

Distinguishing severe asthma phenotypes: Role of age at onset and eosinophilic inflammation

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Background: Asthma is a heterogeneous process, yet little is understood regarding phenotypes.

Objective: To determine whether phenotypic differences exist between early-onset, severe asthma as compared with late-onset disease and whether the presence or absence of eosinophilia influences the phenotypes.

Methods: Cross-sectional analysis of integrated clinical, physiologic, and pathologic data collected from 80 subjects with severe asthma. Subjects were divided into those with asthma onset before age 12 years ($n = 50$) versus after age 12 ($n = 30$) and by the presence or absence of lung eosinophils.

Results: Subjects with early-onset, severe asthma had significantly more allergen sensitivity (skin test positivity, 98% vs 76%, $P < .007$) and more allergic symptoms (P values all $\leq .02$) than subjects with late-onset asthma. In contrast, subjects with late-onset asthma had lower lung function (P values = .05 to .07) than early-onset, despite a shorter ($P < .0001$) duration of illness. Both groups had a high degree of general asthma symptoms, but those with persistent eosinophils from either age at onset group had significantly more (multiple P values $< .05$). Similarly, the presence of eosinophils in either age at onset group was associated with the lowest lung function ($P \leq .02$). Although late-onset asthma was associated with the highest numbers of lung eosinophils ($P < .007$), only early-onset severe asthma was associated with a lymphocytic/mast cell inflammatory process. Finally, subjects with late-onset asthma without eosinophils had no subepithelial basement membrane thickening, suggesting a different pathologic process.

Conclusions: Differentiating severe asthma by age at onset and presence or absence of eosinophils identifies phenotypes of asthma, which could benefit subsequent genetic and therapeutic studies. (*J Allergy Clin Immunol* 2004;113:101-8.)

Key words: Asthma, phenotypes, allergy, inflammation, remodeling

Asthma has long been defined by the presence of reversible airflow limitation and/or bronchial hyperreactivity associated with appropriate asthma symptoms. More recently, an inflammatory component has been added to this definition.^{1,2} This definition of asthma probably is

Abbreviations used

BAL: Bronchoalveolar lavage
LT: Leukotriene
PPU: Pulmonary physiology unit
SBM: Subepithelial basement membrane

broad enough to encompass more than a single disease. In fact, asthma has long been described as a heterogeneous grouping of syndromes, but little advancement has been made in understanding immunologic, physiologic, and pathologic differences among phenotypes.

Several approaches to defining phenotypes have been taken. One of the earliest was the differentiation of asthma into extrinsic (allergy-related) versus intrinsic (non-allergy-related) diseases.^{3,4} Intrinsic asthma has also been associated with adult-onset disease, with some data suggesting intrinsic asthma may have a more rapid decline in lung function than extrinsic asthma.^{5,6} However, recent pathologic studies have suggested little difference at an immunopathologic level between “allergic” or “nonallergic” inflammation, and these terms have generally fallen out of use.⁷⁻⁹

Others have attempted to define phenotypes on the basis of pathophysiology. The presence or absence of eosinophils or neutrophils has been used to define groups with differing structural, physiologic, and therapeutic outcomes.¹⁰⁻¹⁴ Others have described physiologic groups such as patients with “brittle asthma,” who have more rapid development of airway obstruction than other patients with asthma, or who vary from day to day more than others.^{15,16}

No studies to date have integrated the natural history and clinical and immunopathophysiologic outcomes to better define phenotypes. However, as interest grows in genetic approaches to asthma, it is of paramount importance to evaluate genetic information in the light of well-defined phenotypes.¹⁷ This study hypothesized that patients with severe asthma who had the disease early in life would have a different immunologic phenotype from those who had it later in life. In contrast, eosinophilic inflammation could be seen in both groups. Therefore, the integrated data bases, including 80 subjects with severe asthma studied at National Jewish over the last 5 years, were evaluated for differences in atopy and allergic responses, symptoms, physiology, and pathology from the perspective of early- versus late-onset disease, and the presence and absence of eosinophilic inflammation.

