Kerbala Journal of Pharmaceutical Sciences

ISSN: 2221-7207(Print) / **ISSN**: 3006-7189 (Online)

Asthma Characteristics of School Aged Children in Different Asthma Phenotypes

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Received: 17/09/2025
Accepted: 17/11/2025
Published: 31/12/2025

Keywords: Asthma, Asthma phenotypes, Allergic Asthma, Asthma severity

DOI:10.62472/kjps.v16.i27.230-240

Abstract

Background: Asthma is a disease of the airways with different phenotypes in terms of origin, clinical presentation and response to treatment. Knowledge of these phenotypes is important in pediatrics, as it guides and optimizes management. The aim of this study was to study the asthma characteristics in asthma phenotypes of school-aged children.

Patients and methods: This were a cross-sectional study, conducted in the Center of Pediatric Pulmonology/ Karbala teaching hospital for children on 80 asthmatic children (aged between 5 and 17 years) and they were classified into four phenotypes: allergic, eosinophilic, mixed allergic and eosinophilic (MAAE), and non-allergic non-eosinophilic (NANE). Demographic variables, clinical characteristics, and treatment details were also collected.

Results: MAAE (34%) and allergic (32%) were the most frequent phenotypes. In all phenotypes, there was a male dominance and there was not difference of BMI and residence between them. Only 26% of asthma was well controlled, 38% uncontrolled and 36% partially controlled. The prevalence of severe asthma was significantly higher among those in the MAAE group (p-value< 0.001). There is a significant relationship between family history and allergic phenotype (p-value= 0.02).

Conclusion: The findings emphasizes that there is a diversity of asthma phenotypes in school-aged children, and the allergic and the mixed allergic and eosinophilic phenotypes predominate. Most children had moderate asthma, but control was often poor with the allergic and mixed allergic and eosinophilic groups. Furthermore, allergic phenotype had a strong family history association in comparison to another phenotype.

خصائص الربو لدى الأطفال في سن المدرسة في أنماط الربو المختلفة

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الخلاصة

المقدمة: الربو هو مرض يصيب الشعب الهوائية وله أنماط ظاهرية مختلفة من حيث المنشأ والعرض السريري والاستجابة للعلاج .ومعرفة هذه الأنماط الظاهرية مهمة في طب الأطفال، لأنها توجه وتحسن الإدارة .وكان الهدف من هذه الدراسة هو تقييم خصائص الربو في أنماط الربو لدى الأطفال في سن المدرسة.

المرضى وطرق العمل: كانت هذه دراسة مقطعية أجريت في مركز أمراض الرئة للأطفال/ مستشفى كربلاء التعليمي للأطفال على 80 طفلاً مصابًا بالربو تتراوح أعمارهم بين 5 و 17 عامًا وتم تصنيفهم إلى أربعة أنماط ظاهرية: التحسسي، والحمضي، والحساسي المختلط والحمضي، وغير التحسسي غير الحمضي. كما تم جمع المتغيرات الديموغرافية والخصائص السريرية وتفاصيل العلاج.

النتائج: كانت الأنماط الظاهرية الأكثر شيوعًا مختلطة 34٪ وحساسية 32٪.كانت هناك هيمنة ذكورية في جميع الأنماط الظاهرية ولم يكن هناك فرق في مؤشر كتلة الجسم والإقامة بينها .كان26 ٪ ٪ فقط من حالات الربو خاضعة لسيطرة جيدة، و38٪ غير خاضعة لسيطرة و 36خاضعة لسيطرة جزئية. كالمعدل انتشار الربو الشديد أعلى بشكل ملحوظ بين أولئك في المجموعة المختلطة كذلك كان هنالك علاقة بين التاريخ العائلي ونمط التحسسي.

الاستنتاج: تؤكد النتائج على وجود تنوع في أنماط الربو لدى الأطفال في سن المدرسة، وأن النمط الظاهري التحسسي والنمط الظاهري المختلط يسودان،معظم الأطفال يعانون من الربو المعتدل، ولكن السيطرة كانت غالبًا ضعيفة مع المجموعات التحسسية والحساسية المختلطة والحمضية .علاوة على ذلك، كان للنمط الظاهري التحسسي ارتباط قوي بالتاريخ العائلي مقارنة بالأنماط الظاهرية الأخرى.

