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Allergy, total serum immunoglobulin E, and airflow in children and adolescents in TENOR

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In children and adolescents with difficult-to-treat asthma, few data exist characterizing the relationships between basic patient characteristics (e.g., age, sex) and atopic indicators in asthma. These associations were examined in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR), an observational study of a large cohort of patients with severe or difficult-to-treat asthma. To characterize allergy patterns and the relationship between total serum immunoglobulin E (IgE) and airflow in young patients with severe or difficult-to-treat asthma. A total of 1261 patients from the TENOR study were stratified into four age groups at baseline (6–8, 9–11, 12–14, and 15–17 yr). The objective was to characterize allergy patterns and the relationship between total serum immunoglobulin E (IgE) and ratio of pre-bronchodilator forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC) in young patients with severe or difficult-to-treat asthma. The chi-square test for categorical variables and analysis of variance for continuous variables were used to identify significant differences among age groups. Multivariable linear regression was used to evaluate the association between IgE and FEV_1/FVC. Allergic rhinitis was reported in approximately two-thirds of patients. Up to 25% of patients had atopic dermatitis, which differed across age groups in boys ($p < 0.05$). Positive allergen skin test rate differed across age groups in boys ($p < 0.05$). Rates of asthma triggers were higher and differed across age groups in girls ($p < 0.05$), particularly around menarche (12–14 yr). IgE levels were higher in boys and differed across age groups in boys ($p < 0.01$) and girls ($p < 0.05$). IgE was associated with a lower FEV_1/FVC after adjusting for age and sex ($p < 0.01$). Severe or difficult-to-treat asthma in children and adolescents is characterized by high frequencies of comorbid allergic diseases, allergen sensitization, and high IgE levels. This burden is amplified by the association of more airflow limitation with higher IgE levels, suggesting the need for allergy evaluations.

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Over 9.9 million children and adolescents under the age of 18 in the United States (14% of this population) have at some time been diagnosed with asthma, and 6.8 million (9%) currently have this disorder (1). Asthma prevalence is approximately 30% higher for boys than for girls of the same age (1). Compared with non-asthmatic patients, those with asthma experience more limitations in daily activities, are more frequently absent from school, and use more medical resources (2, 3). The burden of asthma increases with increasing asthma severity (4, 5). A recent

analysis of data from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study, an observational study of a large cohort of patients with severe or difficult-to-treat asthma, demonstrated loss of lung function in children and adolescents and high rates of health care utilization, including emergency department visits, bursts of oral corticosteroid treatment, and intubation, despite treatment with ≥3 long-term controller medications (6).

Children and adolescents < 18 yr of age with severe or difficult-to-treat asthma are an understudied population. Data describing the patterns of age and sex with allergic indicators in asthma, such as allergic rhinitis, atopic dermatitis, asthma triggers, allergen skin test reactivity, and total serum immunoglobulin E (IgE) levels are lacking. In addition, the relationship between allergy and airflow in asthmatic children remains unclear.

In this analysis, we examined several measures of allergy and spirometry in young patients enrolled in the TENOR study (7). Our objective was to characterize the patterns of comorbid allergic disease, sensitization to allergens, and the relationship between total serum IgE levels and FEV_1/FVC in children and adolescents aged 6–17 years.

Methods

Study design and participants

The methods and baseline population characteristics of the children and adolescents in the TENOR study have been described previously (7). This prospective, observational 3-yr study was conducted in the United States in patients who were diagnosed with severe or difficult-to-treat asthma. No intervention was involved; the patients continued to receive asthma medications and other treatments as prescribed by their allergist or pulmonologist. The TENOR study design and protocol were approved by a central Institutional Review Board (IRB) and, when necessary, by the IRB at each site. All patients gave assent and their parents/guardians supplied written informed consent.

