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Longitudinal observation of children with enhanced total serum IgE

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ARTICLE INFO

Article history:

Received for publication November 3, 2014.

Received in revised form January 30, 2015.

Accepted for publication February 9, 2015.

ABSTRACT

Background: Long-term studies on the evolution of elevated total IgE (tIgE) concentration are in demand. **Objective:** To investigate the prevalence of allergic diseases and influential factors in children with high tIgE levels during a 5-year period.

Methods: Children with high tIgE levels (>100 IU/mL) were study subjects. After the 5-year follow-up, an interview with the parents, clinical examination, and evaluation of tIgE and specific IgE (sIgE) to selected food and inhalant allergens were performed.

Results: The mean tIgE decreased significantly after 5 years in girls and boys regardless of the place of residence. Monosymptomatic patients accounted for most cases throughout the study, with the highest tIgE level at the beginning. After follow-up, the percentage of polysymptomatic patients increased. Their mean tIgE level was significantly higher than in the other groups. After follow-up, 11.7% of participants remained asymptomatic, and another 11.7% reported relief from symptoms. Allergy symptoms persisted in most children with normal tIgE levels. The 2-allergen sensitization was the most common through the study. Only patients sensitized to 4 allergens had unchanged levels of mean tIgE after follow-up and those with the highest mean tIgE level had a newly diagnosed sensitization to at least 1 allergen. A significant decrease of sIgE level was observed for food allergens. The values of sIgE to inhalant allergens even increased after the 5-year follow-up, despite decreased tIgE levels.

Conclusion: In children with allergy and an elevated concentration of tIgE, the increasing or stable value of tIgE could be a useful parameter for the prediction of the development of polysymptomatic allergy.

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Introduction

The concentration of total IgE (tIgE) in human serum depends on several factors, such as genetic predisposition, sex, race, environmental factors, and type of disease (allergy, parasitic infection, or immune deficiency). Physiologically, tIgE production starts during fetal life and increases gradually, reaching the peak of concentration at 10 to 14 years of age. After this age, tIgE begins to decrease, reaching the lowest levels after 75 years of age. It is well known that a high concentration of IgE is correlated with atopic dermatitis (AD) and asthma.^{1,2} Some observations have indicated increased tIgE in healthy people for unknown reasons.^{1,3}

Most previous studies on the occurrence of IgE in children have been cross-sectional rather than longitudinal. Only a few studies have evaluated correlations between specific IgE (sIgE) and atopy status over time.^{1,4,5} The authors previously reported on an analysis of the clinical manifestation and relation among family history of

allergy, some environmental factors, and increased tIgE level in children.² To the best of the authors' knowledge, there is no longitudinal observation concerning children with high tIgE concentration.

The aim of this study was to evaluate the clinical course of children with high serum tIgE levels in relation to some risk factors, allergic diseases, and presence of sIgE during a 5-year period.

Methods

Two hundred fifteen children with a high serum tIgE level (>100 IU/mL) in the 2003 study were invited to participate 5 years later in a follow-up study.² The study protocol was approved by the ethics committee of Medical University in Białystok (Białystok, Poland). The parents of 77 children agreed to participate in the follow-up study and provided a written consent before entry to the study. Some patients could not be located and some had emigrated or developed a disease other than allergy, so they were not included in the present analysis. The evaluation included an interview with the parents, clinical examination, and blood sampling. Questionnaire information related to the presence of allergic disease (ie, asthma, AD, or allergic rhinitis [AR]) and place of residency were updated.

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Disclosure: Authors have nothing to disclose.

<http://dx.doi.org/10.1016/j.anai.2015.02.004>

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Table 1

Background data of pediatric patients with elevated total serum IgE (n = 77)

	2003	2008	P value
Age (y), median (range)	7	11.5	NS
Total serum IgE (IU/mL), mean (range)	1,354.4 (153–5,001)	609 (9.0–4,360)	<.05
Girls, n (%)	26/77 (33.8%)	26/77 (33.8%)	
Total serum IgE (IU/mL), mean (range)	1,171.8 (163–5,001)	555.6 (14–2,166)	<.05
Boys, n (%)	51/77 (66.2%)	51/77 (66.2%)	
Total serum IgE (IU/mL), mean (range)	1,447.5 (153–5,001)	636.3 (9.0–4,360)	<.05
P value	NS	NS	
Place of residence			
City, n (%)	52/77 (67.5%)	52/77 (67.5%)	
Total serum IgE (IU/mL), mean (range)	1,129.8 (153–5,001)	542.4 (9–3,280)	<.05
Village, n (%)	25/77 (32.5%)	25/77 (32.5%)	
Total serum IgE (IU/mL), mean (range)	1,821 (163–5,001)	747.6 (23–4,360)	<.05
P value	<.05	NS	

Abbreviation: NS, not significant.

The tIgE and sIgE concentrations were determined using a fluoro-enzyme-immunologic assay (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden). The upper detection limit of serum tIgE level was 5,000 IU/mL, so results higher than 5,000 IU/mL were labeled as 5,001 IU/mL. An individual change in tIgE concentration was arbitrarily defined as decreased when its level was at least 20% lower than the first measurement, increased when the IgE level was at least 20% higher, and unchanged when the difference of IgE level was equal to or within 20% of the first measurement.

