Research Paper

The Interrelationship Between Persistent Asthma and Atopy in Children

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ABSTRACT

Background: Childhood asthma is mainly developed by an interplay between genetic and environmental factors. Atopic asthma has been regarded as the most common form of asthma in the pediatric age group. Therefore, we aimed to evaluate the role of atopy in inducing uncontrolled asthma in children.

Materials and Methods: Seventy-five children between 1 to 14 years of age, referred to The Asthma and allergy clinics of Azad University hospitals for a period of one year because of wheezing and or chronic cough with a diagnosis of asthma were enrolled in this cross-sectional study. After scrutinizing the children's medical history relevant to their asthmatic manifestations, they were evaluated with a skin prick test (SPT) for common aero and food allergens.

Results: Thirty-five asthmatic children had positive SPTs with their mean age higher than those with negative skin test results ($P \leq 0.0001$). In those with positive SPTs, the symptoms recurred if the medications were discontinued within a month of symptom improvement ($P=0.001$). The same results were true considering the history of previous atopic disorders in response to the discontinuation of therapy ($P<0.0001$).

Conclusion: To conclude, in most patients with negative skin tests, symptoms of asthma improved in less than a month from the initiation of appropriate therapies. However, in those with positive SPTs and a history of atopy, the symptoms recurred if the medications were discontinued within less than a month of symptom improvement ($P=0.001$ and $P<0.0001$, respectively).

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1. Introduction

Asthma is a heterogeneous allergic disorder and the most common chronic childhood disease worldwide [1] developed mainly due to an interplay between genetic and environmental factors [2] among other indicators. Wheezing is a highly prevalent finding in preschool children with different natural histories and underlying etiologies. However, only certain children may develop persistent asthma in the course of their disease. Based on differences in natural histories and risk factors, diverse wheezing phenotypes have been defined in childhood, with some of them persisting to present as asthma later in adolescence and adulthood. The most common environmental triggering factor in childhood asthma and also later in life are upper respiratory viral infections [3, 4] which may affect normal lung function and progress to enhanced airway reactivity. A significant number of children who present with wheezing in their early life do so because of viral infections without any personal or family history of atopy. The course of disease in these children appears to be less severe. Recurrent viral infections may lead to a wheezing phenotype caused by an inflammatory response leading to airway obstruction. Although it is not directly associated with atopy, it may necessitate inhaler therapies. Allergic diseases such as asthma are associated with atopy but may also coexist in non-atopic subjects. Atopic asthma has been regarded as the most common form of asthma (more than 50% of cases) in the pediatric age group in many studies [1]. It is characterized by eosinophilic airway inflammation and specific IgE sensitization [1]. Because asthma is a particularly heterogeneous illness, the interactions between genes and the environment, as well as epigenetic modifications, possibly explain the influence of various underlying factors and their roles in the disease [5].

Since there is still controversy regarding the causal relationship between atopy and asthma, we made evaluations to find non-allergic triggers of childhood wheezing in comparison to atopy. Many of our patients did not have any family or personal history of atopy; hence, we aimed to investigate if the existence of atopy could be confirmed in those asthmatic children with the recurrence of symptoms soon after the premature cessation of treatment.

2. Materials and Methods

Patient selection

Children between 1 to 14 years with asthmatic signs or symptoms referred to The Asthma and Allergy Clinics of Azad University Hospitals for a period of one year, from March 2020 to February 2021, were enrolled in this cross-sectional study.

The inclusion criteria included children ranging from 1 to 14 years old with asthmatic signs and symptoms. The exclusion criteria were patients being unwilling to continue participating in the study. The sampling method for the determination of the subjects was based on complete census enumeration to prevent selection bias. After asthma was diagnosed and confirmed by an allergist according to the global initiative of asthma guideline, [6] the children underwent a skin prick test (SPT) to evaluate if they had previously been sensitized to aeroallergens or if their signs and symptoms were due to non-atopic triggers (atopic versus non-atopic asthma).