The TENOR study population comprised 4756 patients, ≥6 yr of age, with severe or difficult-to-treat asthma; patients with mild or moderate asthma were eligible for enrollment if their physician considered their asthma difficult-to-treat and they met the additional inclusion and exclusion criteria (7). Patients were selected for inclusion in the TENOR study if they (i) had received care from their health care provider for at least 12 months, (ii) were able to read and understand English, and (iii) had either high use of the health care system or high medication use in the past 12 months. High health care utilization was defined as requiring ≥2 unscheduled visits for asthma or ≥2 oral corticosteroid bursts for asthma. High medication use was defined as currently requiring ≥3 medications to control asthma or currently requiring long term, daily high doses of inhaled steroids or use of ≥5 mg/d of oral prednisone. Patients were excluded if they had a diagnosis of cystic fibrosis (7).

Data collection

Data were collected at semiannual study visits. Demographic and clinical data, including spirometry and total serum IgE, were collected. In addition, patients completed a self-administered questionnaire. For children < 12 yr of age, the parent or guardian was present to help answer interview questions and complete the questionnaires; if needed, adolescents could obtain assistance from a parent or other adult (6).

Asthma severity classification

TENOR study physicians subjectively categorized the severity of each patient's asthma as mild, moderate, or severe. In addition, the physicians reported whether their patient's asthma was considered difficult-to-treat based on specified parameters (i.e., complex treatment regimen, multiple drugs required, unable to avoid triggers, frequent exacerbations, severe exacerbations, and/or unresponsive to therapy).

Asthma control and medication adherence

Asthma control was assessed using the validated Asthma Therapy Assessment Questionnaire (ATAQ, 1997; Merck & Co., Inc., West Point, PA, USA). The ATAQ is a brief self-administered instrument that evaluates asthma symptoms and level of asthma control and provides a simple index of the number of asthma control problems (0 through 4). Medication adherence was measured using a proxy from the ATAQ, 'What best describes how you take this medicine now?'

Spirometry

Spirometry measurements in the TENOR study were taken according to American Thoracic Society guidelines (8). All sites were required to

have a certified spirometer that was calibrated daily (8). For this analysis, predicted values for spirometry measures were race-adjusted. Formulas of Hankinson et al. were applied for the predicted values of white, black, and Hispanic patients (9). About 5% of patients self-described as 'Asian' or 'other' did not have predicted spirometry values calculated but were included in the overall study.

Skin test, asthma triggers, and IgE

Skin test results and asthma triggers (including residential exposures) were self reported. Patients were asked whether they had ever had allergy skin tests, and if so, to describe the test results as positive or negative. Total serum IgE levels (IU/ml) were measured at baseline at each study site using any commercially available assay that met US Food and Drug Administration approval and was calibrated to the World Health Organization Second International Reference Preparation for Human Serum IgE (WHO IRP 75/502).

Statistical analysis

Because of the size of the TENOR study database, we were able to create four age strata, each containing an adequate number of patients to permit multiple age and sex comparisons within the cohort. Therefore, patients were assigned to one of four age groups for this analysis: 6–8, 9–11, 12–14, and 15–17 yr. This approach allowed the unique opportunity to consider the possible influence of growth and hormonal influences on the underlying allergic mechanisms in severe or difficult-to-treat asthma. The chi-square test for categorical variables and analysis of variance for continuous variables were used to identify significant differences between age groups by sex. Chi-square tests and *t*-tests were used for comparisons of boys and girls by age group. When possible, asthma trigger data were cross-referenced with residential exposure data to increase relevancy of these measures. This approach was possible for mold ($n = 356$) and animals ($n = 643$), and these data were analyzed as a unique subset of the total study population. Pearson correlation coefficients were generated to assess the relationship between total serum IgE levels and FEV_1/FVC. Multivariable linear regression was used to evaluate the association between total serum IgE levels and FEV_1/FVC, adjusting for age, sex, and race/ethnicity. All analyses were performed using SAS Version 9.1 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Demographic and atopic relationships by age