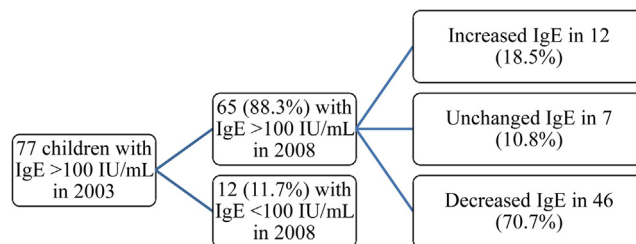
Allergic sensitization (atopic status) was defined as a sIgE concentration above the detection limit (>0.35 kU/L) to at least

Table 2

Clinical manifestation of allergy in study group

	2003	2008	P value
Monosymptomatic	43/77 (55.8%)	32/77 (41.6%)	NS
tIgE (IU/mL), mean (range)	1,426.6 (163–5,001)	446.3 (41–2,408)	<.05
Increased		4/32 (12.5%)	
Unchanged		2/32 (6.2%)	
Decreased		26/32 (81.3%)	
Persistence of symptoms in 2008		22/43 (51.2%)	
tIgE (IU/mL), mean (range)	1,243.7 (210–5,001)	440.1 (54–1,592)	<.05
New cases in 2008 (previously asymptomatic)		8/77 (10.4%)	
New cases in 2008 (previously polysymptomatic)		2/77 (2.6%)	
tIgE (IU/mL), mean (range)	1,311.7 (153–5,001)	460 (41–2,408)	<.05
Relief of symptoms in 2008		6/43 (13.9%)	
tIgE (IU/mL), mean (range)	2,224.7 (163–5,001)	749.7 (23–2,778)	<.05
Polysymptomatic	17/77 (22.1%)	27/77 (35.1%)	NS
tIgE (IU/mL), mean (range)	1,282.3 (508–4,036)	917.4 (32–4,360)	<.05
Increased		8/27 (29.7%)	
Unchanged		4/27 (14.8%)	
Decreased		15/27 (55.5%)	
Persistence of symptoms in 2008		12/17 (70.6%)	
tIgE (IU/mL), mean (range)	1,369.6 (508–4,036)	719.7 (68–2,166)	NS
New cases in 2008 (previously monosymptomatic)		15/77 (19.5%)	
tIgE (IU/mL), mean (range)	1,366.9 (180–5,001)	1,075.7 (32–3,280)	NS
Relief of symptoms in 2008		3/17 (17.6%)	
tIgE (IU/mL), mean (range)	1,072.6 (692–2,106)	269 (102–567)	<.05
Asymptomatic	17/77 (22.1%)	18/77 (23.4%)	NS
tIgE (IU/mL), mean (range)	1,251.6 (153–5,001)	435.6 (23–2,778)	<.05
Increased		0/18	
Unchanged		1/18	
Decreased		17/18	
Unchanged cases in 2008		9/17 (53%)	
tIgE (IU/mL), mean (range)	1,225.4 (271–2,342)	277.1 (9–649)	<.05
New cases in 2008		9/77 (11.7%)	
tIgE (IU/mL), mean (range)	1,760.3 (163–5,001)	594.1 (23–2,778)	<.05

Abbreviations: NS, not significant; tIgE, total IgE.

**Figure 1.** Changes in total IgE level from baseline (in 2003) to follow-up (in 2008).

1 allergen. Only common allergens were considered, such as *Der-matophagoides farinae*, *Dermatophagoides pteronyssinus*, cow's milk, and egg white. The other common reason for high tIgE (ie, parasite infestation) was excluded by stool testing. All measurements of IgE were taken during the same season of the year (winter to spring).

Data were analyzed using Statistica 10 (StatSoft, Inc, Tulsa, Oklahoma). Because tIgE was not normally distributed, the significance of the difference was evaluated by the Mann-Whitney *U* test and a *P* value less than .05 was considered statistically significant. Multiple regression analyses could not be used in this study because none of the examined factors had a significant influence on the level of IgE. Analysis of variance could not be used owing to a lack of normality of IgE distribution.

Results

Of the 77 children included in this study in 2008, 26 were girls and 51 were boys with a mean age of 11.5 years (Table 1). The mean tIgE level of the study group decreased significantly after the 5-year period (1,354 vs 609 IU/mL). However, 65 children (88.3%) had tIgE levels above the upper limit of normal (>100 IU/mL) and only 12

Table 3

Comparison of clinical manifestation of allergy in study group (n = 77)

	2003	2008	P value
Asthma	18/77 (23.4%)	28/77 (36.4%)	NS
Total serum IgE (IU/mL), mean (range)	1,373.4 (519–4,036)	934.4 (43–4,360)	<.05
Persistence of symptoms		15/18 (83.3%)	
Total serum IgE (IU/mL), mean (range)	1,428.7 (519–4,036)	603.5 (54–1,592)	<.05
Increased		1/15 (6.6%)	
Unchanged		1/15 (6.6%)	
Decreased		13/15 (86.6%)	
New cases		13/77 (16.8%)	
Total serum IgE (IU/mL), mean (range)	1,392.8 (153–5,001)	1,316.1 (43–4,360)	NS
Increased		5/13 (38.5%)	
Unchanged		4/13 (30.8%)	
Decreased		4/13 (30.8%)	
Relief of symptoms		3/18 (16.7%)	
Total serum IgE (IU/mL), mean (range)	1,097 (692–1,800)	426 (180–567)	NS
Increased		0/3	
Unchanged		1/3 (33.3)	
Decreased		2/3 (66.7)	
Atopic dermatitis	26/77 (33.8%)	23/77 (29.9%)	NS
Total serum IgE (IU/mL), mean (range)	1,410.6 (163–5,001)	989.7 (32–3,280)	NS
Persistence of symptoms		17/26 (65.4%)	
Total serum IgE (IU/mL), mean (range)	1,437.1 (180–5,001)	1,120.9 (68–4,360)	NS
Increased		7/17 (41.2%)	
Unchanged		2/17 (11.8%)	
Decreased		8/17 (47%)	
New cases		6/77 (7.8%)	
Total serum IgE (IU/mL), mean (range)	1,248.5 (281–4,036)	618.2 (32–1,149)	NS
Increased		2/6 (33.3%)	
Unchanged		1/6 (16.7%)	
Decreased		3/6 (50%)	
Relief of symptoms		9/26 (30.8%)	
Total serum IgE (IU/mL), mean (range)	1,359.3 (163–5,001)	355.5 (23–956)	<.05
Increased		0/9	
Unchanged		0/9	
Decreased		9/9 (100%)	
Allergic rhinitis	36/77 (46.7%)	44/77 (57.1%)	NS
Total serum IgE (IU/mL), mean (range)	1,291.8 (191–5,001)	553.1 (41–3,280)	<.05
Persistence of symptoms		30/36 (83.3%)	
Total serum IgE (IU/mL), mean (range)	1,111.5 (191–4,036)	487.8 (32–2,166)	<.05
Increased		6/30 (20%)	
Unchanged		2/30 (6.7%)	
Decreased		22/30 (73.3%)	
New cases		14/77 (18.2%)	
Total serum IgE (IU/mL), mean (range)	1,734.6 (180–5,001)	692.9 (41–3,280)	<.05
Increased		3/14 (21.4%)	
Unchanged		1/14 (7.1%)	
Decreased		10/14 (71.4%)	
Relief of symptoms		6/36 (16.7%)	
Total serum IgE (IU/mL), mean (range)	2,193.7 (702–5,001)	750.7 (27–2,778)	<.05
Increased		0/6	
Unchanged		1/6 (16.7%)	
Decreased		5/6 (83.3%)	