1. Introduction

Asthma is a lifelong inflammatory disease of the airways which affects people of all ages and has an important impact on quality of life, thus necessity of good management and therapy. Moreover, childhood asthma seems to be a common condition in developed countries and other allergic diseases are strongly related to it (Wypych-Ślusarska et al., 2022; Maspero et al., 2022). Childhood asthma has been classified into 2 groups according to different phenotypes and endotypes by airway inflammation. (Pavord et al., 2018): type 2 (T2)-low (neutrophilic/paucigranulocitic) or type 2 (T2)-high (eosinophilic) asthma (Licari et al., 2018). These categories, however, appear to have little significance since different pathophysiological processes could give rise to the same signs and symptoms as well as visible phenotypes and therefore different endotypes might have similar or even identical phenotypes (Deliu et al., 2018). Moreover, the follow-up of patients over time demonstrated that phenotypes change. A phenotype-based classification of asthma refers to the description of clinical profiles, inflammatory patterns, and underlying pathophysiology that contribute to variability in the presentation of asthma. Allergic asthma, which is widespread among children, occurs in response to allergens such as dust mites and pollen and is frequently concurrent with eczema or hay fever (Kharaba et al., 2022; Abood and Al-Zaubai, 2020). Non allergic asthma is not related to allergens and is caused by infections, cold air exposure, or stress; it is more difficult to control (Pham et al., 2023). Exercise-induced bronchoconstriction (EIB) symptoms occur during or after exercise, particularly in cold or dry air and treated with pre-exercise bronchodilators (Romero-Mesones et al., 2022; Klain et al., 2022). Work-related asthma is caused by irritants encountered while at work, including chemicals or animal proteins (Abood and Al-Zaubai, 2020). Cough-variant asthma manifests primarily as a chronic dry cough that is frequently not accompanied by wheezing, rendering diagnosis more challenging (Manti and Piedimonte, 2022; Rodriguez Bauza and Silveyra, 2021). Severe asthma is not well controlled on high dose and may need specialized care (Wypych-Ślusarska et al., 2022; Zhou et al., 2022). **Aim of this study** was to study the asthma characteristics in asthma phenotypes of school-aged children.

2. Materials, Patients and Methods

2.1. Study Design

This study is a cross-sectional which was carried out in the Center of Pediatric Pulmonology/ Karbala teaching hospital for children. The information was obtained on outpatient visits.

2.2. Patient Selection

In this study, 80 children (aged from 5 to 17 years) were enrolled. All of them must had a clinical diagnosis of asthma according to criteria from GINA were able to realize spirometry. Exclusion criteria were a diagnosis of other chronic lung diseases, acute lower respiratory infection at assessment and inability to do reliable spirometry.

2.3. Asthma Phenotyping

Asthmatic children were classified with regard to allergic status and absolute eosinophil count into 4 phenotypes. The allergic phenotype (presence of one or more of the following: rhinitis, eczema or food allergy) and total IgE >150 IU/mL, eosinophils <300 cells/μL was found in 26 patients (32%). The eosinophil phenotype, defined as negative IgE and ≥300 cells/μL eosinophils, was present in 14 patients (18%). A mixed allergic and eosinophilic (MAAE) phenotype, with positive IgE and a high eosinophil count (≥300 cells/μL), was present in 27 patients (34%), while the non-allergic non-eosinophilic (NANE) phenotype, with negative IgE/eosinophils (<300 cells/μL), was present in 13 patients (16%). Other characteristics, such as school absenteeism (≥9 days/year), any exacerbation in the previous year and a positive family history (if either parents or siblings had asthma) were also registered.

2.4. Assessment of Asthma Severity and Asthma Control

Asthma severity was categorized based on the Global Initiative for Asthma (GINA) guidelines as mild, moderate and severe persistent according to symptoms frequency and requirement of controller medication. Recent asthma control (in the previous 4 wk) was evaluated according to GINA criteria taking into account daytime and nocturnal symptoms, short-acting β2-agonist use, and limitation of activity.

2.5. Data Collection

A structured evaluation comprising in-depth clinical history, categorization into asthma phenotypes according to symptomatic cause was performed for all recruits. Asthma grades were determined according to GINA. Using clinical history, allergen exposure and the response to spirometry patients were divided into various asthmatic phenotypes. The severity and control of asthma were also evaluated.

2.6. Ethical Approval

This study has been performed in accordance with the principles laid down in the Declaration of Helsinki for experiments involving human beings and this prospective protocol was approved by the Ethics Committee, following Ethical guidelines for pediatric participants. Written informed consent was obtained from the legal guardians for voluntary participation.

2.7. Statistical Analysis

Statistics SPSS version 26. was used for data analysis. All variables were described through descriptive statistics. Chi-square tests were performed to examine the relationship between asthma phenotypes and asthma characteristics. p-value < 0.05 was considered to indicate statistical significance.