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METHODS

Subjects with severe asthma were defined as previously described.¹¹ These were patients referred to National Jewish for evaluation of refractory asthma, who were still symptomatic, requiring daily short-acting β -agonists, despite therapy with high-dose inhaled or oral steroids (at least 50% of previous year), and the addition of long-acting β -agonists and/or leukotriene-modulating drugs. For full details please see the Journal's Online Repository at www.mosby.com/jaci. In the interest of limiting the amount and complexity of the data presented, comparisons of severe asthma with milder asthma or normal subjects are not reported. However, for much of the physiology and pathology data shown here, comparisons with these control groups have been previously reported.¹¹

Subjects with severe asthma were divided into those with early-onset disease, defined as physician diagnosis before the age of 12 years, and late-onset disease, with physician diagnosis after the age of 12. Additionally, the subjects were classified as eosinophil positive (+) if their eosinophil numbers in tissue or bronchoalveolar lavage (BAL) exceeded twice the standard deviation of the mean reported in normal control subjects (>21 cells/mm² for EG2, >22 cells/mm² for BMK (+) eosinophils, $\geq 2\%$ for BAL eosinophils), as previously described.^{11,12} For further details on this classification, please see the Journal's Online Repository at www.mosby.com/jaci.

Sources of information

Beginning in 1997, subjects with severe asthma who were enrolled in studies at National Jewish completed an extensive questionnaire, including information on age at disease onset, family history, health care utilization, childhood history, exacerbating factors, current symptoms, and medication use. The questions included were (1) Does your asthma get worse when you are exposed to (a) house dust, (b) furry animals, or (c) seasonal pollens? (2) Does your asthma get worse when you are exposed to (a) tobacco smoke, (b) perfume, (c) cold air? (possible answers for both: never, some, most, or all of the time). (3) Do you have problems with (a) cough, (b) sputum, (c) chest tightness, (d) wheeze, (e) shortness of breath, (f) sleep (caused by asthma)? (possible answers: never, rarely, some, most, or all of the time). In addition, laboratory tests, including a complete blood count with differential, IgE level, urinary leukotriene (LT) E4 level,¹⁸ allergy skin testing, and extensive pulmonary function testing (performed in the clinical pulmonary physiology unit [PPU] at National Jewish) were collected. Allergy testing consisted of skin prick testing to >15 aeroallergens, including both indoor and outdoor. Because subjects lived in diverse geographic locations, allergy testing was customized to their geographic region. Pulmonary function testing was obtained before bronchodilator, by using the medication-withholding standards of the PPU. All subjects underwent bronchoscopy with endobronchial biopsy and BAL. Tissue for immunohistochemistry and lavage were processed as previously reported.¹¹ Tissue eosinophils (enumerated by BMK antibody [major basic protein]), macrophages, neutrophils, and mast cells (both tryptase [+] and chymase [+]) were measured by means of previously reported methods.¹¹ Airway remodeling was evaluated by measuring subepithelial basement membrane (SBM) thickness with collagen I antibody and cells (+) for TGF- β (pan isoforms). The information was stored in a JMP (SAS-based) format.

Not all tests were obtained on all subjects. All subjects had data on age at onset and tissue eosinophils. Questionnaire data were obtained from 75 subjects; spirometric data and skin test data were obtained on 70 total subjects. Tissue cell count data were available from 62 subjects, remodeling data from 68 subjects, and IgE from 61 subjects. Urinary LTE4 ($n = 36$) and PC20 ($n = 36$) were done on smaller subsets. All subjects who participated in these studies signed informed consent, including long-term use of their information, and all studies were approved by the National Jewish Institutional Review Board.