Abbreviation: NS, not significant.

(11.7%) showed a tIgE level lower than 100 IU/mL (Fig 1). In the group with a tIgE level higher than 100 IU/mL, decreased tIgE was observed in 46 children (70.7%; mean age 11.7 years) and an increased level was observed in 12 children (18.5%; mean age 10.9 years) with a tIgE level at least 100% higher than the first measurement. An unchanged tIgE level was found in 7 children (9.1%; mean age 10.7 years).

A significant decrease in tIgE was observed in boys and girls regardless of place of residence (Table 1). Although more participants lived in cities than in villages (67.5% vs 32.5%), the higher mean tIgE level was detected in residents of rural areas in 2003 (1,821 vs 1,130 IU/mL, $P < .05$), but 5 years later this difference was no longer significant.

Association between tIgE and Clinical Manifestation of Allergy

In 2003, 60 children (77.9%) manifested symptoms of allergy, whereas 5 years later 9 (15%) did not report any symptoms.

Monosymptomatic patients accounted for most cases throughout the study, with the highest tIgE level at the beginning. However, in 2008, the percentage of polysymptomatic subjects increased slightly from 22.1% to 35.1% (Table 2). Furthermore, in this group of patients, increased or unchanged tIgE levels were found more often in children with persistent symptoms and those with new-onset allergy (40.7%; eFig 1B, E) compared with monosymptomatic (18.7%; eFig 1A, D) or asymptomatic (5.5%; eFig 1C, F) participants. Thus, the mean tIgE level was significantly higher in polysymptomatic than in monosymptomatic or asymptomatic cases (917 vs 446 vs 435 IU/mL, respectively; Table 2).

Despite the decrease of tIgE, most monosymptomatic children (51.2%) reported the same clinical manifestation and 10.4% were described as new cases (eFig 1A, D).

Asymptomatic patients had a substantially lower tIgE level after the 5-year follow-up (eFig 1C, F).

Based on the examination of tIgE plots of the new mono- and polysymptomatic cases (eFig 1D, E), an increasing or stable value of

Table 4

Analysis of sIgE concentrations in children with high baseline total IgE levels

	2003	2008	P value
sIgE >0.35 kU/L to ≥1 allergen	52/77 (67.5%)	53/77 (68.8%)	NS
New cases (previously sIgE <0.35 kU/L)		8/77 (10.4%)	
Previously sensitized cases		45/52 (86.5%)	
Total serum IgE (IU/mL), mean (range)	1,555.3 (180–5,001)	775.2 (43–4,360)	<.05
Decreased (>20%)		36/53 (67.9%)	
Increased (>20%)		11/53 (20.7%)	
Without change (≤20%)		6/53 (11.4%)	
sIgE >0.35 kU/L to			NS
1 allergen	8/52 (15.4%)	7/53 (13.2%)	
New cases (previously sIgE <0.35 kU/L)		3/7 (42.8%)	
New cases (previously sIgE >0.35 kU/L to >1 allergen)		4/7 (57.1%)	
Unchanged cases		0/8	
Total serum IgE (IU/mL), mean (range)	1,544.8 (194–5,001)	352.8 (43–888)	<.05
2 allergens	26/52 (50%)	35/53 (66%)	
New cases (previously sIgE <0.35 kU/L)		5/35 (14.3%)	
New cases (previously 1 allergen)		1/35 (2.8%)	
New cases (previously >2 allergens)		8/35 (22.8%)	
Unchanged cases		21/26 (80.8%)	
Total serum IgE (IU/mL), mean (range)	1,116.9 (210–3,712)	551.9 (54–2,408)	<.05
3 allergens	13/52 (25%)	6/53 (11.3%)	
New cases (previously ≤2 allergens)		3/53 (5.6%)	
Unchanged cases		3/52 (5.8%)	
Total serum IgE (IU/mL), mean (range)	2,021.8 (255–5,001)	1,249 (424–3,280)	NS
4 allergens	5/52 (9.6%)	5/53 (9.4%)	
New cases (previously ≤3 allergens)		3/53 (5.6%)	
Unchanged cases		2/5 (40%)	
Total serum IgE (IU/mL), mean (range)	2,638.4 (508–5,001)	2,360.8 (809–4,360)	NS
sIgE >0.35 kU/L to milk	14/77 (18.2%)	11/77 (14.3%)	NS
Concentration (kU/L), mean (range)	11.75 (0.45–117.4)	12.12 (0.38–121.4)	<.05
Concentration (kU/L), median (range)	1.03 (0.45–117.4)	0.78 (0.38–121.4)	
Unchanged cases		7/14 (50%)	
New cases		4/77 (5.2%)	
Normalization of result		7/14 (50%)	
Increased value		1/14 (7.1%)	
Decreased value		11/14 (78.6%)	
sIgE >0.35 kU/L to egg white	24/77 (31.2%)	13/77 (16.9%)	<.05
Concentration (kU/L), mean (range)	11.06 (0.38–98.13)	7.99 (0.52–45.3)	<.05
Concentration (kU/L), median (range)	1.03 (0.38–98.13)	1.16 (0.52–45.3)	
Unchanged cases		11/24 (45.8%)	
New cases		2/77 (2.6%)	
Normalization of result		13/24 (54.2%)	
Increased value		3/24 (12.5%)	
Decreased value		20/24 (83.3%)	
sIgE >0.35 kU/L to <i>Dermatophagoides farinae</i>	41/77 (53.2%)	44/77 (57.1%)	NS
Concentration (kU/L), mean (range)	44.7 (0.38–107.5)	46 (0.36–113.4)	NS
Concentration (kU/L), median (range)	41.9 (0.38–107.5)	36 (0.36–113.4)	
Unchanged cases		36/41 (87.8%)	
New cases		8/77 (10.4%)	
Normalization of result		5/41 (12.2%)	
Increased value		19/44 (43.2%)	
Decreased value		16/41 (39%)	
sIgE >0.35 kU/L to <i>Dermatophagoides pteronyssinus</i>	40/77 (51.9%)	47/77 (61%)	NS
Concentration (kU/L), mean (range)	50.65 (0.36–111.4)	49.9 (0.37–126.1)	NS
Concentration (kU/L), median (range)	57.7 (0.36–111.4)	36.4 (0.37–126.1)	
Unchanged cases		38/40 (95%)	
New cases		9/77 (11.7%)	
Normalization of result		2/40 (5%)	
Increased value		12/47 (25.5%)	
Decreased value		9/40 (22.5%)	

