Original Article

Risk factors and characteristics of early-onset asthma in Taiwanese children

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Background and Purpose: Early-onset asthma has been reported to be associated with a family history of allergy and exposure to environmental factors. This study was designed to evaluate the relationship between age of onset of asthma and genetic and environmental factors with asthma severity in Taiwanese children.
Methods: A group of 352 children with asthma (220 males and 132 females), ranging in age from 5 to 15 years, were enrolled in this study. The subjects were divided into 2 groups: early-onset asthma (up to and including age 3) and late-onset asthma. General characteristics including family history of allergies and exposure to domestic pets and tobacco smoke were recorded. The subjects underwent pulmonary function testing and analysis of serum immunoglobulin E (IgE), eosinophil counts, and specific IgE for common allergens.
Results: Early-onset asthma was present in 149 subjects and late-onset asthma in 203. Family history of allergies included a sibling with asthma or urticaria predisposed to early-onset asthma (asthma, p=0.034; urticaria, p=0.024). Food and milk allergen sensitization were more common in early-onset asthma (food allergens, p=0.025; milk, p=0.034). Children with early-onset asthma had higher eosinophil counts (p=0.041). However, there was no correlation between age at onset and pulmonary function testing, the levels of total IgE and IgE specific for *Dermatophagoides pteronyssinus* or *Dermatophagoides farinae*.
Conclusions: A history of asthma or urticaria in a sibling is a risk factor for early-onset asthma. A greater prevalence of food allergen sensitization and high eosinophil counts are characteristic of early-onset disease.

Key words: Age of onset, asthma, disease susceptibility, risk factors, urticaria

Introduction

Asthma is the most common chronic illness among children in Taiwan. Over the past decades, the prevalence of asthma has been rising steadily, from 1.3% in 7-to-15-year-old children in Taipei in 1974 to 5.07% in 1985 and 10.79% in 1995 [1-3]. Asthma is almost certainly influenced by a multifactorial etiology that includes both genetic and environmental factors [4]. Evidence indicates that more than half the cases of persistent asthma start before the age of 3 years [5]. Early-onset asthma has been reported to be associated with a family history of allergy and smoke exposure [6,7]. However, the relationship between asthma and having pets is not as clear. Early- and late-onset asthma may simply represent differing manifestations of the same childhood asthma phenotype. Previous studies have produced conflicting results in terms of outcome in early- versus late-onset asthma. A few studies have reported a worse outcome in early-onset disease [8,9], some a better outcome [10,11], and some no difference at all [12,13].

Little information has been published about early-onset childhood asthma in Taiwan. We designed a cross-sectional study to examine the relationship between age at onset of asthma and genetic and environmental factors, pulmonary function, and atopic markers.

Methods

Study groups

We studied 352 children aged 5 to 15 years who were diagnosed with asthma in the outpatient clinic of Mackay Memorial Hospital from March 2004 to October 2004. The study was approved by the institutional review

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board of the hospital, and informed consent for participation was obtained from all the legally responsible representatives. The diagnosis of asthma was made according to the American Thoracic Society standards [14]. General characteristics including age, sex, age at onset, history of allergies in parents or siblings, and exposure to domestic pets and tobacco smoke were obtained from medical records and a questionnaire completed by the subjects and their parents. All interviews were conducted by trained pediatricians. The subjects were divided into 2 groups: early-onset asthma (up to and including age 3) and late-onset asthma (after age 3). Evaluation consisted of pulmonary function tests and analysis of serum immunoglobulin E (IgE), eosinophil counts, and specific IgE for 8 allergens commonly tested in Taiwan (*Dermatophagoides pteronyssinus* [Dp], *Dermatophagoides farinae* [Df], cat, dog, cockroach, egg white, milk, and fish).

