

RELATION BETWEEN AIRWAY RESPONSIVENESS AND SERUM IgE IN CHILDREN WITH ASTHMA AND IN APPARENTLY NORMAL CHILDREN

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Abstract Background. Although asthma diagnosed by a physician is known to be related to serum IgE levels, it is not known whether there is a relation between the level of IgE and airway hyperresponsiveness to a methacholine challenge. The characteristics of asymptomatic persons that predispose them to airway hyperresponsiveness are also unknown.

Methods. We studied the relation between the serum total IgE level and airway hyperresponsiveness in the presence or absence of asthma and other atopic diseases in a birth cohort of children. Data from a questionnaire regarding respiratory symptoms, plus measurements of the serum total IgE level and airway responsiveness to inhaled methacholine, were obtained for 562 11-year-olds in New Zealand.

Results. The boys had a higher prevalence than the girls of current diagnosed asthma (13 percent vs. 6 percent), current symptoms of wheezing (22 percent vs. 15 percent), and airflow obstruction at base line (6 percent vs. 1 percent) and had a wider distribution of IgE levels, although mean IgE levels (120.8 IU per milliliter in the boys

and 98.1 IU per milliliter in the girls) did not differ significantly between the sexes. The prevalence of diagnosed asthma was strongly related to the serum IgE level (P for trend <0.0001). No asthma was reported in children with IgE levels <32 IU per milliliter, whereas 36 percent of those with IgE levels ≥ 1000 IU per milliliter were reported to have asthma. This relation with the serum IgE level was not explained by a concomitant diagnosis of allergic rhinitis or eczema. Airway hyperresponsiveness to a methacholine challenge also correlated very highly ($P<0.0001$) with the serum IgE level. This relation remained significant even after the exclusion of children with diagnosed asthma ($P<0.0001$) and of all children with a history of wheezing, allergic rhinitis, or eczema ($P<0.0001$).

Conclusions. Even in children who have been asymptomatic throughout their lives and have no history of atopic disease, airway hyperresponsiveness appears to be closely linked to an allergic diathesis, as reflected by the serum total IgE level. (*N Engl J Med* 1991;325:1067-71.)

ASTHMA is often associated, especially in childhood, with atopy manifested by positive skin tests, a clinical history of allergen-induced wheezing episodes, or concomitant eczema or allergic rhinitis.¹ However, some children and many adults with asthma are apparently not atopic and are considered to have intrinsic (nonallergic) disease.² The concept of nonallergic and allergic asthma as two distinct forms has recently been challenged.³ In one study, the prevalence of asthma was closely related to serum IgE levels standardized according to age and sex. Those with low IgE levels reported no asthma, whereas 28 percent of those with the highest IgE levels reported having the disease, and there was evidence of a "dose-response" relation between the IgE extremes. These findings were interpreted to indicate a probable allergic basis for all asthma, even in apparently nonatopic persons with negative skin tests. In that study, however, the diagnosis of asthma was based solely on a questionnaire completed by the subjects themselves and was not validated by objective criteria.

Measurements of airway hyperresponsiveness, although not sufficiently sensitive or specific to provide a definite diagnosis of asthma, are closely correlated with clinical assessments of the presence and severity of the disease.⁴ In several epidemiologic studies, however, airway hyperresponsiveness has been found in persons with no history of symptoms suggesting asthma⁵⁻⁷; the importance of this phenomenon and its relation to allergy and asthma remain unclear. Although increased airway responsiveness has been reported in patients with allergic rhinitis, it is not clear whether the association is predominantly with rhinitis itself or with the elevated serum IgE level.

We analyzed data from a longitudinal study of the health and development of children in New Zealand⁸ to determine whether asthma or airway hyperresponsiveness to methacholine was related to an allergic diathesis, as reflected by elevated serum total IgE levels measured at the age of 11. We further wished to determine whether there was any relation between serum IgE levels and airway hyperresponsiveness in children who did not report ever having had asthma or wheezing.