Statistics

Categoric variables (allergy symptoms, atopy, general symptoms) were compared by using χ^2 analysis. Pulmonary function tests were normally distributed and compared by t test, with data presented as mean $\pm$ SEM. Continuous variables that were right-skewed (cell counts, IgE, and urinary LTE4 levels) were log-transformed. Data with zero values were modified as $y = \ln(x + 1)$, where x = original data point and y = the modified data, which are then log-transformed. For presentation, log-transformed means and SEMs were reconverted to their original scale. Numbers in text or tables are log-transformed means, with upper and lower limits derived from the log-transformed SEMs, all of which have been reconverted back to the original scale. The logarithmic distribution of the data mandates that the SEMs are not equal, with the lower SEM being smaller than the higher SEM. A value of $P < .05$ was considered significant. All testing was done with a JMP program.¹⁹

RESULTS

Subject characteristics

Eighty subjects with severe asthma were entered into the data base. Fifty reported disease onset before age 12 years, whereas 30 reported onset after age 12. The mean age at onset in early-onset disease was 2.6 ± 1.0 years, whereas the late-onset group had a mean age at onset at 27 ± 1.3 years. As expected, subjects with early-onset disease had a significantly longer disease duration than those reporting late onset (26 ± 2 vs 14 ± 2 years, $P < .0001$). There was no difference in sex (56% and 59% female subjects, respectively) or smoking history in the two groups. No subjects had >5 -pack-year history of smoking. However, there were more blacks and Hispanics in the early-onset group than in the late-onset group (22% vs 14%) ($P = .047$). Subjects with late-onset asthma were also significantly older (42 ± 2 years old) as compared with early-onset (29 ± 2 years old) ($P < .0001$). All subjects had been or were currently taking long-acting β -agonists. Finally, there was no difference in oral steroid use ($26, 22$ to 31 mg/d prednisone or equivalent vs $27, 23$ to 31 mg/d, $P = .5$) or suppression of early morning cortisol between the two groups ($3.8, 2.9$ to 4.9 mg/dL vs $4.9, 3.8$ to 6.2 mg/dL, $P = .93$). Note that 25% of each group was not taking daily or every-other-day oral steroids. A secondary analysis of the subset of subjects taking oral steroids did not substantively change any of the results of the study.

Subjects with asthma were further divided by the presence or absence of eosinophils, using published criteria.¹¹ There were significantly more subjects with late-onset asthma (19 of 30) with persistent eosinophils than subjects with early-onset asthma (18 of 50) ($P = .007$). Similar to early- versus late-onset disease, there were no differences in oral steroid use or morning cortisol level.

Relation of age at onset/inflammation to allergic symptoms and allergen sensitization

Individuals with early-onset disease were significantly more likely to respond positively to the questions regarding wheezing to allergic triggers than were subjects with

late-onset asthma (Fig 1). More than 75% of those with early-onset asthma responded positively to wheezing “most or all of the time” to dust and pollens, whereas <40% of those with late-onset asthma responded at that level. In contrast to “allergen-specific” questions, there were no differences in response to nonspecific triggers such as tobacco smoke, perfume, and cold air (P values all $>.25$). Allergy skin test results also differentiated the groups. Allergen sensitization (≥ 1 [+] skin test reaction) was seen in 98% of subjects with early-onset, severe asthma but in only 76% of subjects with late-onset asthma ($P = .007$). Similar differences were seen for positive skin test results to indoor allergens ($P = .07$), whereas there were no differences for outdoor allergens ($P = .45$). In both groups, the percentage of subjects with allergen sensitization was always greater than the percentages of subjects reporting allergic symptoms. Finally, 40% of those with early-onset asthma had a history of current or past eczema, whereas only 4% of those with late-onset asthma had such a history ($P = .0007$). There was a trend to greater IgE levels in the early-onset group (early onset = 108, 84 to 138 IU/L; late onset = 56, 40 to 78 IU/L; $P = .12$). Division of these early- and late-onset groups into those with or without eosinophils did not further differentiate the allergic pattern (allergen sensitization, symptoms or IgE level).

Relation of age at onset/inflammation to general symptoms

There were no differences between subjects with early-onset and those with late-onset severe asthma in general asthma symptoms ($P > .24$ for every symptom), emergency room visits in the last year ($P = .28$), or history of intubations ($P = .64$). However, when dividing either subjects with early- or late-onset asthma into those with or without eosinophilic inflammation, the presence of eosinophils was associated with greater symptoms (Fig 2, *a* and *b*). For early-onset disease, the presence of eosinophilic inflammation was associated with greater reports of chest tightness, shortness of breath, and sleep disturbance, whereas the difference in wheeze was marginal ($P = .1$). Additionally, those with early-onset disease and eosinophilia had a higher percentage of patients with a history of intubation (56% vs 21%, $P = 0.02$). For late-onset disease, the association of worsened symptoms with eosinophilia was not as great as for early-onset disease. Although more symptoms were always seen in the eosinophilic subjects, greater symptoms were only present for wheezing, with chest tightness marginally higher in those with eosinophils ($P = .11$) (Fig 2, *b*). In contrast to early-onset disease, persistent eosinophilia was not associated with differing rates of intubation (31% vs 20%, $P = .56$). The degree of symptoms did not differ when comparing those with persistent eosinophilia in either early- or late-onset disease.

