)	8(2.2)	13(6.1)	3(7.3)	0.031*
Other aeroallergens	30(4.8)	10(2.7)	17(8)	3(7.3)	0.013*
Feather Mix	3(0.5)	1(0.3)	2(0.9)	0(0.0)	---
Pine Mix	1(0.2)	0(0.0)	1(0.5)	0(0.0)	---
Cottonwood/Willow	1(0.2)	1(0.3)	0(0.0)	0(0.0)	---
Eucalyptus	2(0.3)	2(0.5)	0(0.0)	0(0.0)	---
Mulberry Mix	2(0.3)	2(0.5)	0(0.0)	0(0.0)	---
Grass Mix	10(1.8)	6(1.6)	5(2.3)	0(0.0)	---
Bermuda Grass	18(2.9)	8(2.2)	9(4.2)	1(2.4)	0.364
Ragweed Mix 1	8(1.3)	3(0.8)	5(2.3)	0(0.0)	---
Pigweed Mix	3(0.5)	2(0.5)	1(0.5)	0(0.0)	---
Alternaria	6(1.0)	1(0.3)	4(1.9)	1(2.4)	---
Aspergillus	3(0.5)	1(0.3)	2(0.9)	0(0.0)	---
Candida	3(0.5)	0(0.0)	2(0.9)	1(2.4)	---
Cladosporium	3(0.5)	1(0.3)	2(0.9)	0(0.0)	---
Penicillum	6(1.0)	1(0.3)	5(2.3)	0(0.0)	---
Food allergens	80(12.9)	48(13.1)	29(13.6)	3(7.3)	0.536
Seafood	48(7.7)	22(6.0)	23(10.8)	3(7.3)	0.115
Crab	37(6.0)	18(4.9)	17(8.0)	2(4.9)	0.310
Shellfish	35(5.6)	17(4.6)	16(7.5)	2(4.9)	0.345
Shrimp	34(5.5)	16(4.4)	15(7.0)	3(7.3)	0.343
Codfish	2(0.3)	1(0.3)	0(0.0)	1(2.4)	---
Other food	38(6.1)	30(8.2)	8(3.8)	0(0.0)	0.024*
Citrus Mix	3(0.5)	2(0.5)	1(0.5)	0(0.0)	---
Corn	1(0.2)	1(0.3)	0(0.0)	0(0.0)	---
Wheat	3(0.5)	3(0.8)	0(0.0)	0(0.0)	---
Vegetable Mix	2(0.3)	1(0.3)	1(0.5)	0(0.0)	---
Pork	2(0.3)	2(0.5)	0(0.0)	0(0.0)	---
Beef	0(0.0)	0(0.0)	0(0.0)	0(0.0)	---

Age group (years old)	Total N=620	3-6 N=366	7-12 N=213	13-18 N=41	*p* value#
Milk	23(3.7)	18(4.9)	5(2.3)	0(0.0)	---
Yeast (Brewer)	1(0.2)	1(0.3)	0(0.0)	0(0.0)	---
Soybean	3(0.5)	2(0.5)	1(0.5)	0(0.0)	---
Peanut	3(0.5)	2(0.5)	1(0.5)	0(0.0)	---
Egg Yolk	3(0.5)	2(0.5)	1(0.5)	0(0.0)	---
Egg White	9(1.5)	8(2.2)	1(0.5)	0(0.0)	---

Data are numbers (percentages) unless specified otherwise.
p value for chi-square test of percentages of allergen sensitization across age groups
---: the *p* value was unavailable since more than 20% of the expected counts were less than 5.
* *p* value < 0.05., ** *p* value < 0.001

groups, but not to each allergen of the seafood or other food allergen groups.