METHODS

Subjects

The subjects of this study were a birth cohort of children (11 years old at the time of the study) enrolled in the Dunedin Multidisciplinary Health and Development Research Unit longitudinal study.⁸ The cohort was assembled from among the 1661 children born at Dunedin's only maternity hospital between April 1, 1972, and March 31, 1973. The 1139 children who were still living in the province of Otago at the age of three years were invited to participate in a longitudinal study of child health; 1037 (91 percent) entered the study and were asked to return every two years for follow-up. There were no significant differences in birth history or prenatal and postnatal characteristics between the children enrolled in the study and the full birth cohort of 1661 children.

Clinical Assessment

One of the parents of each 11-year-old subject completed a mailed questionnaire regarding any history of allergic rhinitis (hay fever), eczema, asthma, recurrent wheezing, or recurrent cough in the child. The questionnaire was very similar to that administered to the parent by a medical interviewer when the child was nine years old.⁹ The children underwent spirometry, performing at least three acceptable (repeatable within 5 percent or 100 ml) maneuvers to

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measure vital capacity (VC) and forced expiratory volume in one second (FEV₁) on a Godart water spirometer. Methacholine-inhalation challenge was performed with an abbreviated, validated protocol⁶ in which five deep breaths of methacholine concentrations given in 10-fold increments (0.025, 0.25, 2.5, and 25.0 mg per milliliter) were followed by measurements of FEV₁ 30 and 90 seconds after inhalation. The challenge was terminated when FEV₁ fell by more than 20 percent from the best recorded value or after the maximal concentration was given. The provoking concentration of methacholine that produced a 20 percent drop in FEV₁ (PC₂₀) was calculated by interpolation on a logarithmic dose-response plot. All tests of pulmonary function were performed between 1 p.m. and 4 p.m. The methacholine challenge was not performed if substantial airflow obstruction (ratio of FEV₁ to VC, <75 percent) was detected on base-line spirometry, but the response to nebulized albuterol (1.0 mg) was measured instead.

For the first time in this longitudinal study, the subjects were asked at the age of 11 to give blood samples for a number of investigations, including the measurement of serum levels of IgE. The serum was separated from clotted blood within one hour and frozen at -20°C. The serum total IgE level was measured in duplicate by the Phadebas paper radioimmunosorbent test (PRIST) technique¹⁰; if the duplicate measurements were not within 10 percent of one another, the assays were repeated.

All procedures were approved by the ethics committee of the Otago Hospital Board. Written consent for each procedure was obtained from the parent or guardian; consent for venipuncture was also obtained verbally from the children.

Study Definitions

Asthma was recorded as current if the parent answered yes to the question, Has your child had asthma in the past two years? Children reported to have current wheezing not diagnosed as asthma were coded as "wheezing." Those who had reported asthma at the age of 9 but not at the age of 11, as well as the 11-year-olds who reported earlier asthma but no asthma in the past two years, were coded as "previous asthma"; any symptoms of wheezing in the past two years were noted. Those with no reported asthma or wheezing at the age of 9 (when the investigation covered all of childhood up to that age) or at the age of 11 were coded as asymptomatic. Hay fever was recorded if the subject responded positively to a direct question regarding hay fever, amplified if required by reference to an itching nose and sneezing. Eczema was recorded in response to a positive answer to questions about skin allergies or eczema.

We coded airway reactivity to methacholine as hyperresponsive if the PC₂₀ was ≤8 mg per milliliter, and as mildly responsive if the PC₂₀ was >8 but ≤25 mg per milliliter, using the cutoff point found in previous work to differentiate between subjects with asthma and normal subjects.¹¹ Those who did not undergo challenge because of airflow obstruction were classified separately as showing bronchodilator responsiveness.

Duplicate measurements of serum IgE were averaged, and the mean absolute IgE or logarithmic IgE value was used in the analysis.

Statistical Analysis

Data were stored on the University of Otago VAX computer and were also transferred to the University of Arizona for additional analysis. Standard statistical techniques, including analysis of variance, chi-square tests, chi-square tests for trends in proportions, and Mantel-Haenszel analyses of stratified data, were used. Serum IgE levels showed a log-normal distribution, and they were expressed as geometric means and grouped logarithmically. All P values are two-tailed.