Relation of age at onset/inflammation to pulmonary function

Despite a significantly shorter reported duration of disease, subjects with late-onset, severe asthma had a

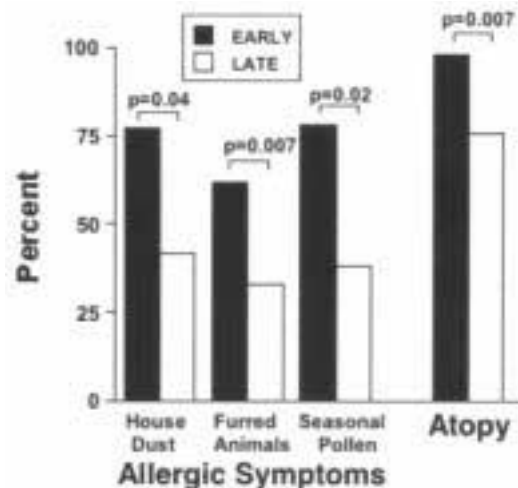


FIG 1. Allergic symptoms and allergen sensitization are higher in subjects with early-onset versus late-onset disease.

lower FVC (percent predicted) and tended to have a lower FEV₁ (percent predicted) than subjects with early-onset asthma (Table I). There were no differences in bronchodilator response, FEV₁/FVC, or PC20 between the groups.

In early-onset disease, the presence of eosinophils was associated with a lower FVC (percent predicted) ($68\% \pm 4\%$ vs $79\% \pm 3\%$, $P = .03$) when compared with those without eosinophils. There were no other pulmonary function differences, although outcomes were always numerically worse in those with eosinophils. In late-onset disease, the presence or absence of eosinophils was not associated with differences in pulmonary function. However, when pulmonary function was compared in those with or without eosinophils, without regard to age at onset, lower lung function was seen in those with eosinophils (FEV₁, $48\% \pm 3\%$ vs $58\% \pm 3\%$, $P = .03$; FVC, $66\% \pm 4\%$ vs $77\% \pm 3\%$, $P = .01$). No other lung function parameters were different.

Relation of age at onset/persistent eosinophilia to inflammatory and remodeling changes

As expected, based on percentage of subjects with persistent eosinophilia (see initial classification), late-onset, severe disease had a higher level of tissue eosinophilia as compared with early-onset disease (Table II). However, there were no differences in macrophages, neutrophils, or mast cells. In contrast to eosinophils, CD3(+) lymphocytes were higher in those with early-onset disease as compared with late-onset disease ($P = .05$). There were no differences in SBM thickness ($8.0, 7.6$ to $8.4 \mu\text{m}$ vs $7.0, 6.4$ to $7.7 \mu\text{m}$, $P = .15$) or TGF- β (+) cells ($24, 20$ to 29 cells/mm^2 vs $25, 20$ to 30 cells/mm^2 , $P = .95$) between the groups.

Urinary leukotriene E4 (LTE4) levels were 50% lower in early-onset than in late-onset asthma ($110, 98$ to 12 pg/mg vs $221, 174$ to $281 \text{ pg/mg creatinine}$) ($P = .009$).