Abbreviations: NS, not significant; sIgE, specific IgE.

tIgE over time seemed to precede the development of new additional allergic symptoms in the near future (eFig 1E). The comparison of clinical manifestation of allergy in the polysymptomatic group is presented in eTable 1.

A tendency toward an increased rate of asthma (23.4% vs 36.4%) and AR (46.7% vs 57.1%; Table 3) over time was observed.

New allergy symptoms appeared in 33 patients (42.8%) in 2008, including AR in 14 (18.2%), asthma in 13 (16.8%), and AD in 6 (7.8%).

Children with newly diagnosed asthma in 2008 had a higher rate of unchanged (30.8%) or increased (38.5%) mean tIgE level

compared with patients with other new allergy symptoms (–AD, 16.7% vs 33.3%; AR, 7.1% vs 21.4%).

Relief from AD symptoms in 2008 was reported by 30.8% of subjects with decreased but still elevated tIgE levels. Relief from AR or asthma symptoms was reported by 16.7% of participants.

Of the 17 initially asymptomatic children (22.1%), after 5-year follow-up, 9 (53%) remained asymptomatic (including 1 with sIgE >0.35 kU/L). However, the other 8 (47%) developed new symptoms, mainly AR, with increased tIgE in only 2 cases. Furthermore, another 9 children (11.7%) reported relief from symptoms in 2008

Table 5

Comparison of mean tIgE of monosensitized, polysensitized, and not-sensitized children estimated in 2003 and 2008

Sensitization change	2003		2008		P value
	Patients, n (%)	tIgE (IU/mL), mean (range)	Patients, n (%)	tIgE (IU/mL), mean (range)	
Monosensitized	8/77 (10.4)	1,544.8 (194–5,001)	7/77 (9.1)	352.8 (43–888)	<.05
No change	—	—	0/8	—	
Decreased or lost	—	1,737.7 (702–5,001)	7/8 (87.5)	332.8 (27–649)	<.05
Increased	—	194	1/8 (12.5)	1,346	
Polysensitized	44/77 (57.1)	1,557.2 (180–5,001)	46/77 (59.7)	839.5 (54–4,360)	<.05
No change	—	1,138 (180–5,001)	26/44 (59.1)	607.5 (54–3,280)	<.05
Decreased or lost	—	1,824.8 (501–5,001)	12/44 (27.3)	587.8 (68–1,158)	<.05
Increased	—	2,838.3 (991–5,001)	6/44 (13.6)	1,927.8 (719–4,360)	NS
Not sensitized	25/77 (32.5)	936.6 (163–5,001)	24/77 (31.2)	312.7 (9–804)	<.05
No change	—	977.6 (163–5,001)	17/25 (68)	204.6 (9–804)	<.05
Increased	—	849.5 (153–2,663)	8/25 (32)	665.5 (43–2,408)	NS

Abbreviations: NS, not significant; tIgE, total IgE.

(Table 2). All asymptomatic cases showed substantially lower tIgE levels (eFig 1C, F).

Allergy symptoms were reported by most children (8 of 12, 66.7%) with normal tIgE levels in 2008. Of these, only 4 patients (30%) had positive sIgE test reactions.

Association between tIgE and sIgE

Fifty-two children (67.5%) in 2003 presented an atopic status (Table 4). Five years later, the number of cases with atopy was almost the same (53, 68.8%), although 7 of 52 children (13.5%) had negative reactions for sIgE. In contrast, 8 of 77 new cases (10.38%) with positive reactions to sIgE were noted.

Sensitization to 2 allergens was most common in 2003 (50%) and 2008 (66%; Table 4). However, only patients sensitized to 4 allergens had unchanged mean levels of tIgE after follow-up (2,638 vs 2,361 IU/mL). All polysensitized children, who developed new sensitization during the study, still manifested abnormal tIgE levels (>100 IU/mL) in 2008 (Table 5). Moreover, changes of tIgE were compared among groups of children sensitized to more, fewer, or the same number of allergens or not sensitized in 2008 (Fig 2, eFig 2).

Although decreased mean tIgE levels were observed in all groups, only the group with sensitization to more allergens (Fig 2, group A; eFig 2A) demonstrated the lowest percentage of children with decreased tIgE levels (46.7% vs 89.5% in group with sIgE reaction to fewer allergens; 76.9% in group with sIgE reaction to the same amount of allergens; 94.1% of not-sensitized subjects). Thus, the mean tIgE level in 2008 was the highest in the cohort with newly diagnosed sensitization.

Interestingly, most monosensitized patients (87.5%) in 2003 showed negative test reactions for sIgE in 2008, despite the still high tIgE level in 5 cases (Table 5). However, the concentration of sIgE in these cases was class 1 to 2.

