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Characteristics of inpatients with atopic asthma in a tertiary center: do age and gender have an influence?

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ABSTRACT

Background: Several studies have demonstrated gender influence on asthma prevalence, being higher among males during early childhood. Little is known about the impact of gender and age on asthma exacerbation characteristics in pediatrics. This study aimed to determine the differences in acute asthma between males and females in three different age groups regarding perinatal characteristics of asthmatic patients, comorbidities, medication adherence, level of blood eosinophils, and pattern of hospitalization.

Methods: The medical records of 130 pediatric patients with asthma, who presented to the emergency department at Jordan University hospital with asthma exacerbations, were retrospectively reviewed. Demographic information and clinical characteristics were collected.

Results: The mean age of patients was 10.7±4.7 years. The age at diagnosis and gestational age were significantly higher in older children. Furthermore, younger children were significantly more likely to experience winter exacerbations and more emergency presentations. Male patients were considerably younger than their female counterparts and were diagnosed younger. In addition, male patients were more likely to have eosinophil levels higher than 3% than female patients.

Conclusion: Gender plays a role in the development and outcome of asthma exacerbations at different ages of pediatrics. A better understanding of gender-based and age-based differences in asthma dictates a personalized approach to treatment.

Key words: Asthma, influence, atopy, prevalence.

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Ethics Approval and consent to participate: The current study was approved by the Institutional Review Board of The University of Jordan and the Jordan University Hospital (no. 2018/295). Data was collected retrospectively and no consent was required.

Availability of data and materials: The data used to support the findings of this study are available from the corresponding author on reasonable request.

Introduction

Worldwide, asthma has a higher prevalence in males than in females before puberty [1] and the distribution of asthma prevalence is variable across the ages. A number of reports have shown gender difference in the prevalence of childhood asthma, where males were reported to have more prevalent asthma than females [2-4]. In adolescence, however, the pattern changes; adolescent-onset asthma is more prevalent in females than males [5-7]. Venn *et al.* reported a reversal in asthma prevalence rate after age 12 [8]. They showed that after this age, the prevalence of wheezing in males decreased, whereas there was a trend for a rise with age in females [8]. Hence this was a questionnaire-based study, the authors acknowledged that a female's tendency to over-report asthma-related symptoms than males may have overestimated the sex difference that was shown after age 12 [8]. However, the same result was shown when parental responses were used, which is a measure that might be less affected by gender [8]. Even in terms of asthma remission rate, it has been reported that the remission rate was higher among young males than females [9]. Several studies have investigated the relationship between asthma diagnosis and gender difference. It has been argued that male prevalence of childhood asthma was attributed to their smaller airway diameter relative to lung volume [10]. In addition, it has been suggested that diminished immunological responsiveness related to changes in hormones during adolescence may explain the overall improvement in asthma around that age [2]. Asthma exacerbations with hospitalization are pivotal events that require careful reevaluation of the previous treatment and a new personalized approach to future management. Increased asthma attack incidence is significant given that asthma-related care depletes pediatric healthcare resources and accounts for substantial healthcare expenditures [2,11]. Despite high disease burden, gender-related differences, and age disparities in clinical presentations and outcomes among pediatric asthmatic patients have been given little attention. Information on the pattern of asthma exacerbations according to age and sex are poorly described, and those that do exist are limited to comparing whole children group with adult and not assessing particular age groups among the pediatric population.In this context, this study aimed to analyze the differences in patterns of asthma exacerbation between male and female patients in three different age groups in the pediatrics cohort and to explore their perinatal characteristics, comorbidities, medication adherence, and level of blood eosinophils, and hospitalization risk.