At baseline, 1261 of the 4756 (27%) patients enrolled in TENOR were aged 6–17 and therefore, eligible for inclusion in this analysis. Demographic and clinical characteristics of the study population are presented in Table 1. Among girls, race/ethnicity was significantly different across age groups (Table 1; $p < 0.001$), with a higher percentage of white girls observed in the 15–17-yr age group and the greatest proportion of black and Hispanic girls in the 9 to 11-yr age group. A history of allergic rhinitis was reported in approximately two-thirds of boys and girls and was consistent across age groups. A history of atopic dermatitis was reported in up to 25% of patients and differed among age groups in boys. The proportion of positive allergen skin tests was higher across age groups in boys ($p < 0.05$), reaching a high of 97% in 15 to 17-yr-olds. Similarly, the proportion of positive skin tests was higher in the older age groups in girls; however, the differences were non-significant. Generally, almost 90% of patients across all age and sex groups evidenced at least 1 asthma control problem and about 30% reported ≥3 asthma control problems, as measured by the Asthma Therapy Assessment Questionnaire. Asthma severity significantly differed across age groups among boys ($p < 0.001$). While asthma severity was greater across age groups in both sexes, the observation in girls did not achieve statistical significance. Medication adherence was consistently high across all age groups, with 81–89% of patients reporting taking their medication every day.

In general, rates for self-reported environmental and intrinsic asthma triggers were higher in girls than boys. The significant differences among age groups were observed for some triggers (exercise, cold or sinus infection, and dust; $p < 0.05$) for boys. For girls, the significant differences across age groups were observed for emotional stress; moldy, musty, or damp places; dust; animals; and pollen; $p < 0.05$). For these triggers, the elevated rates were observed, in particular, around menarche (12–14 yr; Fig. 1).

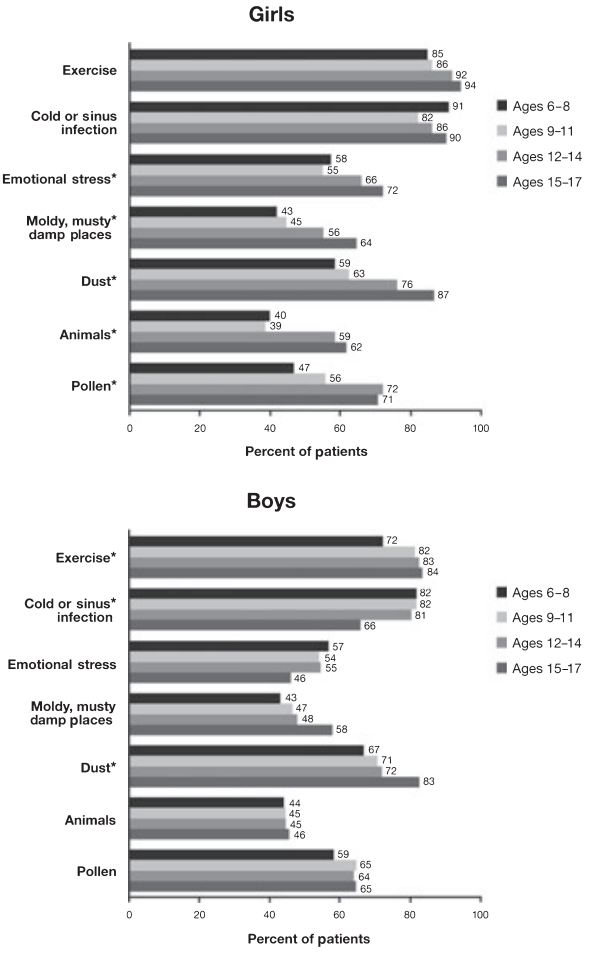
Relationship of serum IgE with age, triggers, and FEV_1/FVC

Total serum IgE levels were generally higher across age groups in both boys and girls, with the highest levels at 12–14 yr (Fig. 2). In boys, total serum IgE levels were higher than girls for the 9 to 11-yr and 15 to 17-yr age groups ($p < 0.01$).