RESULTS

Of the original sample of 1037 enrolled children, 801 (77 percent) returned for assessment at the age of 11. For the purpose of this analysis, the 17 children of non-European descent were excluded. Of the 784 children of European descent who were seen, 742 (95 per-

cent) underwent challenge with methacholine or a bronchodilator and 562 (72 percent) had serum IgE measured. Those who did not agree to blood sampling (either the parent or child refused) did not differ significantly from the remainder in regard to sex, degree of airway responsiveness, diagnosis of asthma, current wheezing symptoms, recent treatment for asthma or wheezing, or spirometric measurements.

Table 1 shows the prevalence of diagnosed asthma, current wheezing, levels of airway responsiveness, and mean IgE levels for boys and girls. A significantly greater prevalence of current asthma and current wheezing not diagnosed as asthma was reported in the boys. There was no sex difference in the prevalence of previous asthma. There was no significant difference in the mean logarithmic IgE levels for boys and girls, but the boys had a wider distribution of values, with slightly more low values (less than 32 IU per milliliter) and more values in the upper range (316 IU per milliliter or higher). Airflow obstruction at base line was more frequent in the boys (23 of 410 [6 percent]) than the girls (4 of 374 [1 percent], $P < 0.005$). However, the prevalence of overt hyperresponsiveness and mild responsiveness did not differ between the sexes.

The prevalence of diagnosed asthma was significantly related to the serum IgE level (Table 2). No current asthma was reported among the subjects with IgE levels of less than 32 IU per milliliter, whereas a progressive increase in the prevalence of asthma was found in each increasing range of IgE levels; in subjects with levels of 1000 IU per milliliter or more, the prevalence was 36 percent. The sex distribution of diagnosed asthma was virtually equal at this highest level of IgE, in contrast to the preponderance of boys with diagnosed asthma at lower levels of IgE.

A direct relation was observed between the serum IgE level and current symptoms at the age of 11, with the lowest mean IgE level in subjects with no history

Table 1. Diagnosed Asthma, Symptoms of Wheezing, Airway Responsiveness, and Serum IgE Levels in 11-Year-Old Children, According to Sex.

VARIABLE	BOYS (N = 410)	GIRLS (N = 374)	P VALUE*
History of disease — no. (%)			
Current asthma (past 2 yr)	54 (13)	24 (6)	<0.01
Previous asthma (not past 2 yr)	31 (8)	26 (7)	NS
Wheezing in past 2 yr not diagnosed as asthma	89 (22)	55 (15)	<0.02
Airway responsiveness — no. (%)			
Airflow obstruction, only bronchodilator given	23 (6)	4 (1)	<0.005
PC ₂₀ (mg/ml)			
≤8	37 (9)	29 (8)	NS
>8 to ≤25	25 (6)	21 (6)	NS
>25	304 (74)	299 (80)	—
Test refused	21 (5)	21 (6)	—
Serum IgE level			
Geometric mean — IU/ml	120.8	99.1	NS
Logarithmic mean ±SD — log IU/ml	2.08±0.71	2.00±0.65	NS
≥316 IU/ml — %	33	24	<0.05

*NS denotes not significant.

Table 2. Relation between Serum Total IgE Level and Diagnosed Current Asthma in 11-Year-Old Children.*

SERUM IgE LEVEL (IU/ml)	NO. OF SUBJECTS			NO. (%) WITH CURRENT ASTHMA		
	BOYS	GIRLS	TOTAL	BOYS	GIRLS	TOTAL
<32	70	53	123	0 (0)	0 (0)	0 (0)
32–99	72	83	155	4 (6)	3 (4)	7 (5)
100–315	63	61	124	11 (18)	3 (5)	14 (11)
316–999	61	43	104	14 (23)	7 (16)	21 (20)
≥1000	38	18	56	14 (37)	6 (33)	20 (36)

*P<0.0001 for all trends.

of wheezing and the highest level in those who had current or previously diagnosed asthma with recent wheezing (Table 3). The children with current wheezing not diagnosed as asthma had a geometric mean level of IgE that was 1.4 times the level in children with no asthma or current wheezing (95 percent confidence interval for the ratio, 0.84 to 2.34), a difference that was not statistically significant. Children with a previous or current diagnosis of asthma, including those with previously diagnosed asthma but no symptoms in the past two years, had significantly increased mean levels of IgE (two to five times those in control children).