Methods

Study design and data collection

This study enrolled 271 children with asthma aged 1 to 16 who visited the Jordan University Hospital (JUH) Emergency Department from January 2014 to September 2018. We conducted a retrospective analysis of the electronic medical records. Asthma was defined as physician-diagnosed asthma with the presence of another allergy such as allergic rhinitis, eczema, or food allergy, ± a positive family history of an allergy with a documented response to a bronchodilator during the episode that was labeled as an asthma exacerbation. Asthma diagnosis was made by one of two-full time pediatric pulmonologists at JUH. An asthma exacerbation was defined as acute dyspnea, tachypnea, oxygen demand, or requirement of systemic steroid therapy. In addition, asthma severity was classified as mild, moderate, or severe based on the extent of symptoms and the pediatric pulmonary consultant's clinical judgment. Children with congenital heart disease, genetic disorders such as cystic fibrosis, complex syndromes affecting the respiratory system, or other significant lung conditions such as bronchopulmonary dysplasia and immunodeficiencies were excluded. All children were on asthma medications.

Fifty-one patients were excluded because they did not fit the definition of asthma. Twenty-one patients were excluded because they had additional respiratory conditions, and 29 patients were excluded because they had other non-respiratory diseases. Thirty-seven patients had missing data, and three died (Figure 1).

The data collected included: demographics and age at diagnosis. Perinatal data included gestational age, mode of delivery, weight at birth, duration of breastfeeding, and exclusive breastfeeding. Data about allergies was collected, and parents were contacted to ask about related symptoms to confirm the diagnosis of the allergy, such as allergic rhinitis (AR) and AR-related symptoms (sneezing, runny nose, and congestion), eczema and its related symptoms (itchy rash at any time affecting any of the following locations: the fold of elbows, behind the knee, in front of the ankle, under the buttocks or around the neck), hay fever (itchy eyes), food allergy, family history of atopy, Information regarding medications (inhalation medication mainly corticosteroid/ICS), symptoms control (less than two admissions in the last year), and symptoms in winter were gathered. Laboratory tests such as neutrophil and eosinophil percentages were also gathered during admission for an exacerbation.

The current study was approved by the Institutional Review Board of The University of Jordan and the Jordan University Hospital (no. 2018/295).

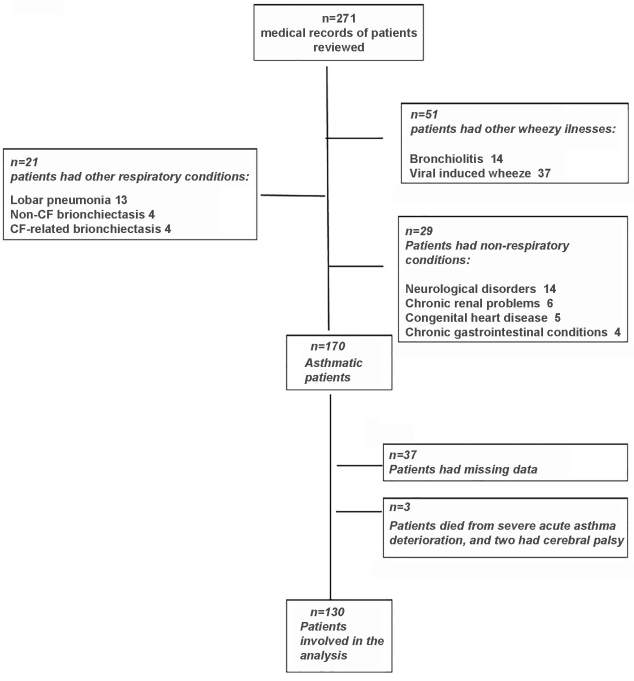

Figure 1. Subjects included in the study.

Statistical analysis

All data was entered and organized in Microsoft Excel. Subsequently, all statistical analyses of the final 130 participants were conducted on SPSS version 23. Continuous variables were described as means ± standard deviation (SD), and categorical data were expressed as frequencies (n [%]). Comparisons of categorical variables (e.g., clinical characteristics with age group, asthma severity, or atopy status) were estimated using the Chi-square test. Differences between categories were evaluated using the student's t-test for dichotomous categories and ANOVA for categories composed of more than two labels. Odds ratios and associated confidence intervals were calculated using a generalized regression model. All analyses were conducted under a 5% error margin and 95% confidence interval. A $p<0.05$ was considered statistically significant, respectively.