Table 1. Demographic and clinical characteristics of patients at baseline

	Boys					Girls				
Age group, years	6–8 (n = 145)	9–11 (n = 282)	12–14 (n = 240)	15–17 (n = 124)	p Value	6–8 (n = 88)	9–11 (n = 120)	12–14 (n = 171)	15–17 (n = 91)	p Value
Race/ethnicity, n (%)										
White	87 (60)	165 (59)	141 (59)	76 (61)	NS vs. non-white	62 (70)	65 (54)	115 (67)	73 (80)	<0.001 vs. non-white
Black	38 (26)	70 (25)	69 (29)	31 (25)		17 (19)	33 (28)	39 (23)	11 (12)	
Hispanic	9 (6)	31 (11)	16 (7)	11 (9)		7 (8)	17 (14)	12 (7)	3 (3)	
Asian/Pacific Islander	3 (2)	3 (1)	3 (1)	1 (1)		1 (1)	1 (1)	3 (2)	0 (0)	
Other	8 (6)	13 (5)	11 (5)	5 (4)		1 (1)	4 (3)	2 (1)	4 (4)	
History of comorbid allergic diseases and skin tests with allergen, n (%)										
Allergic rhinitis	89 (61)	189 (67)	169 (70)	81 (65)	NS	54 (61)	68 (57)	109 (64)	59 (65)	NS
Atopic dermatitis	36 (25)	57 (20)	34 (14)	22 (18)	< 0.05	18 (20)	23 (19)	35 (20)	21 (23)	NS
Skin test result, n (%)										
Yes, negative	9 (11)	17 (10)	6 (4)	3 (3)	< 0.05	10 (19)	7 (11)	12 (12)	3 (5)	NS
Yes, positive	76 (89)	157 (90)	148 (96)	86 (97)		43 (81)	55 (89)	88 (88)	55 (95)	
Spirometry (Pre-bronchodilator)										
Mean FEV_1/FVC	80.7	77.4	75.6	72.8	< 0.001	83.9	81.3	78.9	76.8	<0.001
Mean $FEV_{1\%}$ predicted	100.4	86.8	81.3	81.5	< 0.001	98.4	86.6	86.7	81.9	<0.001
Asthma Therapy Assessment Questionnaire (ATAQ) control problems, n (%)										
0	5 (5)	17 (8)	22 (11)	10 (9)	NS	4 (6)	11 (12)	14 (10)	5 (6)	NS
1–2	75 (69)	127 (63)	122 (63)	75 (68)		35 (59)	55 (62)	84 (59)	51 (62)	
3+	29 (27)	58 (29)	50 (26)	26 (23)		23 (35)	23 (26)	45 (31)	26 (32)	
Physician-assessed asthma severity, n (%)										
Mild	8 (6)	17 (6)	8 (3)	6 (5)	< 0.001	4 (5)	4 (3)	9 (5)	2 (2)	NS
Moderate	88 (61)	164 (58)	133 (55)	45 (36)		55 (63)	71 (59)	90 (53)	42 (46)	
Severe	49 (34)	101 (36)	99 (41)	73 (59)		29 (33)	45 (38)	72 (42)	47 (52)	
Medication adherence, n (%)										
I take it every day	93 (89)	165 (86)	149 (83)	91 (87)	NS	54 (89)	68 (81)	118 (86)	69 (86)	NS
Some days I take it but others I don't	8 (8)	24 (13)	23 (13)	12 (11)		3 (5)	7 (8)	13 (9)	9 (11)	
I used to take it but now I don't	2 (2)	2 (1)	5 (3)	1 (1)		2 (3)	4 (5)	2 (1)	2 (3)	
I only take it when I have symptoms	2 (2)	1 (1)	3 (2)	1 (1)		2 (3)	5 (6)	4 (3)	0 (0)	
I never took it	0 (0)	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	1 (1)	0 (0)	

FEV_1, forced expiratory volume in one-second; FVC, forced vital capacity; NS, not significant.



*Differences among age groups are statistically significant at $p < 0.05$

Fig. 1. Self-reported asthma triggers by sex.

In girls, IgE levels were marginally lower between ages 12–14 yr and 15–17 yr ($p < 0.10$).

Significantly higher mean total IgE levels were observed in several age groups when dust, pollen, and the presence of animals were reported as triggers compared with patients not reporting such triggers (Fig. 3). This was not seen when mold was reported as a trigger.