Similarly, there was a strong relation between the serum IgE level and the presence and degree of airway responsiveness (Table 4). This relation persisted when the children in whom asthma had ever been diagnosed were excluded (P<0.0001), and it remained significant (P<0.0001) even when all those with any current or past asthma, wheezing symptoms, rhinitis, or eczema were excluded, providing a subgroup of 198 subjects who had been asymptomatic and nonatopic throughout their lives. Airway hyperresponsiveness was not found in any asymptomatic child with a serum IgE level of less than 32 IU per milliliter, but it increased in both prevalence and degree as serum IgE levels increased ($\chi^2 = 14.6$, P<0.001) (Fig. 1).

The relation between airway responsiveness and symptoms at the age of 11 was more strongly linked to the recent occurrence of symptoms than to the diagnosis of asthma (Table 5). The prevalence of airway hyperresponsiveness (PC₂₀ ≤8 mg per milliliter) in children who had had asthma but who had not had symptoms in the past two years was not significantly different from the prevalence in children who had been asymptomatic throughout their lives.

The relation between asthma and serum IgE levels was not due to confounding by the coexistence of hay fever (allergic rhinitis) affecting serum IgE levels in children with current, previous, or no asthma. The presence of hay fever was associated with increased IgE levels in control children with no asthma (geometric mean IgE level in those without hay fever, 73 IU per milliliter, and in those with hay fever, 216 IU per milliliter; P<0.001) or previous asthma with no recent symptoms (IgE levels, 117 and 547 IU per milliliter, respectively; P<0.01). However, IgE levels were persistently higher in the children with current diagnoses

of asthma than in the control children, irrespective of a diagnosis of hay fever (geometric mean IgE level in those with hay fever, 388 IU per milliliter [95 percent confidence interval, 264 to 571], and in those without hay fever, 599 IU per milliliter [95 percent confidence interval, 402 to 892]; P not significant).

Among the children with no asthma or wheezing, there was a significantly higher prevalence of airway hyperresponsiveness and mildly increased responsiveness (PC₂₀ ≤25 mg per milliliter) in the 62 with hay fever than in the 508 without hay fever (18 percent vs. 8 percent; odds ratio, 2.6 [95 percent confidence interval, 1.27 to 5.26]). After stratification according to IgE level, the relation of bronchial responsiveness to hay fever became insignificant (odds ratio, 1.6; 95 percent confidence interval, 0.7 to 3.5). On the other hand, airway responsiveness remained closely related to IgE level even in those without hay fever (P<0.0001).

DISCUSSION

These data extend previous findings, showing not only that childhood asthma is very strongly linked to allergy, but also that airway hyperresponsiveness is significantly correlated with allergy as determined by the serum IgE level. Furthermore, we have shown that airway hyperresponsiveness in children who do not report ever having had asthma or wheezing is related to the serum IgE level. The absence of any diagnosed asthma in the children with IgE levels of <32 IU per milliliter, as well as the finding of only one child in whom the PC₂₀ was ≤8 mg per milliliter among the children with low IgE levels, is noteworthy. At the other end of the spectrum, more than one third of the children with IgE levels of 1000 IU per milliliter or more had current diagnosed asthma, and 28 percent had airway hyperresponsiveness, with a PC₂₀ of ≤8 mg per milliliter. This latter finding might be expected among children with diagnosed asthma, but we found a strong relation between airway hyperresponsiveness and the serum IgE level even in those who had never had wheezing. This relation persisted after the exclusion of all children with a history of allergic rhinitis or eczema, indicating that although airway hyperresponsiveness is dependent on the serum

Table 3. Serum Total IgE Level and Symptoms of Asthma in 11-Year-Old Children.