Results

Baseline characteristics of the study subjects

Our study examined 130 pediatric patients with asthma at a mean age of 10.7±4.7 years. The majority of participants were males (61.5%), and the mean age at asthma diagnosis was 3.5±3.1 years. Most of the participants were delivered vaginally (66.9%) and had a mean gestational age, birth weight, and duration of exclusive breastfeeding of 38.3±2.2 weeks, 3.0±0.6 kilograms, and 0.6±0.7 years, respectively. The participants' general characteristics are provided in Table 1. Many patients had chronic rhinosinusitis (53.8%) and a family history of asthma (67.7%). The majority of participants used inhaled steroids (73.1%), experienced winter exacerbations (70.8%), and frequently visited the emergency department (55.4%). In terms of severity, mild, moderate, and severe asthma was present in 54.3%, 37.0%, and 8.7% of participants.

Age-specific clinical characteristics

The univariate analysis demonstrates that age at diagnosis and gestational age were significantly higher in older children ($p<0.001$, all) (Table 2). On the other hand, younger children were significantly more likely to experience winter exacerbations ($p=0.049$), emergency presentations ($p=0.017$) and were characterized by higher average respiratory rate ($p<0.001$) (Tables 2 and 3).

Gender-specific clinical characteristics

Regarding gender, males were significantly younger than their female counterparts ($p=0.005$) and were diagnosed younger ($p=0.048$). In addition, males have higher eosinophil levels (more than 3%) than their female counterparts ($p=0.041$). In contrast, females were twice as likely to use steroids ($p=0.009$) and were less likely to experience winter symptoms/exacerbations ($p=0.003$) Table 4). Furthermore, female patients were associated with higher heart rates ($p=0.028$), but lower respiratory rates ($p=0.019$), and O_2 saturation ($p=0.048$) compared to their male counterpart (Table 5).

Discussion

In this study, asthma diagnosis in males was more common than in females and males accessed the emergency department more frequently than females, which is consistent with other asthma prevalence data [1,2,11-13]. Similar to what has been published, our study showed that the average age of patients with asthma in males was found to be younger than females [12,14-17]. Studying the relationship between perinatal characteristics with gender and age, asthma had been associated with pregnancies shorter than 36 weeks and that age at diagnosis was younger in patients with lower gestational age regardless of gender. Some investigations showed that prematurity increases a child's risk of developing asthma in preschool, but not in children >10 [18]. On the other hand, prematurity was not associated with asthma in a study of school-aged Finnish children; nevertheless, children who were born preterm and developed wheezing by the age of 10 were found to be atopic [19]. Differences in research cohorts and demographics may explain this discrepancy in results. Studies have examined the link between cesarean section delivery and pediatric asthma, but the subject remains contentious [20,21]. However, in this study, cesarean delivery was not independently linked with childhood asthma. Furthermore, consistent with other findings, our data imply that the association between cesarean section and bronchial asthma may be explained by the influence of other confounding variables rather than the delivery technique itself [20-25]. Several studies, including two meta-analyses, have shown a significant connection [26-31]. We found that asthma is diagnosed at a younger age in those with lower birth weight and a shorter time of exclusive breastfeeding. One study, however, showed that males are at increased risk for pediatric respiratory morbidity, independent of birth weight and gestational age [32].

Several parameters were assessed in this study suggesting age and gender-based differences in the severity of asthma exacerbation. The frequency of ER presentations was more significant in younger patients and males after adjusting for prevalence. Worse winter symptoms were seen in 5-12-year-old with the majority being males when compared to females ($p=0.003$). Comparing the clinical presentation of asthma exacerbations between the two genders, we found that males were more tachypneic than age-matched

Table 1. Demographics and clinical characteristics of the study population (n=130).