3. Results

Investigation of demographic characteristics by phenotypes in terms of age (years) and BMI, revealed no statistically significant differences between the groups. For age, the mean of participants was 9.23 years in allergic, 9.57 years in eosinophilic, 10.52 years in MAAE and 9.38 years in no allergy; p-value=0.20. The

mean BMI values were 17.17 for allergic, 17.32 for eosinophilic, 17.41 for MAAE and 17.28 for NANE with a *p*-value of 0.99, Table1.

Table1: Comparison of Age and Body Mass Index (BMI) Across Asthma Phenotypes

Variables	Allergic, no:26 (32.5%)	Eosinophilic, no:14 (17.5%)	MAAE, no:27 (34%)	NANE, no:13 (16%)	*p*-value
Age	9.23±2.2	9.57±2.56	10.52±2.2	9.38±2.32	0.20
BMI	17.17±3.46	17.32±3.46	17.41±3.63	17.28±2.41	0.99

The prevalence of different asthma phenotypes among patients with the asthma phenotype is shown in Table2. By sex, most of the cases were males in all groups compared (69% in allergic group; 71% in eosinophilic group; 81% for MAAE and, 77% for NANE group), *p*-value = 0.75. For the place of residence, 65% values were positive in the allergic group, 71% were positive in the eosinophilic group, 74% values were positive in the MAAE group and 53% in NANE group (*p*-value= 0.61). Smoking exposure was documented in 30% of allergic, 50% of eosinophilic, 60% of MAAE and 38% NANE group (*p*-value = 0.19). There was history of pets in 42% of allergic patients, 36% in eosinophilic, 66% MAAE and 47% NANE (p = 0.18). A strong relationship was found with positive family history; 80% of allergic, 50% of eosinophilic, 66% of MAAE and 76 % of NANE patients reported a positive family history (*p*-value= 0.02). Among the allergic group, food allergies were noted in 20% of the patients compared with 35, 14 and 7% among eosinophilic) MAAE and NANE (*p*-value=0.27). Lastly, allergic rhinitis had complained by 54% of the allergic group; 71% in eosinophilic; 48% in MAAE and 69% NANE (p-value =0.349). School absenteeism and exercise restriction among the different phenotypes do not differ across groups. As for school absence we observed 50% of allergic participants were absent at school versus 29% with eosinophilic, 48% of MAAE and 38% of NANE with a *p*-value of 0.56. Similarly, on exercise restriction 65% of notable patients had restrictions as compared to 78% of eosinophilic, 70% of MAAE and only 53% NANE, which was also not statistically significant (*p*-value =0.56).

Table2: Comparison of Demographic and Clinical Characteristics Among Asthma Phenotypes

Variables		Allergic no:26 (32.25%)	Eosinophilic no:14 (17.75%)	MAAE no:27 (34%)	NANE no:13 (16%)	*p*-value
Sex	Male	18 (69%)	10 (71%)	22 (81%)	10 (77%)	0.75
	Female	8 (31%)	4 (29%)	5 (19%)	3 (23%)	
Residence	Urban	17 (65%)	10 (71%)	20 (74%)	7 (53%)	0.61
	Rural	9 (35%)	4 (29%)	7 (26%)	6 (47%)	
Smoking	Yes	8 (30%)	7 (50%)	16 (60%)	5 (38%)	0.19
	No	18 (70%)	7 (50%)	11 (40%)	8 (62%)	

Pets	Yes	11 (42%)	5 (36%)	18 (66%)	6 (47%)	0.18
	No	15 (56%)	9 (64%)	9 (34)	7 (53%)	
Positive Family history	Yes	21 (80%)	7 (50%)	18 (66%)	10 (76%)	*0.02
	No	5 (20%)	7 (50%)	9 (34%)	3 (24%)	
Food allergy	Yes	5 (20%)	5 (35%)	4 (14%)	1 (7%)	0.27
	No	21 (80%)	9 (65%)	23 (86%)	12 (93%)	
Allergic Rhinitis	Yes	14 (54%)	10 (71%)	13 (48%)	9 (69%)	0.35
	No	12 (46%)	4 (29%)	14 (52%)	4 (31%)	
School absence (more than 9 days)	Yes	13 (50%)	4 (29%)	13 (48%)	5 (38%)	0.56
	No	13 (50%)	10 (71%)	14 (52%)	8 (62%)	
Exercise limitation	Yes	17 (65%)	11 (78%)	19 (70%)	7 (53%)	0.56
	No	9 (35%)	3 (22%)	8 (30%)	6 (47%)	