Definitions
Age of onset
Asthma is more likely to be underdiagnosed than overdiagnosed [15], and the diagnosis is likely to be delayed. To overcome this problem of ascertainment, the age of onset was based on responses to the following questions: (1) When did the child first have an asthma attack? (2) When did the child begin experiencing episodes of shortness of breath with wheezing? (3) When did the child first experience wheezing, chest tightness, cough, and breathlessness in any of the following situations: at rest, at night, with exertion, with emotional stress, with exposure to cold air, with chest infections, or a head cold? (4) When did the child begin experiencing wheezing after exposure to dust, fumes, molds, pollen, food, pets, or drugs? The earliest age reported in answer to any of the questions was regarded as the age of onset.

Total IgE and specific IgE antibodies
Serum total IgE concentration was determined by the immulite chemiluminescent immunoassay system (Diagnostic Products Corporation, Los Angeles, CA, USA). Specific IgE antibodies to Dp, Df, cat dander, dog dander, cockroach, egg white, milk, and fish were measured using the CAP system (Pharmacia, Uppsala, Sweden). Specific IgE levels ≥0.7 kU/mL were considered positive. If the levels of specific IgE were over 100 IU/mL, further dilution was performed to ascertain precise values. Aerogens and food allergens were further compared within the 2 groups. We looked for a correlation between the number of allergens to which a child was sensitized and the age of onset.

Measurement of lung function
Pulmonary function testing was performed before bronchodilation in all participants using an automated spirometer (Model 2130; SensorMedics, Yorba Linda, CA, USA). A well-trained, full-time technologist performed all the procedures, and the children were trained to perform spirometry correctly. Values recorded included forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), FEV_1/FVC, forced expiratory flow rate over the middle 50% of the FVC ($FEF_{25\%-75\%}$), and peak expiratory flow rate (PEFR). The values of FVC, FEV_1, $FEF_{25\%-75\%}$, and PEFR were expressed as percentage of predicted value and FEV_1/FVC as a percentage. Reference values were those reported by Quanjer et al [16] and Shyur et al [17].

Statistical analysis
Categorical variables (sex, family history, environmental factors, and allergen sensitization) were compared with age at onset using chi-squared analysis. Results of pulmonary function tests were normally distributed and compared using an unpaired *t* test, with data presented as mean ± standard deviation (SD). Continuous variables that were right skewed (levels of IgE, Dp, and Df) were log-transformed. Data with zero values were modified as follows: $y = \ln(x + 1)$, where x = the original data point and y = the modified data, which were then log-transformed. Variables that were left skewed (eosinophil counts) were square-root transformed. For presentation, log-transformed or square root-transformed means and SDs were reconverted to their original scale. All analyses were performed using the SAS (SAS Institute Inc., Cary, NC, USA) statistical analysis system. A *p* value of <0.05 was considered statistically significant.

Results

Subject characteristics
The 352 subjects included in our study comprised 220 males (62.5%) and 132 females (37.5%). The mean age was 7.80 ± 2.26 years. The severity of their asthma at the time of diagnosis is shown in Fig. 1. Early-onset asthma was reported by 149 (42.3%) subjects and late-onset asthma by 203 (57.7%) patients. Overall, the mean age at onset of asthma was 4.38 ± 2.55 years; for males it was 4.60 ± 2.75 years and for females 4.08 ± 2.13
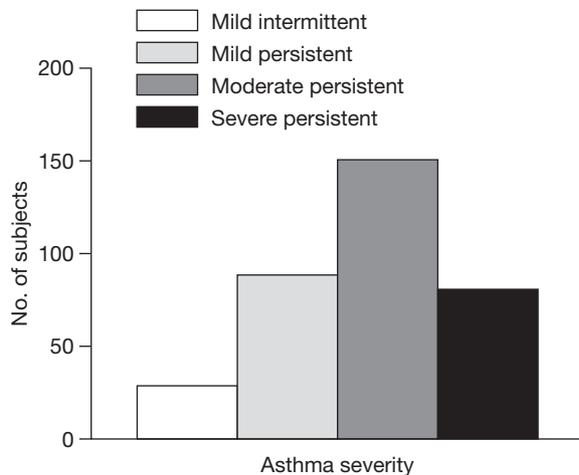
Fig. 1. Asthma severity in the study group at the time of diagnosis.