A significant decrease of sIgE concentration was obtained only to food allergens after the 5-year follow-up (Table 4, eFig 3A, B). Moreover, 50% of children showed normalization of sIgE level to milk and 54.3% to egg white. In contrast to food allergens, the number of sensitized subjects to inhalant allergens remained almost unchanged even with increased sIgE levels in most cases, despite decreased tIgE levels (Table 4, eFig 3C, D).

Of the 24 of 77 children (31.2%) without sIgE reaction to tested allergens in 2008, only 7 had a previously detected sIgE reaction to

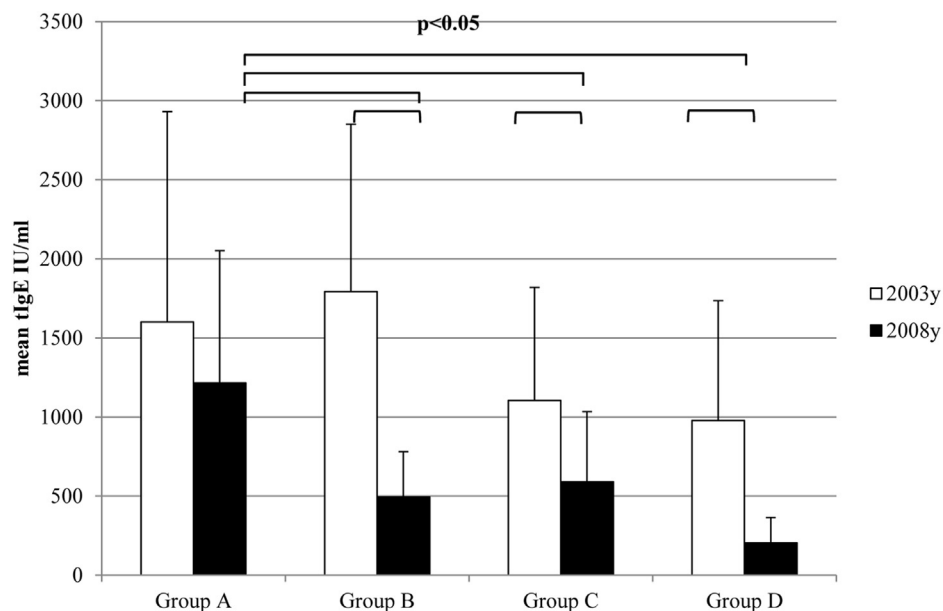


Figure 2. Comparison of mean total IgE from 2003 (white bars) to 2008 (black bars) in children sensitized to 0, 1, 2, 3, or 4 allergens estimated in 2008. Group A, Patients sensitized to more allergens (n = 15). Group B, Patients sensitized to fewer allergens (n = 19). Group C, Patients sensitized to the same number of allergens (n = 27). Group D, Patients not sensitized (n = 17). Figure shows the results of measurements performed in the same children in 2003 and 2008.

Table 6

Changes in sensitization and clinical manifestation during the study in children not sensitized in 2003 (n = 25)

Sensitization and clinical change in 2008	Patients, n (%)	tIgE (IU/mL), mean (range)		P value
		2003	2008	
Sensitization				
Still not sensitized	17/25 (68)	977.6 (163–5,001)	204.6 (9–804)	.05
New sensitization	8/25 (32)	849.5 (153–2,663)	665.5 (43–2,408)	NS
P value		NS	<.05	
Clinical symptoms				
Still without symptoms	6/25 (24)	872.8 (248–2,127)	151.5 (9–337)	<.05
New symptoms	5/25 (20)	912.4 (153–2,663)	697.2 (41–2,408)	NS
P value		NS	NS	

Abbreviations: NS, not significant; tIgE, total IgE.

food or aeroallergens (Table 4, eFig 2B). Twenty-two children (91.7%) showed a decreased tIgE level, and 8 even showed a normal range in (33.3%; eFig 2B, D).

Evaluation of the 25 subjects with high tIgE but normal sIgE levels at baseline showed that during the study, 8 (32%) had developed positive sIgE reactions (with new symptoms in 4 cases). One child with a new manifestation of allergy still had a negative reaction to sIgE (Tables 4 and 6). Moreover, the mean tIgE value of these patients was significantly higher than the mean level of still not-sensitized subjects in 2008 (665.5 vs 204.6 IU/mL).

Discussion

There are reports of a higher atopic prevalence with elevated tIgE levels in men than in women.^{7,8} In the authors' previous study, boys constituted the predominant group, although there were no correlations between sex and level of IgE.² In the present study, no correlation between sex and changes in tIgE level were observed, similar to other studies.^{9,10}

The environmental condition affects the development of allergy (hygiene theory).¹¹ Previously, the authors did not find any relation between residence and high IgE concentration.² A higher level of mean tIgE was noted only at the beginning of the present study in children from rural areas. It is worth mentioning that similar rates of allergy were observed in subjects from rural and urban areas.

In children without atopy, the relation between age and IgE level is well known.^{6,8} According to Hattevig et al,¹² IgE concentration depends more on sexual maturity and the decrease of lymphatic tissue rather than a child's age. Nickel et al⁸ evaluated correlations between tIgE values at different time points from birth to 10 years of age. They reported fluctuations of extreme (>90 percentile) tIgE phenotypes over time. In the present study, there was no relation between level of tIgE and age, and in most cases (75.3%) this concentration was decreased by more than 20% of the starting value. However, the tIgE level in 88.3% of children still remained above 100 IU/mL after the 5-year period. Evaluation of the study by Matricardi et al⁶ of a general population of children from birth to 13 years old indicates that the evolution of tIgE levels is extremely heterogeneous in childhood and that the increase of tIgE level from normal is connected to the onset of allergic disease. This result is contrary to the present results because most newly mono-symptomatic patients had lower tIgE levels compared with those at the beginning of the study. In contrast, 82.3% of them still had tIgE levels above the normal range. In polysymptomatic patients, the longitudinal IgE course tended to increase or stay unchanged (in new cases and cases with persistent symptoms). Moreover, 69.2% of children with newly diagnosed asthma and 50% of new AD cases in 2008 demonstrated unchanged or higher tIgE levels. Most were

polysymptomatic. These observations suggest that in children with allergy and high tIgE levels, unchanged or increasing tIgE values could predict the development of asthma or AD. Some investigators have reported elevated tIgE levels in adults with asthma or AD.^{13–15} Extraordinarily high tIgE levels (>10,000 IU/mL) were found in patients with AD older than 68 years with a long-term course of disease.¹⁵ The limitation of these studies is the single time point, not the longitudinal tIgE measurements.