Weak inverse relationships were noted between total serum IgE levels and pre-bronchodilator FEV_1/FVC values for both sexes and for most age groups (r values ranged from −0.07 to −0.29), except for the youngest age strata. In the entire cohort, after adjustments for age, sex, and race/ethnicity ($p < 0.001$), total serum IgE and FEV_1/FVC were inversely correlated. The predicted IgE for an average patient with an FEV_1/FVC of 70 or an FEV_1/FVC of 90 was 227 and 158, respectively, based on the multiple regression model.

Discussion

Children and adolescents with severe or difficult-to-treat asthma are an understudied population. With 1261 participants between the ages of 6 and 17 years, the TENOR cohort is the largest population of young patients with severe or difficult-to-treat asthma. We examined the relationships of age and sex with allergic comorbidities and total serum IgE levels with airflow in this cohort and observed a high rate of allergic rhinitis, atopic dermatitis, and sensitization to allergens, with patterns related to age and sex. The rate of self-reported environmental and intrinsic asthma triggers was higher in girls than boys and was highest around menarche. Total serum IgE levels, while higher overall in boys at all age groups, were highest during puberty in both boys and girls and lower thereafter, with the largest difference in girls. Additionally, elevated total serum IgE levels were seen in patients reporting dust, pollen, and animals as asthma triggers compared with patients who did not report them as asthma triggers. Higher total serum IgE levels were associated with lower pre-bronchodilator FEV_1/FVC, independent of age, sex, and race/ethnicity.

Patients enrolled in the TENOR study had primarily moderate (55%) or severe (41%) physician-assessed asthma. Other large asthma cohorts of >1000 patients of similar age studied children with only mild-to-moderate (10) or mild (11) asthma. Children and adolescents in the Childhood Asthma Management Program (CAMP) consisted of a cohort of 5 to 12-yr-olds with less severe asthma, with 52% having moderate asthma and 48% – mild asthma. Allergic manifestations in the CAMP patients were as frequent as in the TENOR study cohort, with 29% of patients having atopic dermatitis, 54% having allergic rhinitis, and 88% reporting sensitization to at least 1 allergen. Median IgE levels in the TENOR cohort, however, were higher than in the CAMP cohort (median 247 vs. 180 IU/ml, respectively), suggesting a more highly atopic population in the TENOR study (10, 12). The Steroid Treatment as Regular Therapy (START) trial studied children ($n = 1004$) between the ages of five and 10 with mild persistent asthma, but allergic features were not reported (11).

The IgE levels measured in the TENOR study cohort were similar to those reported by Wittig and colleagues who noted that school-aged children with asthma had total serum IgE levels as high as 305 IU/ml (13) and similar to previous reports showing that total serum IgE levels

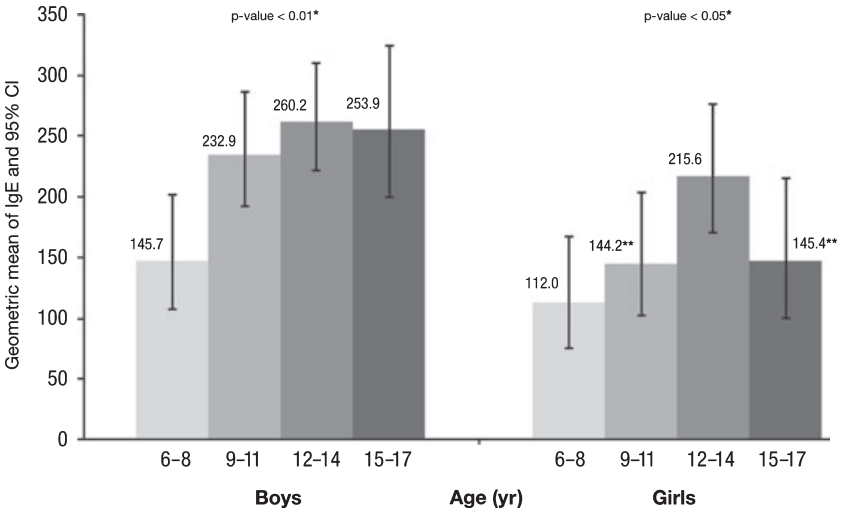


Fig. 2. Geometric means of total serum immunoglobulin E (IgE) levels and 95% confidence intervals (CI) by age and sex.