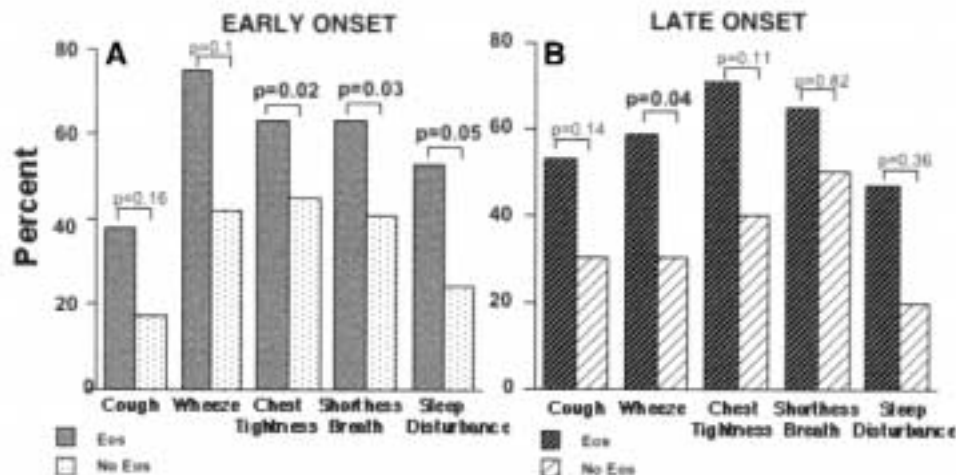


FIG 2. General asthma symptoms in subjects with early-onset (A) or late-onset (B) asthma are greater in those with eosinophilia.

TABLE I. Pulmonary function tests by age at onset

Group	FEV ₁ *	FVC*	FEV ₁ /FVC	% Change after bronchodilator	PC20†
Early	56 ± 3	76 ± 3	60 ± 2	27 ± 4	0.39(0.30-0.49)
Late	48 ± 4	66 ± 4	55 ± 2	31 ± 4	0.39(0.28-0.55)
P value	.07	.05	.11	.52	.96

*Percent predicted, mean ± SEM.

†Mean with upper and lower range of standard error, reconverted from log-transformed data back to original scale.

TABLE II. Tissue cell counts by age at onset

Group	Cell type/mm ² *				
	Eosinophils	CD3 cells	Macrophages	PMNs	Mast cells
Early	18 (15-22)	49 (38-63)	49 (43-57)	81 (68-98)	22 (18-27)
Late	40 (30-55)	20 (14-29)	45 (40-61)	49 (38-64)	20 (15-27)
P value	.05	.05	.07	.09	.80

*Values are means with upper and lower limits of standard errors, reconverted from log-transformed data back to original scale.

Persistent eosinophilia in early-onset disease was associated with a pattern of inflammation that included higher CD3 (+) lymphocytes, macrophages, tryptase, and chymase (+) mast cells than those without eosinophils (Fig 3). In early-onset/eosinophilic asthma, the ratio of chymase to tryptase (+) mast cells was nearly 100%. There were no differences in the SBM thickness, but TGF-β(+) cells were higher in those with eosinophils (Fig 4, a and b). Urinary LTE4 tended to be low in early-onset disease, and there were no differences between the groups.

In contrast to early-onset disease, persistent tissue eosinophilia in late-onset asthma was not associated with any specific pattern of inflammation. There were no differences in CD3(+) lymphocytes, macrophages, neutrophils, tryptase, or chymase (+) cells between those with or without eosinophils (*P* values all >.25). There were no subjects with late-onset asthma with a high ratio of chymase/tryptase (+) mast cells. Subjects with late-onset asthma with eosinophils had a thicker SBM than those without (*P* = .008), whereas there were no differences in TGF-β(+) cells (Fig 4, A and B). Urinary LTE4 also did not differentiate the groups with or without eosinophils.

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A direct comparison of the pattern of inflammation in early-onset eosinophil (+) asthma with late-onset eosinophil (+) asthma further supported differences in the groups. Despite similar or lower numbers of eosinophils, early-onset eosinophilic asthma had greater numbers of airway CD3(+) cells (*P* = .003), tryptase (+) cells (*P* = .05), and chymase (+) mast cells (*P* = .05) than late-onset eosinophilic asthma (Fig 5). Additionally, urinary LTE4 levels were markedly lower in early-onset eosinophilic disease (110, 87 to 140 pg/mg Cr vs 270, 200 to 365 pg/mg Cr, *P* = .05).