SYMPTOM	NO. OF SUBJECTS	SERUM IgE LEVEL*	P VALUE†
		IU/ml	
No asthma or current wheezing	431	83.9 (72.8–96.8)	—
Current wheezing, no diagnosed asthma	30	118.0 (72.4–192.6)	NS
Previously diagnosed asthma, no symptoms in past 2 yr	22	169.8 (89.1–323.6)	<0.05
Previously diagnosed asthma no longer reported, but wheezing in past 2 yr	17	300.6 (137.1–658.9)	<0.001
Current asthma	62	456.6 (351.0–617.6)	<0.0001

*Values are geometric mean levels and 95 percent confidence intervals.

†For the comparison with the group with no asthma and no current wheezing. NS denotes not significant (see text).

IgE level, its occurrence does not depend on the existence of overt atopic disease.

Our findings differ from those of some earlier studies that failed to detect an association between airway hyperresponsiveness and serum IgE levels. Muranaka et al. studied subjects who currently had asthma, subjects whose asthma had been in remission for more than three years, and normal subjects and found no correlation between reactivity to acetylcholine and serum IgE level in any of the groups.¹² Likewise, Bryant and Burns found no significant correlation between serum IgE level and airway responsiveness to histamine in atopic and nonatopic subjects with asthma, atopic subjects with rhinitis, and atopic and nonatopic normal subjects.¹³ Lam et al. found no relation between responsiveness to methacholine and levels of specific IgE in adults with occupational asthma.¹⁴ Woolcock et al. also reported the lack of a relation between atopy and bronchial reactivity in Australian and Melanesian populations.¹⁵ On the other hand, O'Connor et al. found a statistically significant rela-

Table 4. Percent of Study Children with Airway Responsiveness, According to Symptoms and Serum IgE Levels.*

SERUM IgE LEVEL (IU/ml)	HYPER- RESPONSIVE†	ANY RESPONSE‡		
		ALL	NO DIAGNOSED ASTHMA	NO DIAGNOSED ASTHMA OR WHEEZING
		<i>percent (no. of children at risk)</i>		
<32	1 (114)	2 (114)	2 (112)	0 (74)
32-99	5 (147)	10 (147)	7 (133)	8 (98)
100-315	14 (115)	23 (115)	17 (96)	13 (62)
316-999	17 (95)	26 (95)	17 (71)	18 (44)
>1000	28 (53)	38 (53)	28 (29)	21 (19)
P for trend	<0.0001	<0.0001	<0.0001	<0.0001

*Numbers in parentheses represent the children at risk. The 18 children given only albuterol and the 20 children who declined to undergo methacholine challenge are not included.

†Hyperresponsive was defined as a PC₂₀ of ≤8 mg per milliliter.

‡Any response was defined as a PC₂₀ of ≤25 mg per milliliter. Numbers include children with hyperresponsiveness.

tion between serum total IgE levels and the slope of the methacholine dose-response curve in middle-aged and elderly men, but the association was weak.¹⁶ It was, however, unchanged after the exclusion of the subjects who had asthma or a history of asthma, suggesting that, as in our study, allergic airway inflammation may be present in the absence of symptoms of asthma and may be manifested only as increased airway responsiveness. Similarly, Grainger et al.¹⁷ showed that airway responsiveness to methacholine was associated with atopy, although not strongly.

In a student population, Cockcroft et al. found a significant relation between atopic status and airway responsiveness to histamine.¹⁸ In children and young adults without asthma and rhinitis, the peak serum IgE level occurs between the ages of 6 and 15 years.¹⁹ Our findings thus relate to the age when IgE is at or near its peak, and perhaps for this reason our study