The followings are some definitions we used in this regard:

Atopy: Atopy is defined by elevated allergen-specific immunoglobulin E or SPT positivity to common allergens.

Relapse: Returning symptoms despite receiving inhaled corticosteroid therapy within the first month of therapy during a total of three months follow-up.

Skin prick test: A test useful in the diagnosis of a variety of allergic diseases involving IgE-mediated type 1 immediate reactions including allergic rhinitis, asthma, conjunctivitis, food allergy, allergies to certain medications, venom allergy, and latex allergy.

Initial assessment

After scrutinizing the children's history relevant to their asthmatic manifestations, they were evaluated with an SPT (Greer company, USA) for common aero and food allergens only in cases deemed essential as a prerequisite for the sake of optimal patient care before initiating the study. The SPT was performed by the same nurse with adherence to standard protocols. All antihistaminic medications (including cetirizine, diphenhydramine, loratadine, desloratadine, and fexofenadine) were stopped at least five days before the test. All patients enrolled in this study were diagnosed with persistent moderate to severe

asthma and therefore were treated with fluticasone propionate as the first treatment step. In those patients without sufficient response to inhaled corticosteroid therapy, montelukast was added in the next step. The patients were followed for at least three months to evaluate their response to therapy and the occurrence of any relapses.

Statistical analysis

Data analysis was performed using SPSS software, version 24 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows). Statistical analysis was done using t-test, Chi-square test, and Fisher's exact test, and a $P<0.05$ was considered significant.

3. Results

This study was conducted on 75 asthmatic children, aged 1 to 14 years old, referred to The Allergy Clinics of Azad University Hospitals from March 2020 to February 2021. The mean age of the patients was 8.12 years. Of all the patients evaluated, 48(64%) were male and 27 (36%) were female. Thirty-eight patients (50.7%) had a positive family history of asthma in their first-grade relatives. Thirty-three patients (44%) had a positive history of atopy. In sixty-three of these patients (84%), signs and symptoms of asthma were initiated after experiencing upper respiratory infections. While 56 patients (74.7%) completely improved after cessation of the treatment, 19 patients (25.3%) were still symptomatic.

All these asthmatic children underwent an SPT, of whom 35 patients had positive SPTs. The mean age of the asthmatic patients with positive and negative prick tests was 10.22 and 6.27 years, respectively. According to the analysis, the mean age of asthmatic patients with positive SPT results was higher than those with negative skin test results ($P\leq0.0001$). There was no significant difference between male and female patients. Table 1 compares the results of SPT in asthmatic patients with positive family histories and previous atopic disorders.

Most of the patients who had negative skin tests improved shortly after receiving relevant therapies and therefore their parents stopped the treatment themselves. However, in those with positive skin tests, the symptoms recurred if the medications were discontinued soon after symptom improvement. The difference between these two groups of patients was significant ($P=0.001$) (Table 2). The same results were true considering the history of previous atopic disorders in response to the discontinuation of therapy ($P<0.0001$) (Table 2).

4. Discussion

Asthma is a very complex disease [7] known as the most common chronic respiratory disease in childhood, [8] with its prevalence increasing in recent years [9]. Genetic and environmental factors appear to play more important roles than other factors in the pathogenesis of the

Table 1. Comparison of SPT results in asthmatic patients with positive family histories and previous atopic disorders

Parameters		Skin Prick Test No.(%)		Total	P
		Positive	Negative		
Family history	Positive	30(78.9)	8(21.1)	38	<0.0001
	Negative	5(13.5)	32(86.5)	37	
Previous allergy	Positive	26(78.8)	7(21.2)	33	<0.0001
	Negative	9(21.4)	33(78.6)	42	
Atopic disease	AR	18(90)	2(10)	20	0.01
	FA/AR	2(100)	0(0)	2	
	FA/AD	0(0)	2(100)	2	
	AD/AR	2(100)	0(0)	2	
	FA	2(40)	3(60)	5	
	AD	2(100)	0(0)	2	
Total		35(46.7)	40(53.3)	75	-