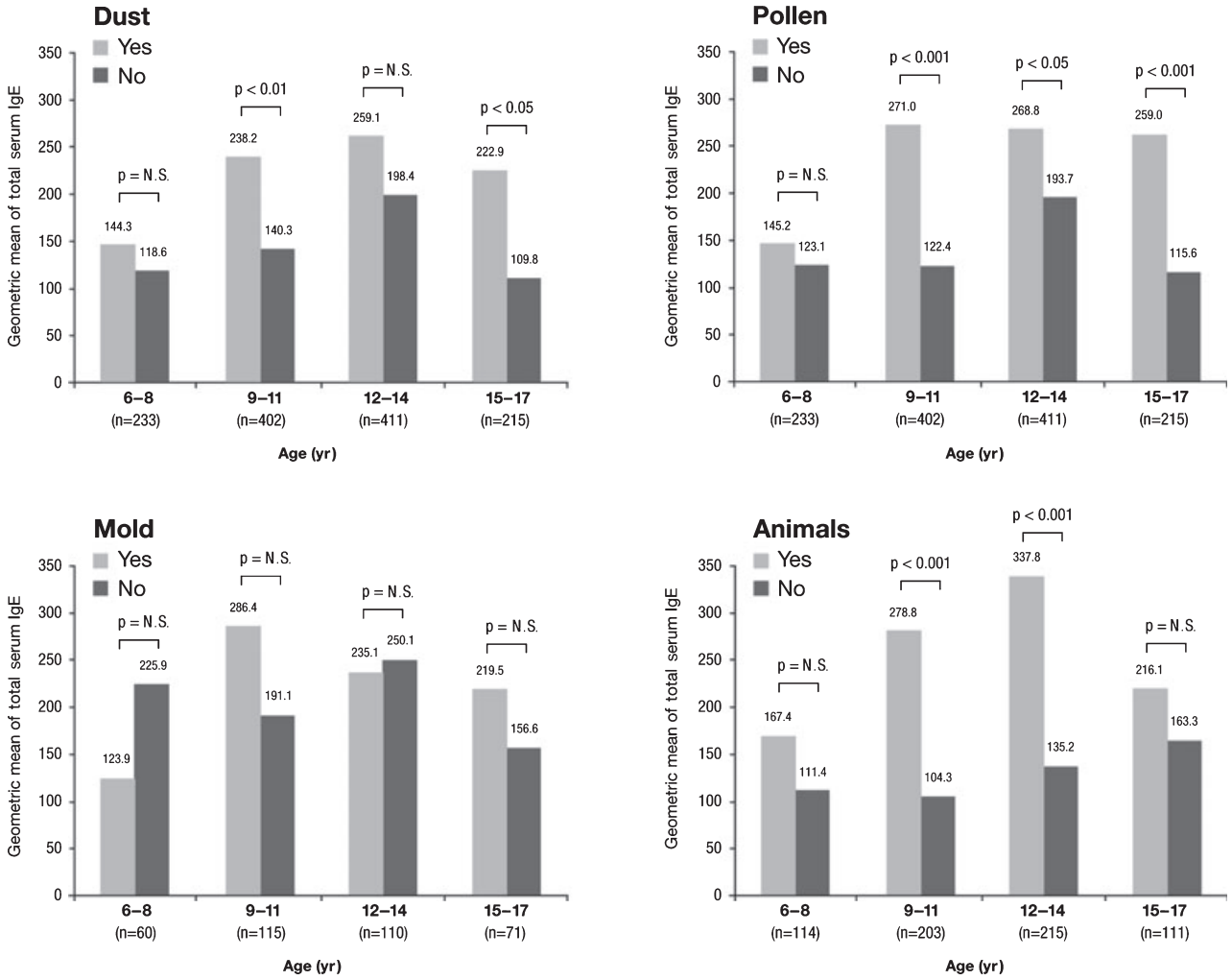


Fig. 3. Geometric mean of total serum immunoglobulin E (IgE) levels for patients self-reporting dust, mold, pollen, and animals as asthma triggers (Yes) and those who did not (No). NS = not significant; data for mold and animals based on self-reported exposure to these triggers in the home.