General characteristics	
Gender, n (%)	
Males	80 (61.5)
Females	50 (38.5)
Mean age ± SD (years)	10.7±4.7
Mean age at diagnosis ± SD (years)	3.5±3.1
Mean gestational age ± SD (weeks)	38.3±2.2
Mean birth weight ± SD (kg)	3.0±0.6
Mean duration of exclusive breast-feeding ± SD (years)	0.6±0.7
Mode of delivery, n (%)	
Vaginal delivery	87 (66.9)
Cesarean section	43 (33.1)
Clinical characteristics, n (%)	
Chronic rhinosinusitis	70 (53.8)
Chronic eczema	18 (13.8)
Hay fever	45 (34.6)
Food allergy	20 (15.4)
Family history of asthma/atopy	88 (67.7)
Inhaled corticosteroid use	95 (73.1)
Frequent exacerbations in winter	92 (70.8)
Frequent presentations to the Emergency Room	72 (55.4)
Mean blood eosinophils ±SD (%)	2.9±7.4
Blood eosinophils >3%	20 (23.3)
Asthma severity, n (%)	
Mild	69 (54.3)
Moderate	47 (37.0)
Severe	11 (8.7)

Table 2. Demographics and clinical characteristics according to age groups.

Variable	Less than 5 (n=14)	Between 5 and 12 (n=71)	More than 12 (n=45)	p
Mean age ±SD (years)	4.57±0.5	8.46±1.8	16.20±3.3	0.000
Mean age at diagnosis ±SD (years)	2.70±1.2	3.46±1.5	7.04±3.8	0.000
Mean gestational age ±SD (weeks)	36.53±3.4	38.65±2.1	38.27±1.6	0.010
Mean birth weight ±SD (kg)	2.56±0.8	3.11±0.7	3.05±0.5	0.056
Mean exclusive breast-feeding time ±SD (years)	0.27±0.4	0.58±0.7	0.71±0.7	0.132
Mean eosinophil level ±SD (%)	2.4±3.1	3.3±9.7	2.5±4.5	0.876
Blood eosinophils >3%	6 (33.0)	1 (6.7)	13 (24.5)	NA
Mode of delivery				0.151
Cesarean section	6 (42.9)	27 (38.0)	10 (22.2)	
Vaginal delivery	8 (57.1)	44 (62.0)	35 (77.7)	
Chronic allergic rhinitis				0.327
Yes	6 (42.9)	36 (50.7)	28 (62.2)	
No	8 (57.1)	35 (49.3)	17 (37.8)	
Eczema				0.242
Yes	0 (0)	10 (14.1)	8 (17.8)	
No	14 (100)	61 (85.9)	37 (82.2)	
Hay fever				0.182
Yes	3(21.4)	22 (31.0)	20 (44.4)	
No	11 (78.6)	49 (69.0)	25 (55.6)	
Food allergy				0.764
Yes	3 (21.4)	11 (15.5)	6 (13.3)	
No	11 (78.6)	60 (84.5)	39 (86.7)	
Family history				0.215
Yes	12 (85.7)	44 (62.9)	32 (71.1)	
No	2 (14.3)	26 (37.1)	13 (28.9)	
ICS use				0.069
Yes	8 (57.1)	49 (69.0)	38 (84.4)	
No	6 (42.9)	22 (31.0)	7 (15.6)	
Asthma severity				0.704
Mild	3 (23.1)	43 (61.4)	23 (52.3)	
Moderate	7 (53.8)	21 (30.0)	19 (43.2)	
Severe	3 (23.1)	6 (8.6)	2 (4.5)	
Symptoms worse in winter				0.049
Yes	13 (92.9)	52 (73.2)	27 (60.0)	
No	1 (7.1)	19 (26.8)	18 (40.0)	

Table 3. The severity of acute exacerbation among different age groups.

Variable	Less than 5 (n=14)	Between 5 and 12 (n=71)	More than 12 (n=45)	p
ER presentation ≥1				0.068
No	3 (21.4)	30 (42.3)	25 (55.6)	
Yes	11 (78.6)	41 (57.7)	20 (44.4)	
Average ER presentations	1.55±1.0	1.51±0.9	1.20±0.9	0.017
Age at ER presentation	0.93±0.4	4.11±1.8	11.03±2.7	0.000
Length of hospital stay	6.25±4.2	3.79±2.1	4.00±1.6	0.055
Heart rate	138.3±24.2	123.6±23.5	116.9±25.6	0.095
Respiratory rate	53.6±20.1	42.9±45.0	27.50±12.2	0.000
O_2 saturation	91.4±10.5	90.3±4.2	91.3±5.9	0.701
CO_2 35.9±10.5	32.1±5.1	31.9±3.6	0.271	
Accessory muscle use				--
None	2 (18.1)	6 (15.8)	5 (33.3)	
Mild	3 (27.3)	9 (23.7)	5 (33.3)	
Moderate	3 (27.3)	21 (55.2)	4 (26.6)	
Severe	3 (27.3)	2 (5.3)	1 (6.7)	
Outcome				--
Admission	8 (72.7)	29 (76.3)	9 (56.3)	
Discharge	3 (27.3)	9 (23.7)	7 (43.7)	
Admission				
Floor	6 (75.0)	27 (93.2)	8 (88.9)	--
Floor to PICU	1 (12.5)	1 (3.4)	--	
PICU	1 (12.5)	1 (3.4)	1 (11.1)	