years (p=0.252). The mean age at onset was 2.15 ± 0.76 years and 6.02 ± 2.13 years in the early-onset group and late-onset group, respectively. Subjects in the late-onset group were significantly older (8.06 ± 2.47 years) than those in the early-onset group (7.46 ± 1.90 years) [p=0.005].

Relationship between age at onset and family history

Individuals with siblings who had asthma were 1.85 times (p=0.034) more likely to have early-onset asthma, while those whose siblings had urticaria were 3.6 times (p=0.024) more likely to have early-onset asthma (Table 1). The mean age of onset was significantly lower for those with a sibling with asthma as compared to those without a sibling with asthma (3.74 ± 2.22 vs 4.57 ± 2.61 years, p=0.025) or urticaria (2.93 ± 1.27 vs 4.50 ± 2.60 years, p=0.038). A history of allergic rhinitis in a sibling was unrelated to the age of onset (Table 1). An unexpected finding was that a parental history of allergy had no association with the age of onset of asthma in a child (Table 1).

Relationship between the age at onset and environment

In all, 183 subjects (54.3%) were exposed to environmental tobacco smoke. Among these subjects, 82% reported paternal smoking, in contrast to 2.1% who reported maternal smoking. The remaining subjects were exposed to smoking by regular household visitors or other adult household members. Children with early-onset asthma had experienced a greater extent of exposure to environmental smoke, particularly because of their fathers' smoking habits; however, the differences between the early- and late-onset groups were not statistically significant (Table 1). Subjects exposed to maternal smoking had a significantly later age of onset (7.50 ± 3.10 vs 4.39 ± 2.55 years, p=0.037).

Table 1. Analysis of possible genetic and environmental risk factors for early-onset asthma

Factor	Prevalence		p
	Early-onset No. (%)	Late-onset No. (%)	
Family history			
Paternal asthma	20/142 (14.1)	20/198 (10.1)	0.261
Maternal asthma	22/142 (15.5)	21/198 (10.6)	0.181
Sibling asthma	31/142 (21.8)	26/198 (13.1)	0.034[a]
Paternal allergic rhinitis	33/142 (23.2)	61/195 (30.8)	0.104
Maternal allergic rhinitis	38/142 (26.7)	49/196 (25.0)	0.715
Sibling allergic rhinitis	40/142 (28.8)	55/196 (28.1)	0.983
Paternal urticaria	14/128 (9.8)	14/194 (7.2)	0.387
Maternal urticaria	15/127 (11.8)	16/194 (8.2)	0.469
Sibling urticaria	10/142 (7.0)	4/194 (2.1)	0.024[a]
Environment			
Environmental smoke exposure	83/142 (58.4)	100/195 (51.3)	0.192
Paternal smoking	71/142 (50.0)	81/195 (41.5)	0.123
Maternal smoking	0/142 (0.0)	4/195 (2.1)	0.141
Pet	18/142 (12.7)	35/194 (18.0)	0.183
Cat	4/142 (2.8)	10/194 (5.2)	0.166
Dog	8/142 (5.6)	19/194 (9.8)	0.166

[a]Statistically significant.