DISCUSSION

This is the first study to integrate data from a detailed clinical questionnaire with extensive physiologic and pathologic data in a large number (*n* = 80) of asthmatic subjects with similar level of severity to evaluate pheno-

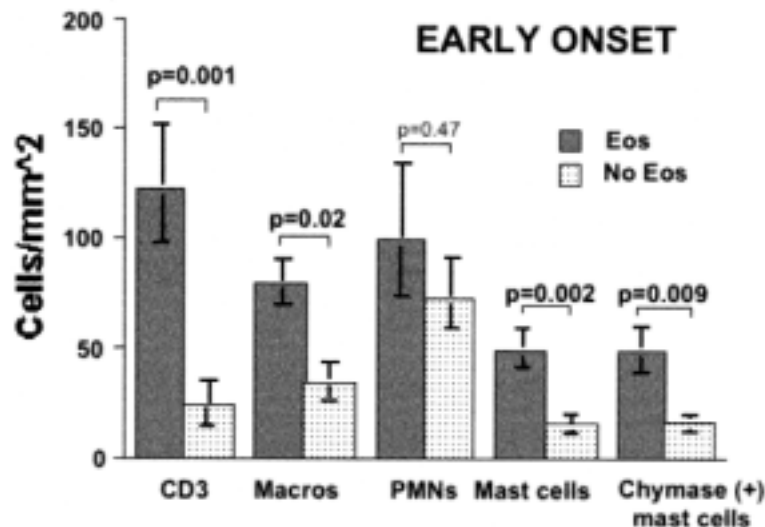


FIG 3. Eosinophilic inflammation in early-onset asthma is associated with increases in CD3 (+) cells, mast cells, and chymase (+) mast cells.

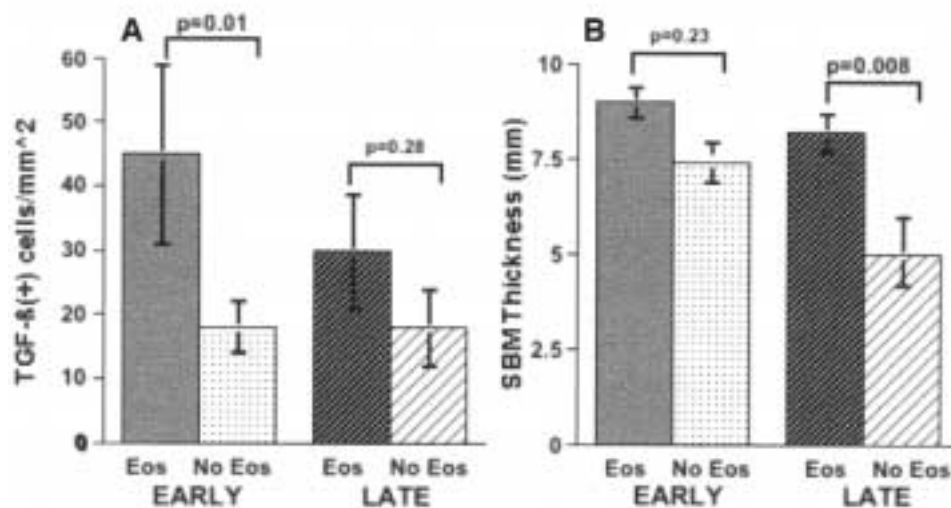


FIG 4. A, Eosinophilic inflammation in early-onset asthma is associated with increased TGF- β (+) cells. Eosinophils do not associate with differences in TGF- β (+) cells in late-onset asthma. **B,** Eosinophilic inflammation in early-onset asthma is not associated with differences in SBM thickness. The absence of eosinophilic inflammation in late-onset asthma is associated with a thinner SBM than late onset asthma with eosinophilia.

types. This integrated approach suggests substantial differences between severe asthma that develops early in childhood as compared with disease that develops in adolescence or beyond. These data support the original distinctions between extrinsic/atopic and intrinsic/nonatopic asthma³ but provide further evidence for differences between groups. In addition, these data suggest that mechanisms for late-onset asthma, immunologically and pathologically, may be distinct from those related to a classic allergic/ T_H2 paradigm.