ER, Emergency Room; PICU, pediatric intensive care unit.

Table 4. Gender effect.

Variable	Males (n=80)	Females (n=50)	p	OR (95%)
Age (years)	9.81±4.4	12.18±5.0	0.005	--
Age at diagnosis (years)	4.13±2.7	5.23±3.8	0.048	--
Gestational age (weeks)	38.10±2.5	38.67±1.6	0.144	--
Birth weight (kg)	3.04±0.7	3.04±0.5	0.990	--
Breast feeding time (years)	0.94±0.7	0.99±0.7	0.696	--
Exclusive breast-feeding time (years)	0.57±0.7	0.63±0.7	0.620	--
Blood eosinophils >3%	16 (30.8)	4 (22.8)	0.041	0.300 (0.091 - 2.001)
Mode of delivery			0.702	1.238 (0.587 - 2.610)
Cesarean section	25 (31.4)	18 (36.0)		
Vaginal delivery	55 (68.6)	32 (64.0)		
Allergic rhinitis			0.284	1.500 (0.733 - 3.068)
No	40 (50.0)	20 (40.0)		
Yes	40 (50.0)	30 (60.0)		
Eczema			0.435	0.573 (0.191 - 1.718)
No	67 (83.7)	45 (90.0)		
Yes	13 (16.3)	5 (10.0)		
Hay fever			0.851	1.104 (0.527 - 2.315)
No	53 (66.2)	32 (64.0)		
Yes	27 (33.8)	18 (36.0)		
Food allergy			0.807	0.839 (0.310 - 2.270)
No	67 (83.7)	43 (86.0)		
Yes	13 (16.3)	7 (14.0)		
Family history			0.999	0.984 (0.460 - 2.104)
No	25 (31.2)	16 (32.0)		
Yes	54 (68.7)	34 (68.0)		
Steroid use			0.009	3.308 (1.316 - 8.313)
No	28 (35.0)	7 (14.0)		
Yes	53 (65.0)	43 (86.0)		
Asthma severity			0.103	0.103
Mild	36 (45.0)	33 (66.0)		
Moderate	33 (41.3)	14 (28.0)		
Severe	8 (10.0)	3 (6.0)		
Symptoms worse in winter			0.003	0.318 (0.146 - 0.696)
No	16 (20.0)	22 (44.0)		
Yes	64 (80.0)	28 (56.0)		

Table 5. Gender and clinical presentation.

Variable	Males (n=80)	Females (n=50)	p
ER presentation at least once			0.589
No	34 (42.5)	24 (48.0)	
Yes	46 (57.5)	26 (52.0)	
Age at ER presentation	4.74±4.0	6.29±3.7	0.134
Heart rate	119.95±25.2	137.7±21.1	0.028
Respiratory rate	43.15±17.3	27.89±14.6	0.0198
O_2 saturation	91.48±4.3	89.0±5.0	0.048
CO_2	32.28±6.6	33.75±5.2	0.471
Accessory muscle use			--
None	10 (22.7)	3 (15.0)	
Mild	11 (25.0)	6 (30.0)	
Moderate	19 (43.2)	9 (45.0)	
Severe	4 (9.1)	2 (10.0)	
Outcome			0.771
Admission	32 (72.7)	14 (66.7)	
Discharge	12 (27.3)	7 (33.3)	
Admission			--
Floor	28 (87.5)	13 (92.9)	
Floor to PICU	2 (6.3)	--	
PICU	2 (6.3)	1 (7.1)	
Length of hospital stay	4.45±2.9	3.86±1.9	0.485