Table 2. Allergen sensitization in early- and late-onset asthma

Sensitization	Prevalence		p
	Early-onset No. (%)	Late-onset No. (%)	
Sensitization to common allergens[a]	91/122 (74.6)	118/177 (66.7)	0.162
Sensitization to aeroallergens[b]	90/122 (73.8)	122/177 (68.9)	0.365
Sensitization to food allergens[c]	15/122 (12.3)	9/177 (5.1)	0.025[d]
Number of sensitizations			0.493
0	31/122 (25.4)	58/177 (32.8)	
1	4/122 (3.3)	7/177 (4.0)	
2	61/122 (50.0)	81/177 (45.8)	
≥3	26/122 (21.3)	31/177 (16.9)	
Sensitization to			
Dp	86/122 (70.4)	113/177 (63.8)	0.231
Df	87/122 (71.3)	114/177 (64.4)	0.211
Cockroach	16/122 (13.1)	17/177 (5.1)	0.341
Cat	5/122 (4.1)	10/177 (5.7)	0.546
Dog	3/122 (2.4)	9/177 (5.1)	0.585
Egg white	2/122 (1.6)	2/177 (1.1)	1.000
Milk	9/122 (7.4)	4/177 (2.3)	0.034[a]
Fish	2/122 (1.6)	1/177 (0.5)	0.745

[a]Levels of specific immunoglobulin E (IgE) antibodies ≥0.7 kU/mL to at least one common allergen (aeroallergens: *Dermatophagoides pteronyssinus* (Dp), *Dermatophagoides farinae* (Df), cockroach, cat, dog; food allergens: egg white, milk and fish).
[b]Levels of specific IgE antibodies ≥0.7 kU/mL to at least one aeroallergen.
[c]Levels of specific IgE antibodies ≥0.7 kU/mL to at least one food allergen.
[d]Statistically significant.

Of the enrolled subjects, 15.7% owned pets, including dogs, cats, birds, or rodents. A lower rate of pet ownership was found in subjects with early-onset asthma, but the difference was not significant (Table 1). The age of onset of those owning pets was not significantly greater than that of those without pets (any pet, 4.96 ± 2.95 vs 4.31 ± 2.48 years, p=0.228; dogs, 5.37 ± 3.34 vs 4.33 ± 2.48 years, p=0.186; cats, 5.00 ± 2.63 vs 4.39 ± 2.56 years, p=0.304).

Relationship between age at onset and atopic markers
The most common allergens to which children were sensitized were the house dust mites Dp (66.5%) and Df (67.2%), followed by cockroaches (11.0%), cat dander (5.0%), and dog dander (4.0%). As expected, a lower rate of food allergen sensitization was found in our subjects (egg white, 1.3%; milk, 4.3%; and fish, 1.0%). However, there was no association between the age of onset and any specific common allergen or the number of allergens the subject was sensitized to (Table 2). Among the food allergens, milk sensitization was more prevalent in children with early-onset asthma (Table 2). The relative risk for early-onset asthma in children sensitized to food was 2.6 times and that in

children sensitized to milk was 3.4 times greater than for those children without such sensitizations. However, there was no correlation between early-onset asthma and aeroallergen sensitization (Table 2).

The mean eosinophil count in all subjects was 403.78 ± 343.47 cells/mm³. The mean levels of total IgE, and specific IgE for Dp and Df were 465.40 ± 795.41 IU/mL, 59.47 ± 119.72 kU/mL, and 50.11 ± 90.97 kU/mL, respectively. Subjects with early-onset asthma had higher eosinophil counts, but there was no significant correlation with total IgE or specific IgE for Dp and Df (Table 3). A few subjects who did not own pets were sensitized to cat (3.7%) or dog dander (2.3%). However, among those who owned cats, only 28.6% were sensitized to cat dander. Among dog owners, only 21.7% were sensitized to dog dander.