The present data could support the observations of Matricardi et al⁶ that variations, rather than determination at a single time point, of serum tIgE deserve further attention. Increasing tIgE level over time could be a useful parameter for the prediction of allergy in so far healthy children or polysymptomatic allergy in children with previously elevated tIgE levels.

Interestingly, in the 2008 study group, 8 children (10.4%) with already normalized tIgE levels still demonstrated allergic symptoms. This finding could suggest that, after a few years of chronic inflammation in these patients, non-IgE-mediated allergic reactions are involved in disease.

Regardless of the very high tIgE concentration at the onset of the study, 11.7% of participants remained asymptomatic, including 1 with an sIgE level higher than 0.35 kU/L in reaction to egg white. All showed lower tIgE levels after 5 years; however, in 5 cases tIgE levels were above normal. The cause of polyclonal IgE production remained unexplained in these children. According to other studies, the prevalence of high tIgE and sIgE concentrations in children without any allergic disease ranged from 17% to 20%.^{1,16} A similar group was tested by Smart et al³ who demonstrated that allergen-induced T-helper cell type 2 cytokine response was related to atopic status but not necessarily to atopic manifestations. They suggested an association of the presence of allergic symptoms with a defect in interferon- γ production. Sherrill et al⁵ reported on a group of children presenting with increased tIgE levels before manifestation of persistent wheezing. This might characterize the present group of new asthma cases described previously as asymptomatic with initial high tIgE levels. The remaining asymptomatic patients with high tIgE levels might manifest allergy symptoms in the future.

Reports of the natural history of sensitization have shown that most children outgrow their food allergies (milk and egg mainly), whereas the sensitization frequency to inhalant allergens increases with age.¹⁷ The present patients' data support such observations: the prevalence of sIgE sensitization to food allergens decreased, whereas sensitization to aeroallergens increased. The same was observed with sIgE concentration in response to aeroallergens (despite a general decrease of tIgE level).

The study of de Jong et al¹⁸ showed that polysensitization was more common than monosensitization in children. Moreover, patients sensitized to more than 1 allergen demonstrated higher tIgE levels. These results are similar to the present results. The children with elevated sIgE levels in response to 4 allergens showed the highest mean tIgE level in 2003 and 2008.

Based on longitudinal analyses, Sherrill et al⁵ suggested that late allergic sensitization (ie, at the year-11 survey) is associated with a lower level of tIgE than early sensitization (ie, at the year-6 survey). In the present cases of new sensitization (mean age 13.5 years) in 2008, the mean value of tIgE was lower than the mean value of tIgE in children sensitized before 7 years of age at the beginning of the study (666 vs 1,099 IU/mL). Examination of children sensitized to more allergens than in 2003 showed that their mean tIgE level in 2008 was higher than in children not sensitized or with sensitization to the same or smaller number of allergens.

At the time of follow-up, 22.1% of children remained not sensitized, regardless of an elevated tIgE level. These children might have been allergic to other antigens not analyzed in this study.

The limitation to the present study was the small number of participants and the fact that the population was selected based on an IgE level higher than 100 IU/mL, so the results would not be relevant to the general population. The authors could not rule out the possible impact of allergens not tested in this study on tIgE concentration. The value of the present data might be augmented by follow-up results that will be collected after another 6-year period.

The increase in serum tIgE over time in so far healthy children could predict the development of allergy.⁶ In children with allergy and previously elevated tIgE levels, higher or unchanged levels of tIgE over time could precede the development of polysymptomatic allergy. Thus, serial measurements of tIgE level might be more useful than an evaluation at a single time point to predict the onset of allergic disease. The present results suggest that a tIgE level that decreases over time in so far asymptomatic children could help exclude the initiation of new sensitizations.

Acknowledgments

The authors thank Agnieszka Bazydło for skillful technical assistance with the IgE analyses at the Department of Clinical Immunology at the Medical University in Białystok.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2015.02.004>.