Asthma is divided into atopic (IgE-mediated) and non-atopic phenotypes.[23] We used the MAST-CLA system to detect allergen-specific IgEs in asthmatic children.[14,17-21] MAST was reported to have a sensitivity of 85% and a specificity of 82% compared with 88% and 83% for RAST, when they were compared with skin test reactions.[21] MAST-CLA and RAST (i.e., Immuno CAP) are similar in their ability to measure allergen-specific IgE, and have been reported to correlate equally well with skin tests and clinical history in asthmatic children.[19,24] A total of 620 asthmatic children were enrolled in our study, of whom 54.8% had the atopic phenotype and 45.2% the non-atopic phenotype (**Table 2**). This finding is similar to other studies which reported that 48.8% to 68% of asthmatic children were atopic in Taiwan,[18,25] compared to 49% to 52.4% in New York and England.[26,27]

We divided the children into three groups: preschool (3-6 years old, n=366), school-aged (7-12 years old, n=213), and adolescent (13-18 years old, n=41). According to the healthcare system in Taiwan, adolescents visit family physicians and other specialty physicians for asthma treatment in addition to only visiting a pediatrician.[28] As the design of this study was hospital-based and cross-sectional instead of a longitudinal survey, data collection for the adolescents in remission or resolution was limited, and this partially contributed to the small number of cases in the adolescent group. We observed the non-atopic phenotype more frequently than the atopic phenotype in the preschool group, and conversely the atopic phenotype was observed more frequently than the non-atopic phenotype in school-aged children and adolescents. The percentage of the atopic phenotype increased with increasing age in the whole group and in both genders (**Table 2**). The positive trend was more emphasized when the children were divided into more detailed age groups (**Figure 1**). The birth cohort study by Roberts et al. also reported that allergic sensitization continued to increase through childhood into adolescence in the Isle of Wight, United Kingdom.[29] Taussig et al. also reported that in non-atopic wheezers, viral-associated wheezing played an important role in younger children, and atopic wheezers increased significantly with age in the Tucson Children's Respiratory Study (TCRS).[31] Viral-associated wheezing decreases in asthmatic children with age. A child can develop an atopic disease after repeated exposure to allergens, especially those with allergic diathesis.[30] These findings account for the positive trend in asthmatic children in southern Taiwan.

The avoidance of common allergens and pollutants is one of the main strategies to improve control of asthma and reduce the amount of medication needed. The European Academy of Allergy and Clinical Immunology (EAACI) report and the Expert Panel Report 3 (EPR-3) recommended that patients with persistent asthma receive indoor and outdoor allergen tests to assist in allergen avoidance and immunotherapy.[15,32] We found that there was a higher rate of sensitization to aeroallergens than to food allergens in all three age groups (**Table 3**). Huang et al. also reported that aeroallergens were more important than food allergens in hyperactive airways.[6] We divided the aeroallergens into a main aeroallergen group (including dust mites) and a second group for other aeroallergens (including pollen). The prevalence rate of sensitization to the main aeroallergen group was higher than that to the other aeroallergen group. This may be due to the crowded, high temperature and humid environment which is quite common in Taiwan, in addition to having fewer flowering plants in the urban areas where people predominantly live.[33] Therefore, atopic asthma and allergic rhinitis are usually perennial and not seasonal in Taiwan. There were positive trends between aging and prevalence rates of sensitization to the main aeroallergen and other aeroallergen groups when stratified by age group. The highest prevalence rate was in the adolescent group, and this partially reflects the close relationship between IgE synthesis and persistent exposure to aeroallergens in the environment (**Table 3**). Sensitization to aeroallergens contributed more to pediatric asthma than food allergens, since a lower prevalence rate (12.9%) of sensitization to food allergens was detected.[7-10] The children with sensitization to food allergens (12.9% of all subjects) were almost all sensitized to aeroallergens as well (11.9% of all subjects).

There are some limitations with regards to this retrospective study that are worth noting. The participants included on-controller therapy asthma cases and controller naïve cases, and the medications used at the time of blood sampling for allergen-specific IgE exams were not considered.

A prospective study with stricter inclusion and exclusion criteria is warranted to confirm the effect of age on allergen response in asthmatic children. In addition, we used 36 kinds of frequently encountered specific IgEs instead of total IgE to define the atopic phenotype. This means that the children who had sensitization to other rare allergens were excluded. Furthermore, there were insufficient data to adequately explain the reason behind the small number of cases in the adolescent group. A population study is needed to better enroll a definite number of asthma patients for the different age groups.

In conclusion, we found an increasing trend in the atopic phenotype with age when stratified by age group in asthmatic children in southern Taiwan. Non-atopic asthma was more common than atopic asthma in preschool children, and the atopic phenotype became predominant at school age and in adolescence. Aeroallergens contributed more to pediatric asthma than food allergens. Sensitization to aeroallergens increased with increasing age, however there was no similar effect between food allergens and increasing age.

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