Relationship between age of onset and pulmonary function
The pulmonary function of the children enrolled in the study was well preserved (PEFR = 90.63% ± 20.27%; FEV_1 = 87.79% ± 19.15%; and FVC = 104.32% ± 16.01% of predicted value, FEV_1/FVC = 88.00% ± 8.34%,), except for $FEF_{25\%-75\%}$ (52.19% ± 19.35% of predicted value). Subjects with early-onset asthma

Table 3. Levels of atopic marker by age of onset

Atopic marker	Early-onset	Late-onset	p
Eosinophil (cells/mm^3)^a	453.67 ± 376.18	368.92 ± 315.06	0.041^c
IgE (IU/mL)^b	578.55 ± 1069.44	386.00 ± 516.59	0.122
Dp (kU/mL)^b	79.27 ± 160.66	45.87 ± 77.86	0.156
Df (kU/mL)^b	63.35 ± 117.74	41.00 ± 65.39	0.271

Abbreviations: IgE = immunoglobulin E; Dp = *Dermatophagoides pteronyssinus*; Df = *Dermatophagoides farinae*
^{a}Values are mean ± standard deviation (SD), reconverted from square root-transformed data back to original scale.
^{b}Values are mean ± SD, reconverted from log-transformed data back to original scale.
^{c}Statistically significant.

tended to have lower FEF$_{25\%-75\%}$ than children with late-onset disease, but the difference was not significant (p=0.076). No differences were observed in PEFR, FEV$_1$, FVC, and FEV$_1$/FVC between the 2 groups (Fig. 2).

Discussion

This cross-sectional study integrated the data from a detailed clinical questionnaire with extensive physiologic and laboratory examinations in a large number of children with asthma. The integrated approach suggests substantial differences between early- and late-onset asthma in childhood. These results support the concept that asthma is a disorder with a multifactorial pathogenesis and provide further evidence for differences between groups.

London et al used a cut-off age of 3 years to evaluate the influence of family history [6], similar to Kjellman and Hesselmar in their cohort study on early- and late-onset wheezing [8]. Here, we defined early-onset asthma as onset up to and including 3 years. Martinez reported that more than half the cases of persistent asthma start before the age of 3 years [5] as compared with 42.3% of subjects in our study. Childhood asthma is more prevalent among boys than girls [16]. This was true of our sample overall, but there was no sex predominance in our subjects with early-onset asthma (Table 1). The increased risk for boys has been attributed to increased airway tone, relatively narrow airways, and higher IgE levels [18-20]. Several studies have shown an association between early-onset asthma and a parental history of allergy [21], with a consistently stronger association with maternal allergy [22,23]. The differences in risk conferred by maternal versus paternal allergy might arise from preferential inheritance through the maternal line [24,25] or the perinatal environment [24,26]. Unexpectedly, our study did not show any
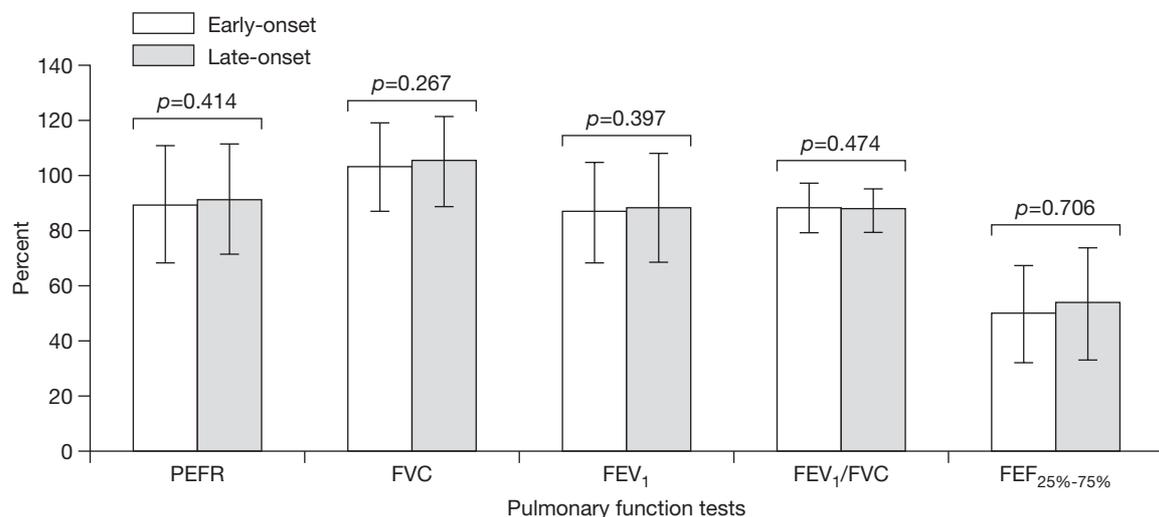