There were significant differences in asthma severity and control among the various asthma phenotypes. The proportion of patients reporting exacerbations was the same in other groups with 62 % in allergic, 42 % in eosinophilic, and 60 % MAAE and 61% NANE (p-value=0.68). Notably, at a p-value of 0.05, eosinophils used the SABA significantly more (28%) pre-exercise than allergic 4%, MAAE 18% and NANE 0%. As for severity half of patients had severe asthma that was caused by a MAAE phenotype (p-value< 0.001). The following 50% was evenly divided among groups with other phenotypes. Quality of asthma treatment was also lacking within every group, 22% in the eosinophilic group and 47% in the allergic group had not well controlled asthma which again resulted less than p-value=0.001. There were not any notable variations between the groups when uses and types of controllers were examined based on asthma phenotypes. In terms of inhaled corticosteroid (ICS) use, 15.4% of allergic participants reported using ICS, compared to 28.6% of eosinophilic, 33.3% of MAAE, and 15.4% of NANE, with a p-value of 0.11. The use of ICS-LABA was particularly notable in allergic participants (61.5%) compared to lower rates in eosinophilic (21.4%) and MAAE (48.1%) groups, while 38.5% of those with no allergies used this combination. Montelukast was reported by 23.1% of allergic participants and 50.0% of eosinophilic participants, whereas 18.5% of MAAE and 46.2% of NANE reported its use. Regarding ICS types, the majority of allergic participants used budesonide (50.0%), with similar usage in eosinophilic (21.4%) and MAAE (25.9%) groups, Table3.

Table3: Clinical Outcomes by Asthma Phenotypes

Variables		**Allergic no:26 (32.5%)**	**Eosinophilic no:14 (17.5%)**	**MAAE no:27 (34%)**	**NANE no:13 (16%)**	***p*-value**
Exacerbation	Yes	16 (62%)	6 (42%)	16 (60%)	8 (61%)	0.68
	No	10 (38%)	8 (58%)	11 (40%)	5 (39%)	
SABA use before exercise	Yes	1 (4%)	4 (28%)	5 (18%)	0 (0%)	* 0.05
	No	25 (96%)	10 (72%)	22 (82%)	13 (100%)	
Asthma severity	Mild	8 (30%)	2 (14%)	3 (11%)	1 (7%)	** < 0.001
	Moderate	17 (65%)	11 (78%)	21 (78%)	11(86%)	
	Severe	1 (5%)	1 (7%)	3 (11%)	1 (7%)	
Asthma control	Well control	6 (23%)	4 (28%)	7 (27%)	4 (31%)	** <0.001
	Partial control	8 (30%)	7 (50%)	9 (33%)	5 (38%)	
	Uncontrolled	12 (47%)	3 (22%)	11 (40%)	4 (31%)	
Controller use	ICS	4 (15.4%)	4 (28.6%)	9 (33.3%)	2 (15.4%)	0.11
	ICS-LABA	16 (61.5%)	3 (21.4%)	13 (48.1%)	5 (38.5%)	
	Montelukast	6 (23.1%)	7 (50.0%)	5 (18.5%)	6 (46.2%)	
ICS type	Beclomethasone	4 (15.4%)	4 (28.6%)	9 (33.3%)	2 (15.4%)	0.12
	Budesonide	13 (50.0%)	3 (21.4%)	7 (25.9%)	3 (23.1%)	
	Fluticasone	3 (11.5%)	0 (0%)	6 (22.2%)	2 (15.4%)	

4. Discussion

Asthma phenotypes are crucial for effective diagnosis and personalized management, particularly as asthma symptoms can overlap with other respiratory conditions, complicating clinical assessments (Dharmage et al., 2019; Dick et al., 2014). The predominance of males in our study aligns with previous research indicating a higher prevalence of asthma in boys during childhood (Chowdhury et al., 2021; Ibrahim et al., 2021). This gender disparity is often attributed to differences in airway size and hormonal influences, which may predispose boys to more severe asthma symptoms (Rodriguez Bauza and Silveyra, 2021; Russo et al., 2022). However, the transition to adolescence often sees a reversal of this finding, with females experiencing higher asthma prevalence and severity (Chowdhury et al., 2021). Our results suggest that the different asthma phenotypes in this sample do not differ significantly according to the of BMI, with *p*-value of 0.99. Specifically, 29% of eosinophilic, 48% MAAE, and 38% children NANE reported missing more than 9 days of school compared with allergic group (50%). The non-significance (*p*-value= 0.56) means that school attendance is not much different for phenotypic asthma but rather remains close to home or parent's workplace despite these changes. Children with eosinophils may be more prone to exercise-induced bronchoconstriction, as illustrated by the statistically significant difference in SABA use before exercise (eosinophilic 28%; allergic 4%; MAAE 18%, NANE 0%, *p*-value= 0.05) (Malewska-Kaczmarek et al.,2022).