increase with age (14–16), peak between 8 and 15 yr, and decline in adults (13, 17–20). Our observation that total serum IgE levels were higher for boys across all age groups is consistent with previous cross-sectional (13, 21) and longitudinal (19, 22) studies that included children and

adolescents with asthma. Higher IgE levels in boys compared with girls have also been observed in the general population (13, 19).

Sex hormones appear to play an important role in the development of allergies and asthma. Previous reports have noted that the prevalence of asthma is higher in prepubescent boys than girls of a similar age, but in adolescence, the pattern changes and asthma becomes more prevalent in girls (23). Possible explanations for these sex differences include hormonal changes during puberty as well as responses to triggers such as emotional stress (24). IgE was also noted to be at or near its highest level in girls during the years marking the transition from childhood to adolescence, suggesting that sex hormones may play an important role in the development of the allergic immune response and asthma; however, this hypothesis awaits further study.

The relationship between IgE and airflow in children with asthma is poorly elucidated. The association of increased total serum IgE levels with asthma may reflect the fact that specific IgE-mediated allergic reactions contribute to asthma severity or the total serum IgE concentration mirrors the Th_2 cytokine milieu (interleukin-4 and interleukin-13) (25) that characterizes allergic inflammation. Elevated total serum IgE levels may also contribute indirectly to pulmonary inflammation. Peat and colleagues found a strong correlation between total serum IgE levels and airway hyperresponsiveness (AHR) (26), and others have reported a close association between total serum IgE levels, AHR, and reduced FEV_1/FVC when IgE was at least moderately elevated (27). After studying 562 eleven-year-olds with asthma, Sears et al. concluded that IgE has a major effect on lung function (28). Carroll et al. reported that young patients, 7–18 yr of age, with elevated total serum IgE levels had greater decrements in FEV_1 compared with those whose IgE was within the normal range (17). Other studies have reported that sensitization to ≥1 allergen was predictive of impaired pulmonary function (29–31). Conversely, Yang and colleagues observed no correlation between total serum IgE levels and lung function in 242 children (mean age 11.8) with clinically stable asthma regardless of atopy (32). Our findings support an association between higher total serum IgE levels and lower pre-bronchodilator FEV_1/FVC. In addition, the association was independent of age, sex, and race/ethnicity, suggesting that IgE may be a marker of asthma severity that adversely affects FEV_1.

It is unclear when the pathologic features of asthma first appear. Saglani suggests that the characteristic pathologic features of asthma develop in children between the ages of 1 and 3 and that by age 2, allergic mechanisms appear to drive the persistence of asthma (33). Data from the TENOR study suggest that airflow limitation in children with asthma may already be present as early as 6 yr of age. This supports data from the CAMP study, in which a significant reduction in percent predicted post-bronchodilator FEV_1 was observed in 26% of the 5 to 12-yr-old children with mild-to-moderate asthma followed for 4–6 yr (34). Among all children enrolled in the CAMP study, FEV_1/FVC gradually declined during the study, regardless of intervention (35). In a cross-sectional study, lung function impairment was associated with asthma duration in children and in adults with onset of asthma in childhood; however, there was no relationship between disease severity and asthma duration among those with adult-onset asthma (36). Although differences in methods and in clinical phenotypes of patients prevent a direct comparison of lung function values observed in these studies with those noted in the TENOR study cohort, these reports suggest that airflow limitation in patients with asthma is compromised at an early age.