Fig. 2. Relationship between age at onset and pulmonary function tests, including peak expiratory flow rate (PEFR), forced vital capacity (FVC), forced expiratory volume in the first second (FEV$_1$), forced expiratory flow rate over the middle 50% of the FVC (FEF$_{25\%-75\%}$; percent of predicted value), and FEV$_1$/FVC. There were no significant differences between the 2 groups, although FEF$_{25\%-75\%}$ tended to be lower in the early-onset group.

correlation between the parents' history and age of asthma onset in the children (Table 1). London et al stated that asthma in a sibling was strongly associated with early-onset persistent asthma [6]. Kurukulaaratchy et al found sibling and maternal asthma and maternal urticaria to be significant risk factors for early-onset persistent wheezing [27]. In our study, asthma or urticaria in a sibling was a risk factor for early-onset asthma (Table 1). This could be consistent with shared early-life environmental factors or the interaction of genetics and the early environment. The stronger association with sibling rather than with parental allergy suggests that early environmental exposure along with a genetic predisposition may facilitate earlier symptom onset.

The evidence for aggravation of asthma in children by environmental tobacco smoke exposure is strong, with some authors stating that passive smoking is the most important environmental factor in the etiology of early asthma [28]. Maternal smoking has been found to have a stronger correlation with children's respiratory dysfunction than paternal smoking [28], and there is evidence that maternal smoking increases the risk of early-onset persistent asthma [5]. Maternal smoking during pregnancy is indisputably linked to fetal growth retardation and a decrease in lung function in newborn and school-aged children [6]. Passive smoke exposure may have similar effects [6]. Environmental smoke exposure and paternal smoking were more prevalent in our early- than in the late-onset group, but the differences were not significant (Table 1). Maternal smoking in early-onset asthma was not more prevalent (Table 1) and, in fact, the age of onset for those exposed to maternal smoking was greater. This discrepancy with other studies may be because of the very low prevalence of maternal smoking (1.2%) in our study population.

Whether avoidance of pet allergens early in infancy and childhood can prevent specific allergic sensitization or reduce the risk of allergic airway disease remains controversial [29-32]. Indeed, there is some evidence that early exposure to dogs and cats may prevent the development of asthma-like symptoms and allergic sensitization [30-32]. This might explain the finding that nearly three-quarters to four-fifths of our subjects with cats or dogs were not sensitized to those particular danders. Arbes et al detected pet allergens in a variety of public places and suggested that it is this type of low-dose exposure that appears to maintain clinical allergy and sensitization [33]. This could explain our finding of sensitization in subjects without pets. Although the result

did not show statistical significance, Kurukulaaratchy et al found that early exposure to a cat seemed to reduce the risk of early-onset persistent wheezing [27]. In our study, the risk of early-onset asthma was not significantly decreased by pet ownership (Table 1).

The skin prick test has been widely used to detect sensitization in previous studies. Feger at al reported a high sensitivity (79%) and specificity (90%) for the CAP system using results of skin prick tests as the standard [34]. We used the CAP system to determine serum specific IgE in our study. The high prevalence of sensitization (69.9%) to common allergens in our subjects supports the idea that allergies play a major role in childhood asthma [35]. More than half the children who are sensitized to aeroallergens and food allergens early in life develop asthma at a later age [36, 37], although the onset of asthma after sensitization may be delayed for 3 or more years [38]. Food allergies in infancy also correlate strongly with early-onset persistent wheezing [27]. In our subjects, milk sensitization was a significant risk factor in the early-onset group (Table 2). Transient sensitization and clinical allergies to basic foodstuffs develop mostly during infancy and generally disappear after a few years [39].