ER, Emergency Room; PICU, pediatric intensive care unit.

females. However, females tend to be more tachycardic and oxygen desaturated than male peers. Similar to other studies, hospitalization rates were not significantly different in asthmatic males compared to females [33]. The majority of males are admitted to the hospital with a statistically non-significant longer average time of stay compared to their female counterparts. Similar results were reported in the literature [33], whereas a contrary study published that female gender and older age are associated with longer length of stay for pediatric asthma hospitalizations [34]. Our data is in accordance with a recent report showing no difference in sex between the ICU and non-ICU cohorts [35].

Scarce data is available yet to suggest the relationship between eosinophil count and gender in patients presenting with asthma exacerbation in the pediatrics group. In the present study, eosinophils (EOS) count was significantly higher in males. There is increasing evidence that EOS levels are linked to disease outcomes and treatment response in asthma. Exacerbations are more frequent in patients with high counts (>3%) than those with counts below this threshold [36]. Statistically non-significant conflicting findings reported that the number of eosinophils (>300/μl) did not have an effect on emergency visits and readmission rate [37], and that increased blood eosinophil count was independently associated with bronchial hyperresponsiveness in the male subjects, but not in the female subjects [38].

Moreover, the presence of various comorbidities (allergic rhinitis, eczema, hay fever, and food allergy) with asthma has been widely described in the literature, but few papers have reported the gender and age-based prevalence of these comorbidities [39]. Similar to what has been previously reported, our data showed that they are more common in males than females, with allergic rhinitis being the most common and eczema the least common [40-44]. However, there was no statistically significant association observed between asthma comorbidities and gender. These comorbidities are more common in the asthmatic group aged more than 12 years old, but to our knowledge, this relationship has not been published before and needs to be confirmed and justified.

Although no clear explanations have been found for the differences in occurrence and severity between the three studied age groups, most studies have attributed these changes to a complex mix of socioeconomic variables, differential access to resources (including diet and quality of air), comorbidities, and healthcare in developing compared to developed countries. Several etiologies have been theorized to explain gender differences in asthma prevalence. Anatomy and physiology differences, such as airway size, airway muscle bulk, airway reactivity, airway tone, and cough reflexes [45] have been proposed. Males and females have distinct asthma manifestations during childhood, linked back to fetal and postnatal lung development [46-48]. Mead initially documented dysanaptic lung development in 1980, a mismatch between the size of the airway tree and lungs in proportion to airway flow rates that was largely noticeable in males compared to females [49]. Moreover, Mortola *et al*. suggested that this dysanapsis may have implications on the efficiency of breathing since the size of the airways is the determinant of the amount of the dead space ventilation and of airflow resistance [50]. These qualities are also influenced by genetic differences between asthmatic males and females, such as changes in gene expression and epigenetic modifications [51-55].

In accordance with our findings, recent studies have shown that most of the patients reported being non-adherent to controller medications [56,57]. Sparse information is available on gender and age influencing compliance. Our study reveals that female sex and younger age at diagnosis are strongly associated with better corticosteroid adherence in children with asthma, as noted previously [58].

This study had a few limitations, including its retrospective nature and the relatively small number of children enrolled, which could have resulted in a selection bias that influenced our findings. Furthermore, several potentially confounding variables were not available in this study, including obesity, skin prick test (SPT), socioeconomic status, and pulmonary function testing (PFT). These findings may have been influenced by these data, which may also provide important areas for future research. Our study only included one center; we would recommend a multi-center study to obtain more conclusive results.

Conclusion

Gender plays a role in the development and outcome of asthma exacerbations in children of various ages. A better understanding of gender-based and age-based differences in asthma dictates a personalized approach to treatment. Asthma has a high prevalence, and new treatment strategies based on gender and age are required to adequately control patients with severe asthma. Personalized medicine has recently been linked to biological therapies for asthma.

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