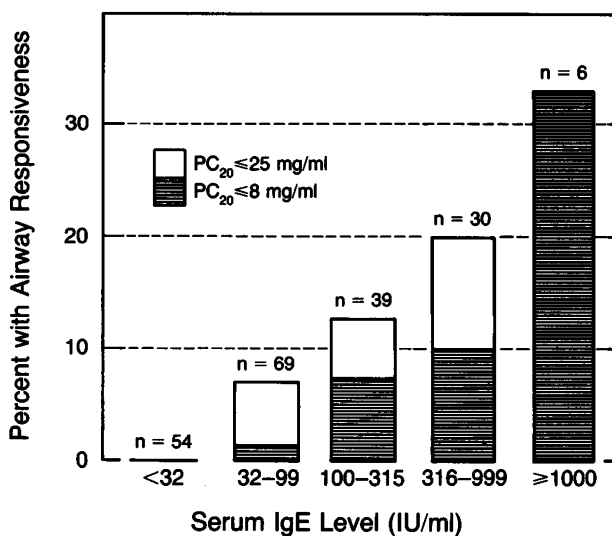


Figure 1. Proportion of Children with No Reported History of Asthma, Wheezing, Hay Fever, or Eczema Who Had Airway Responsiveness to Methacholine, According to Serum IgE Level.

P<0.001 by the chi-square test for trend.

was more likely than others to show the positive association.

Previous studies have shown a relation between serum total IgE levels and the impairment of lung function in older subjects if symptoms suggesting asthma or bronchitis are present.²⁰ There is also a relation between reduced base-line pulmonary function and the likelihood that airway hyperresponsiveness will be detected, at least in children.^{21,22} These relations may provide the indirect link between increased serum IgE levels and airway hyperresponsiveness, through impaired lung function. Not all our subjects with elevated IgE levels had evidence of airway hyperresponsiveness, indicating that the relation is complex and the causal link may be indirect. Our finding that the association between allergic rhinitis and airway hyperresponsiveness became insignificant after we controlled for the IgE level supports the hypothesis of an

Table 5. Airway Responsiveness and Symptoms of Asthma in 11-Year-Old Children.*

SYMPTOM	NO. OF SUBJECTS	HYPER- RESPONSIVE†	ANY RESPONSE‡	P VALUE§
no. (%)				
No asthma or current wheezing	570	21 (4)	50 (9)	—
Current wheezing, no diagnosed asthma	37	5 (14)	9 (24)	<0.02
Previously diagnosed asthma, no symptoms in past 2 yr	28	1 (4)	3 (11)	NS
Previously diagnosed asthma no longer reported, but wheezing in past 2 yr	21	7 (33)	9 (43)	<0.0001
Current asthma	59	32 (54)	41 (70)	<0.0001

*The 18 children given only albuterol and the 20 children who declined to undergo methacholine challenge are not included.

†Hyperresponsive was defined as a PC₂₀ of ≤8 mg per milliliter.

‡Any response was defined as a PC₂₀ of ≤25 mg per milliliter. Numbers include children with hyperresponsiveness.

§For the comparison with the group with no asthma and no current wheezing, for both hyperresponsive and any response. NS denotes not significant.

IgE-mediated mechanism. The fact that the prevalence of airway responsiveness rose as serum IgE levels increased strongly suggests that allergy plays a critical part in facilitating the development of both airway hyperresponsiveness and clinical asthma.

It has often been shown that patients with rhinitis have increased airway responsiveness, especially in the allergen season^{11,23}; airway responsiveness generally increases after exposure to allergens.^{24,25} In the present study, however, children were seen throughout the year, since their assessments took place near their birthdays, and any seasonal influence on airway responsiveness should have been obviated.

A previous study in adults³ found that elevated serum IgE levels could be present even with negative skin tests. Serum IgE levels are not appreciably elevated in subjects with airway inflammation due to chronic bronchitis, suggesting that a specific type of inflammation (probably allergic) is required to produce the association we found. The mechanism of airway hyperresponsiveness is not certain, but it probably involves components of increased mucosal permeability, modulation of the reflex pathways in the airways, and sensitization of airway smooth muscle.²⁶ We have shown that airway hyperresponsiveness is closely linked to the serum IgE level, even in children with no clinical expression of allergy. This finding suggests that allergic inflammation of the airways can be present in children who are asymptomatic, with no clinical features of atopy, and that this inflammation causes either temporary or persistent airway hyperresponsiveness.

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