The low rate of sensitization to food allergens (8%) in our subjects might be consistent with the early development of lasting tolerance to such allergens [39]. Food allergen sensitization may be a presentation for early-onset asthma and an etiology of persistent symptoms. Tolerance to inhaled allergens develops only in a few subjects from childhood to adulthood [39], which may explain the high prevalence of aeroallergen sensitization (68.9%) in our subjects. Martinez et al reported that children with early persistent wheezing, i.e., before the age of 3 years, were as frequently sensitized to common aeroallergens as were those with late-onset wheezing [40]. We found no difference in the prevalence of aeroallergen sensitization between our subjects with early- and late-onset asthma (Table 2).

Although serum IgE levels and eosinophil counts are not diagnostic of asthma, both are biomarkers of atopy. Eosinophilia is common in allergic asthma [39]. In childhood, IgE levels depend on age, genetic background, and environmental factors such as allergen exposure and parasitic disease [18]. The findings of supranormal IgE levels and eosinophil counts in our children with asthma are consistent with other studies. Significantly higher eosinophil counts in early-onset asthma indicate more severe allergic responses (Table 3). However, levels of specific IgE for the common

allergens Dp and Df were not correlated with the age of onset of asthma in our series (Table 3) or in the study by Tang et al [41].

No consistent relationship has been found between age of onset of asthma and prognosis, with most studies showing no correlation with disease onset in childhood [42]. Nevertheless, some studies have reported that development of symptoms of allergy in the first 3 years of life is associated with more severe asthma and impaired pulmonary function at an older age [40]. Another study showed that patients with late-onset asthma tended to have lower FVC and FEV_1 [43]. The FEV_1, FVC, and FEV_1/FVC were not correlated with age of onset in our subjects (Fig. 2), while the $FEF_{25\%-75\%}$ was marginally lower, although not to a significant extent, in early-onset than in late-onset disease (p=0.076). The data suggest that the deficit is based not on poorer initial lung function in early-onset asthma but may rather reflect the effects of the chronic inflammatory process on the small airways. Merkus et al showed that total lung capacity (TLC) and FVC are greater than normal in subjects who had childhood asthma [44]. FEV_1 would be expected to be lower in an individual who had a small TLC for stature as compared with someone with a large TLC. Alternatively, when patients have supranormal lung volumes, a "normal" FEV_1 may still indicate enhanced bronchomotor tone. The explanation for this could be developmental change rather than a destructive or degenerative change. Hyperinflation during early childhood — the period of alveolar growth and multiplication — may stretch the alveolar tissue, with subsequent normal growth adding to an already expanded lung volume [44]. This could explain the normal FEV_1 and higher FVC in our subjects and the similarity of results in children with early- and late-onset asthma (Fig. 2). Another possible physiologic explanation for these findings may be the marked increase in pulmonary ventilation (minute volume) with activity that approaches peak levels during the ages of 6-14 years [43]. The markedly abnormal $FEF_{25\%-75\%}$ in our subjects further supports the suggestion by others that $FEF_{25\%-75\%}$ is a more sensitive assessment of asthma in children than other pulmonary function parameters [45].

In conclusion, this report reveals that asthmatic children with siblings with asthma or urticaria are predisposed to early-onset asthma. The early life environment plays a major role in the age of onset along with genetic predisposition. Food and milk allergen sensitization also appears to be a presentation of early-onset asthma. Higher eosinophil counts represent more severe allergic responses in children with early-onset asthma. Although not statistically significant, the tendency toward a lower $FEF_{25\%-75\%}$ in early-onset asthma suggests the effects of chronic inflammation on the small airways are clinically relevant in these subjects.

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