For simplicity of presentation, this study was limited to subjects with severe, predominantly oral steroid-dependent asthma. These subjects were homogeneous at several lev-

els, including the degree of symptoms and health care utilization (mean of 3 emergency room visits in the last year for both groups) and high (and similar) use of medications. Therefore, a comparison across these subjects would seem justified. In the interest of limiting complexity, although similar patterns of disease appear to exist in milder asthma (at a lower level), those comparisons will be the subject of a follow-up study. However, at this time, these observations should only be applied to severe asthma.

Allergic responses by phenotype

Asthma has long been associated with an allergic process. However, a precise or practical definition for

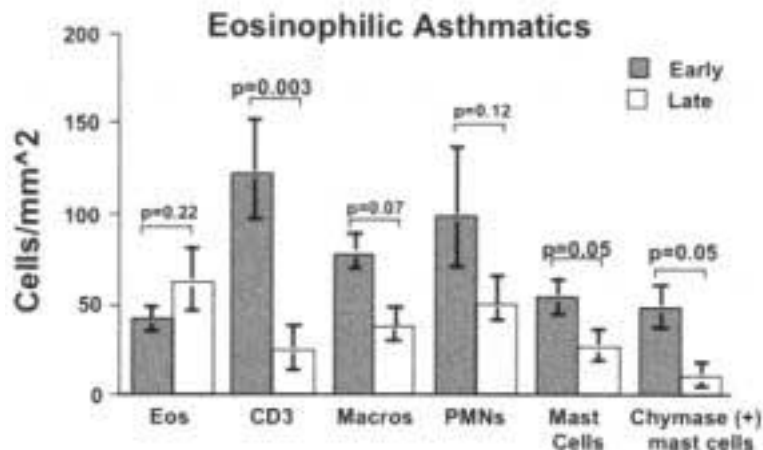


FIG 5. Eosinophilic inflammation in early-onset asthma is associated with greater CD3(+) cells, mast cells, and chymase positive mast cells as compared with late-onset asthma.

allergic asthma has been elusive. The definition has included clinical/allergic symptoms, allergy skin or radioabsorbant (RAST)-specific IgE testing, and occasionally, total serum IgE.²⁰ However, a recent study suggested considerable discordance between these parameters.^{21,22} As a surrogate for a more precise definition, early age at onset may reasonably define a group of asthmatic subjects in which allergic factors contribute to a large portion of their symptoms and disease. Fully 98% of early-onset severe asthma had evidence for allergen sensitization, whereas 76% of late-onset asthma had similar findings. Nearly 75% of those with early-onset asthma reported asthma symptoms in response to classic allergic triggers “most or all of the time,” which was significantly higher than in those with late-onset asthma. Although there was only a 25% difference in allergen sensitization between the two groups, the difference in allergic symptoms was closer to 50%, implying that allergen sensitization is less closely related to asthma symptoms in late-onset asthma. Although not significantly different, IgE levels in early-onset asthma were nearly twice those seen in late-onset disease. In distinction to allergic factors, the responses to nonspecific triggers (perfume, tobacco smoke, cold air) did not differentiate the groups. Finally, although the data suggest that early-onset disease defines a group with a very strong allergic component, the high degree of allergen sensitization and presence of allergic symptoms in ~35% of those with late-onset asthma implies that a portion of late-onset disease has a similar process.⁴

General asthma symptoms by phenotype

In contrast to allergic symptoms, age at onset did not associate with general asthma symptoms. However, similar to other reports, eosinophilia, when seen in either group, was strongly associated with higher levels of asthma symptoms, particularly chest tightness and wheezing.^{13,23} In addition, early-onset eosinophilic disease was associated with a higher percentage of subjects with a history of a near-fatal event.

Lung function by phenotype

Age at onset and presence of eosinophils were both associated with differences in lung function. Despite the reported duration of illness being significantly less in late-onset asthma, the FEV₁ and FVC were marginally lower in late-onset disease than in early. Whether this is due to a more rapid decline in lung function in late-onset disease or “recall bias” cannot be determined from this study; however, similar differences have been reported previously.^{4,5} The multiple differences between early-onset and late-onset asthma described in this study would argue for the former.