References

- [1] Sigurs N, Hattevig G, Kjellman B, Kjellman NI, Nilsson L, Björkstén B. Appearance of atopic disease in relation to serum IgE antibodies in children followed up from birth for 4 to 15 years. *J Allergy Clin Immunol*. 1994;94:757–763.
- [2] Daniluk U, Kaczmarek M, Sidor K. Chosen factors and high total concentration of immunoglobulin E (IgE) in children. *Pol J Environ Stud*. 2008;17:473–478.
- [3] Smart JM, Tang ML, Kemp AS. Polyclonal and allergen-induced cytokine responses in children with elevated immunoglobulin E but no atopic disease. *Clin Exp Allergy*. 2002;32:1552–1557.
- [4] Bruno G, Cantani A, Ragno V, Milita O, Ziruolo G, Businco L. Natural history of IgE antibodies in children at risk for atopy. *Ann Allergy Asthma Immunol*. 1995;74:431–436.
- [5] Sherrill DL, Stein R, Halonen M, Holberg CJ, Wright A, Martinez FD. Total serum IgE and its association with asthma symptoms and allergic sensitization among children. *J Allergy Clin Immunol*. 1999;104:28–36.
- [6] Matricardi PM, Bockelbrink A, Grüber C, et al. Longitudinal trends of total and allergen-specific IgE throughout childhood. *Allergy*. 2009;64:1093–1098.
- [7] Barbee RA, Halonen M, Kaltenborn W, Lebowitz M, Burrows B. A longitudinal study of serum IgE in a community cohort: correlations with age, sex, smoking, and atopic status. *J Allergy Clin Immunol*. 1987;79:919–927.
- [8] Nickel R, Illi S, Lau S, et al. Variability of total serum immunoglobulin E levels from birth to the age of 10 years. A prospective evaluation in a large birth cohort (German Multicenter Allergy Study). *Clin Exp Allergy*. 2005;35:619–623.
- [9] Shirakawa T, Hayakawa K, Shimizu T, Morimoto K. Association of life style with high risk of hyperimmunity and of immunosuppression mediated by IgE. *J Clin Epidemiol*. 1996;49:1059–1065.
- [10] Sears MR, Burrows B, Flannery EM, Herbison GP, Hewitt CJ, Holdaway MD. Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. *N Engl J Med*. 1991;325:1067–1071.
- [11] Kilpeläinen M, Terho EO, Helenius H, Koskenvuo M. Farm environment in childhood prevents the development of allergies. *Clin Exp Allergy*. 2000;30:201–208.
- [12] Hattevig G, Kjellman B, Björkstén B, Johansson SG. The prevalence of allergy and IgE antibodies to inhalant allergens in Swedish school children. *Acta Paediatr Scand*. 1987;76:349–355.
- [13] Burrows B, Martinez FD, Cline MG, Lebowitz MD. The relationship between parental and children's serum IgE and asthma. *Am J Respir Crit Care Med*. 1995;152:1497–1500.
- [14] Sharma S, Kathuria PC, Gupta CK, Nordling K, Ghosh B, Singh AB. Total serum immunoglobulin E levels in a case–control study in asthmatic/allergic patients, their family members, and healthy subjects from India. *Clin Exp Allergy*. 2006;36:1019–1027.
- [15] Tanei R, Katsuoka K. Clinical analyses of atopic dermatitis in the aged. *J Dermatol*. 2008;35:562–569.
- [16] Saarinen UM, Juntunen K, Kajosaari M, Björkstén F. Serum immunoglobulin E in atopic and non-atopic children aged 6 months to 5 years. A follow-up study. *Acta Paediatr Scand*. 1982;71:489–494.
- [17] Kulig M, Bergmann R, Klettke U, Wahn V, Tacke U, Wahn U. Natural course of sensitization to food and inhalant allergens during the first 6 years of life. *J Allergy Clin Immunol*. 1999;103:1173–1179.
- [18] de Jong AB, Dikkeschei LD, Brand PL. Sensitization patterns to food and inhalant allergens in childhood: a comparison of non-sensitized, mono-sensitized, and polysensitized children. *Pediatr Allergy Immunol*. 2011;22:166–171.