This finding is consistent with analyses comparable to those of Chung et al. (2022) who prove that, due to the greater level of airway inflammation and hyperreactivity, individuals suffering from eosinophilic asthma more often use bronchodilators. This indicates that the majority of patients with eosinophilic asthma may receive greatest benefit from anticipatory management, including the use pre-exercise bronchodilators (Chung et al., 2022).

The differences were particularly striking when considering asthma severity classification; in the allergic group, 30% of them were classified as mild compared to eosinophilic (14%), MAAE (11%) and NANE (7%), with p-value <0.001. A study by Van Hulst et al. (2021), these findings indicate that subjects with allergic asthma generally present a more severe profile overall than individuals with either eosinophilic or MAAE phenotypes. This is in agreement with that of Wenzel et al. (2021), who found that eosinophilic asthma, characterized by more severe and persistent symptoms, is overall associated with more severe clinical and pathologic presentations than allergic asthma (Wenzel, 2021). All phenotypes had inadequate asthma control with a large proportion considered uncontrolled: 22% (eosinophilic), and 47% (allergic) which were both statistically significant (p-value <0.001). The awareness that uncontrolled asthma has the potential to lead to higher morbidity and diminished quality of life, suggests an important target for management. The observation of high prevalence of poor control in each group suggests that, irrespective of the severity grade, other aspects related to asthma management (such as medication compliance, access to medical care, and exposure to environmental conditions) could be widespread. This confirms the findings of studies conducted by Reddel et al. (2022) and underscoring the need for improved strategies in asthma management in different populations of patients (Reddel et al., 2022). Environmental exposures also impact on asthma phenotypes. The patients, in particular allergic and eosinophilic groups, resided in urban areas significantly more often based on residential information. This is in agreement with findings from Pate et al. (2021) and Grant et al. (2022), suggest that urban residency is associated with increased exposure to allergens and pollutants which can exacerbate asthma (Pate et al., 2021). Given that significantly lower proportion of the NANE group lived in an urban area, this could be a protective factor for asthma in a cleaner or less allergen-rich environment. Cities are often associated with increased air pollution levels, exposure to allergens and environmental factors that may exacerbate asthma (Chatkin et al., 2022). On the other hand, children living in farming environments are exposed to a diverse profile of allergens potentially including exposures such as farm animals or agricultural chemicals that might influence asthma phenotypes differently in rural settings (Andersén et al., 2021). The distribution of ownership was different across groups, and the highest proportion of pet owners belonged to MAAE. There is a relationship between owning a pet and asthma, even though the p-value of 0.18 tells us that we cannot conclude this statement as true from the sample. Early pet exposure may reduce the risk of having asthma, although some evidence also suggests that it potentially exposes people to worse

allergic sensitization (Pinot de Moira et al., 2022). Positive family history was significantly correlated to asthma phenotypes, especially in allergic. This finding is supported by the strong evidence that a genetic predisposition to allergy conditions substantially contributes to this, as known for decades. The importance of family history as a risk factor is also underscored by the study from Venter and colleagues. (2021) who demonstrated a large increase in asthma and related conditions with a familial history of allergic disease (Venter et al., 2021). The high prevalence of asthma in the family is in accordance with previous studies indicating that atopy (asthma among other atopic disorders) is heritable (Baker et al., 2024). Asthma and related allergic diseases (e.g., food allergy, hay fever) often develop due to the interaction between environmental conditions and individual genetic susceptibility. Differences in the severity of food allergies between groups despite were non significance (p-value= 0.27) suggests that food allergies while common may not correlate with the type or severity of asthma according to this study. Also, there were no differences in the proportion of allergic rhinitis among groups (p-value= 0.349). However, Luo et al. (2023) reported a powerful association between asthma and allergic rhinitis, indicating that both diseases coexist widely and share common pathophysiological mechanisms. This is also supported by the high prevalence of allergic rhinitis, and in particular in the eosinophilic group (71%).

5. Conclusion

The findings emphasizes that there is a diversity of asthma phenotypes in school-aged children, and the allergic and the mixed allergic and eosinophilic phenotypes predominate. Most children had moderate asthma, but control was often poor with the allergic and mixed allergic and eosinophilic groups. Furthermore, allergic phenotype had a strong family history association in comparison to other phenotypes.

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