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Table 2. A comparison of the relapse rate in asthmatic patients after cessation of therapy based on their skin prick test results and their previous history of atopic disorders

Parameters		Skin Prick Test No.(%)		Total	P
		Positive	Negative		
Relapse rate	+	15(78.9)	4(21.1)	19	0.001
	-	20(35.7)	36(64.3)	56	
Parameters		**Previous Atopic Disease No.(%)**		**Total**	**P**
		Positive	**Negative**		
Relapse rate	+	15(78.9)	4(21.1)	19	<0.0001
	-	18(32.1)	38(67.9)	56	

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disease. In those patients who wheeze before the age of 3, asthma remission occurs in more than 50% of cases by 6 years of age [10]. Atopy has been suggested as an important risk factor in the development of asthma in many studies [9, 11] due to reduced IFN-γ responses in infancy [12]. In the present study, most of the older children with a presentation in late childhood were allergically induced with a more severe and significant inflammation which is consistent with the results of the previous studies [11]. The later the onset of wheezing in a child in association with allergic sensitization, the higher the likelihood of persistent asthma up to adolescence [13-15].

The mean age of our patients with previous sensitization presenting with a positive SPT was higher than those with wheezing episodes occurring due to non-atopic causes and negative sensitization results (P<0.0001). However, some of the older patients had wheezing episodes early in their preschool years, which later changed to allergically triggered asthma based on the history obtained from their caregivers. Those patients who initially showed symptoms only after viral infections, later revealed aeroallergen sensitizations and persistent symptoms not easily relieved by standard treatments. These patients constituted a smaller group in this study. Seeking their family history, we found a positive genetic background in them.

In most of the patients studied in the present study, symptoms of asthma began after upper respiratory tract infections (63 vs 12). As hypothesized before, the altered expression and or function of virus sensors is associated with impaired innate immune response during viral infections, modifying the clinical and inflammatory profiles of the patients not only in steady states but also in exacerbations [16].

Most of these patients who had negative SPTs (36 patients out of 75), improved shortly after receiving relevant therapies (including inhaled corticosteroid and leukotriene receptor antagonists), and the treatment was discontinued by their parents in less than a month, without subsequent relapses in the next three months of their follow-ups.

Among those with positive skin tests, most of the patients were sensitized to aeroallergens (and not to food allergens). Weeds and cow's milk were the two most common aeroallergens and food allergens detected, causing sensitization in the studied children.

However, we believe there are some limitations to our study. The first limitation is the small sample size of patients who participated in the study. The second limitation is that the study was mostly based on the parents' recall of their child's disorder and the probable provocative factors.

5. Conclusion

To conclude, this study reinforced the fact that most of the wheezing episodes in younger children in early preschool years were not associated with a strong history of atopy in the index case and their family. However, in older children and adolescents, prior aeroallergen or food allergen sensitization was the leading cause of persistent asthma requiring maintenance therapy for longer durations. Therefore, according to our findings, emphasizing the existence of atopy by performing an SPT in older children and adolescents with asthma, is a useful method to predict the etiology, natural course, and outcome of therapy. However, it is not very useful in early onset wheezing in the first three years of life.

Ethical Considerations

Compliance with ethical guidelines

This study was carried out following the recommendations of the "Ethics Committee of Islamic Azad University of Medical Sciences". All parents provided written informed consent. The study protocol was approved by the "Ethics Committee of Tehran Medical Sciences Branch, Islamic Azad University (Code: IR.IAU.TMU.REC.1399.285).

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Authors' contributions

Conceptualization and methodology: Sepideh Darougar and Rahman Pouyanfar; Supervision: Sepideh Darougar and Mahboubeh Mansouri; Formal analysis: Rahman Pouyanfar; Writing the original draft: Paniz Hashemitari; Data curation, writing, review and editing: All authors

Conflicts of interest

The authors declared no conflict of interest.

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