The overall phenotype of the TENOR cohort is severe or difficult-to-treat asthma patients, rarely studied in such large numbers as in this study. This overall phenotype is likely composed of subgroups with subphenotypes which could be different by age, and in that manner, possibly responsible for at least some of the effect sizes of the differences by age. For example, it is possible that in the younger children, severity/control was being prominently driven by allergy-related issues and to the extent that total IgE reflects severity of allergy, those children demonstrated higher IgE levels. In contrast, it is possible that different elements were driving the severity/control issues in adolescents, such as compliance and psychological/social issues. Regardless of age, however, it is evident that early sensitization and exposure to allergens are major risk factors for persistent asthma (37–39).

Additional limitations of this analysis include that patients enrolled in the TENOR study represent a select population under the care of an asthma specialist. Many were using standard of care medications; therefore, this cohort might not represent the general asthma population. TENOR study data in this analysis are cross-sectional and thus provide a description of these patients at a single point in time. Medication compliance was based on a proxy measure from the self-reported ATAQ, introducing the

possibility for error or misclassification of these data. This analysis examined the relationship between total serum IgE levels and severe or difficult-to-treat asthma but does not provide information about specific IgE levels. In addition, total serum IgE levels were measured once at baseline, and any conclusions extrapolated from these data assume that these levels remained stable over time in this cohort. Previous analyses of the TENOR study data show that children and adolescents with severe asthma had higher total serum IgE levels than those with moderate or mild asthma (7). However, more detailed investigation into the relationship between IgE and asthma in the TENOR study is limited by the absence of a control group, the relatively few patients (4%) with mild asthma enrolled in this study, and the fact that skin test results were based on recall rather than actual measures.

Conclusion

In summary, this analysis of children and adolescents with severe or difficult-to-treat asthma demonstrated a high rate of allergy and allergic comorbidities that varied with age and sex. Self-reported rates of environmental and intrinsic asthma triggers were higher in girls, and total serum IgE levels were higher in boys, with the peak levels occurring near puberty for both sexes. Patients with higher total serum IgE levels had more airflow limitation. These data further support the concept that allergic mechanisms underlie severe or difficult-to-treat asthma in children and adolescents and underscore the need for evaluation of comorbid allergic diseases in this population.

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Conflict of Interest

T. Haselkorn is a paid consultant to Genentech, Inc. S.J. Szefler has consultant arrangements with AstraZeneca LP, Genentech, Inc., GlaxoSmithKline plc, MAP Pharmaceuticals, Inc., Merck & Co., Inc., Novartis Pharmaceuticals, Inc., Sanofi-aventis U.S. LLC, and Schering-Plough Corporation. F.E.R. Simons serves as a consultant to Genentech, Inc. on the TENOR project. R.S. Zeiger has consultant arrangements with Aerocrine AB, AstraZeneca LP, DBV Technologies, Dynavax Technologies Corporation, Genentech, Inc., GlaxoSmithKline plc, MedImmune LLC, Merck & Co., Inc., Novartis Pharmaceuticals, Inc., Sanofi-aventis U.S. LLC, and Schering-Plough Corporation; and has received grants/research support from AstraZeneca LP, Genentech, Inc., GlaxoSmithKline plc, Merck & Co., Inc., Sanofi-aventis U.S. LLC, Teva Pharmaceuticals Industries, Ltd., and the National Heart, Lung, and Blood Institute. D.R. Mink is employed by ICON Clinical Research, a company that receives funding from Genentech, Inc. B.E. Chipps has consultant arrangements with Alcon, Inc., AstraZeneca LP, Genentech, Inc., GlaxoSmithKline plc, MedPointe, Merck & Co., Inc., Novartis Pharmaceuticals, Inc., Sanofi-aventis U.S. LLC, Schering-Plough Corporation, and Sepracor Inc.; and receives grants/research support from Alcon, Inc., AstraZeneca LP, Genentech, Inc., GlaxoSmithKline plc, Merck & Co., Inc., Novartis Pharmaceuticals, Inc., Sanofi-aventis U.S. LLC, Schering-Plough Corporation, and Sepracor Inc. L. Borish has been a paid consultant for Genentech, Inc., and Novartis Pharmaceuticals Corporation; and is on the speakers' bureau for Merck & Co., Inc. D.A. Wong works for and owns stock in Genentech, Inc.

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