In addition to age at onset, lung eosinophilia was also associated with worsened lung function. Subjects with early-onset asthma with eosinophils had a lower FVC than those without, but no other significant differences were seen in either group. In contrast, and similar to reports with blood eosinophils, all asthmatic subjects with eosinophils (without regard to age at onset) had markedly and significantly lower values for FEV₁ and FVC than asthmatic subjects without eosinophils.²⁴ Unfortunately, this association of eosinophils with both airflow limitation and asthma symptoms cannot presume causality.²⁵ A study of the effects of targeted removal of the eosinophil in this population would be highly desirable.

Inflammation and phenotype

One of the most surprising results of this study was the different pattern of inflammation in early- and late-onset asthma, which became more pronounced when adjusting for the presence of eosinophils. First, and surprisingly, eosinophilic disease was more prominent in late-onset asthma than in early-onset, without difference in steroid treatment between the groups. Second, the pattern of inflammation associated with that eosinophilia was strikingly different in the two groups. In early-onset disease with eosinophilic inflammation, CD3(+) lymphocytes, mast cells, and chymase (+) mast cells were present in high numbers, consistent with a T_H2 pattern of inflam-

mation.²⁶⁻²⁸ In contrast, although the highest numbers of eosinophils were seen in late-onset disease, there was no evidence for an associated T_H2 pattern of inflammation, or, in fact, any other cellular inflammation. This lack of evidence for an associated lymphocytic (probably T_H2) process is contrary to published reports⁷⁻⁹ but consistent with the diminished clinical allergic/ T_H2 pattern seen in this group. This isolated increase in eosinophils may be due to a defect at the level of the eosinophil itself or perhaps in a resident cell, such as a fibroblast, smooth muscle, or epithelial cell. The finding of significantly higher urinary LTE4 levels (probably primarily from eosinophils) in late-onset disease, even when matched for numbers of eosinophils, could suggest the eosinophil itself may be different. A chromosomal abnormality, such as that recently described on chromosome 4q, could contribute to the late-onset hypereosinophilia, possibly through augmentation of a specific eosinophil clone.²⁹ Although it is also likely that this late-onset group is enhanced for aspirin-sensitive subjects, known to have high numbers of eosinophils and elevated LTE4 levels, questionnaire data alone were not adequate to identify an increase in this subset.

Another surprising pathologic result was that even in the absence of identifiable inflammation, subjects with severe asthma of early- or late-onset disease could have severe airflow limitation and a high degree of asthma symptoms at least 40% of the time. Although inflammation contributes to asthma severity, other, perhaps structural, factors may be important as well.³⁰ These observations suggest that previous investigations of steroid resistance, which have focused on the inability of steroids to suppress inflammation, may only be addressing the cause in a minority of the severe asthma population.³¹⁻³³ In the cases of subjects with eosinophil (-), early-onset asthma who remain symptomatic, it would appear that steroids have had the desired anti-inflammatory effect, and yet the severe asthma remains.

Finally, the data reported here suggest that late-onset asthma, without evidence for eosinophilic inflammation, may define yet another relatively distinct phenotype. These asthmatic subjects have minimal inflammation, the lowest mast cell numbers and, in contrast to early-onset asthma, have little evidence for some of the remodeling seen in the other phenotypes; specifically, there is no thickening of the SBM. It is possible that this group represents a disease that follows infection or gastroesophageal reflux, implying that effective treatment for this group is likely to be different from that for the other groups.³⁴

In conclusion, the data suggest that severe asthma can be separated into four phenotypes. Early-onset disease represents those asthmatic subjects with a strong allergic component. Those with early-onset asthma and eosinophils may have a diminished anti-inflammatory response to steroids (classic steroid resistance), whereas those without eosinophils have an appropriate anti-inflammatory response but are left with symptoms and physiologic changes resistant to steroid therapy. Late-onset asthma is often eosinophilic, with less evidence for

an allergic process or lymphocytic/mast cell component to the inflammation. Finally, late-onset asthma without eosinophilia may be a distinct disease. Differentiating asthma on the basis of onset of disease and presence of eosinophilia should enhance our ability to isolate genetic differences, understand pathophysiology, and ultimately improve approaches to therapy.

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