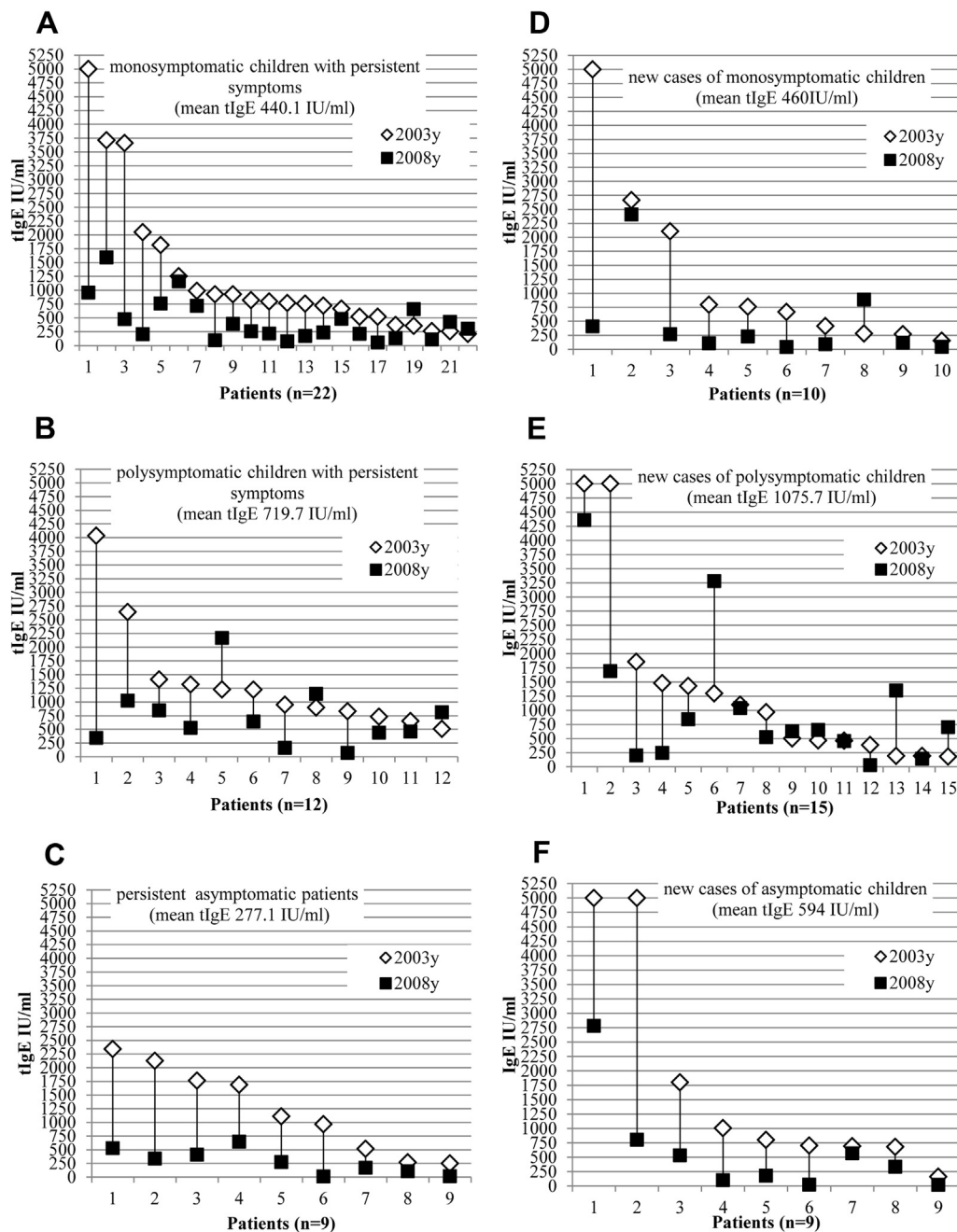
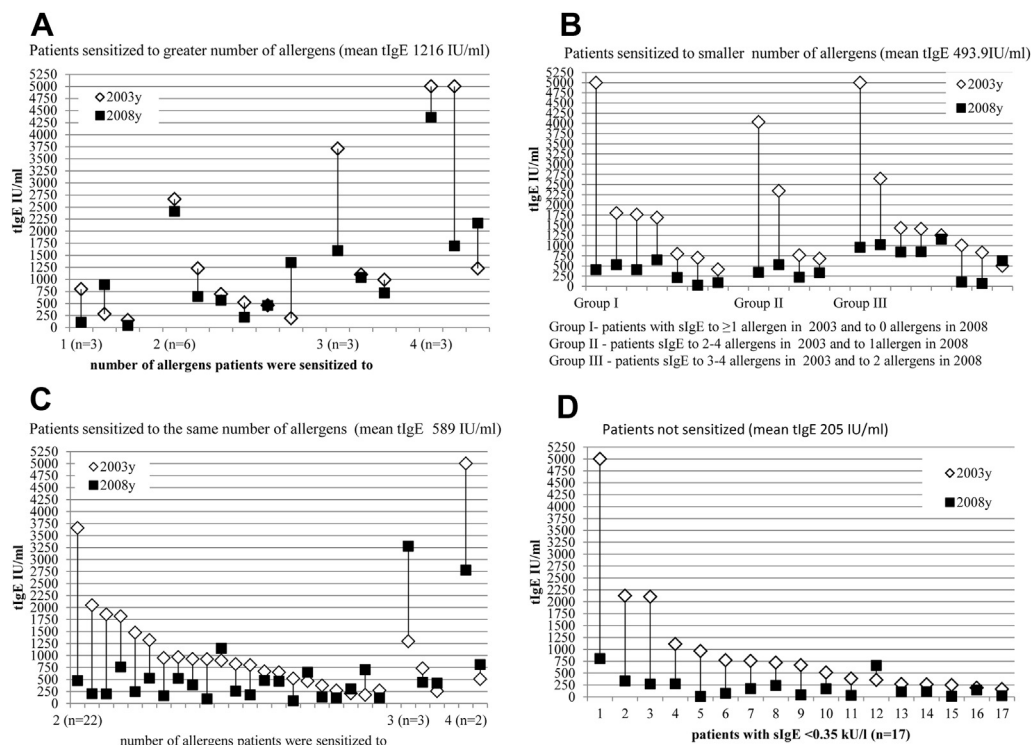
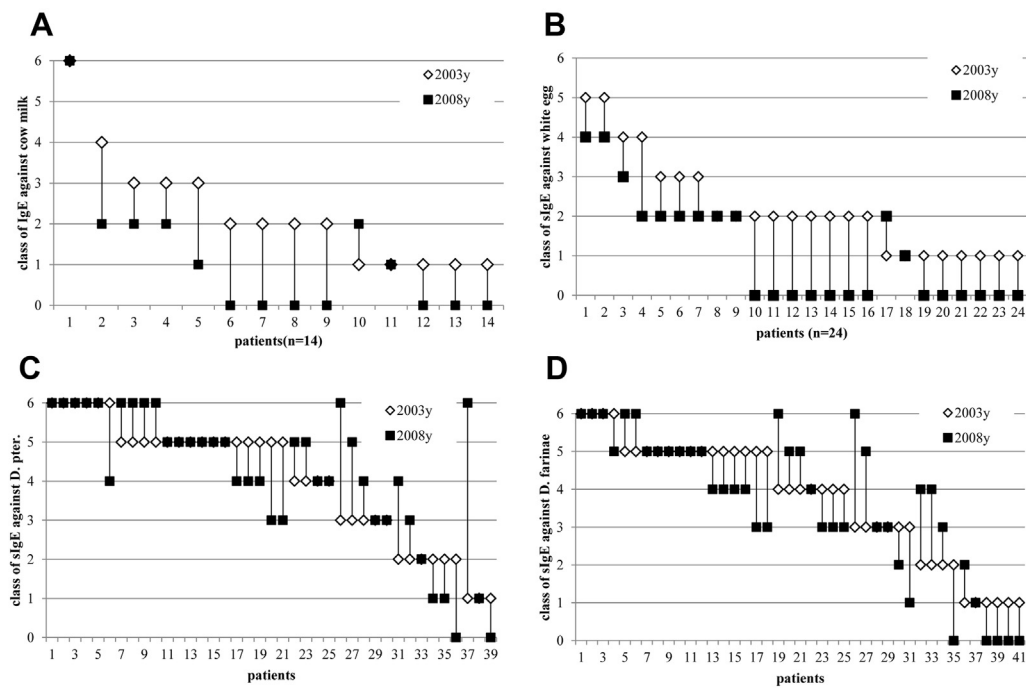


Figure 1. Change in levels of total IgE (tIgE) from 2003 (diamonds) to 2008 (squares) in mono-, polysymptomatic, and asymptomatic children who reported persistence of symptoms (A–C) or the appearance of new symptoms (D–F) in 2008. Figure shows the results of measurements performed in the same children in 2003 and 2008.



eFigure 2. Change in levels of total IgE (tIgE) from 2003 (diamonds) to 2008 (squares) in children sensitized to 0, 1, 2, 3, or 4 allergens evaluated in 2008. (A) New cases of sensitized children. (B) Children sensitized to fewer allergens in 2008. (C) Children sensitized to the same number of allergens in 2008. (D) Children not sensitized in 2003 as in 2008. Figure shows the results of measurements performed in the same children in 2003 and 2008.



eFigure 3. Change in levels of specific IgE (sIgE) against (A) cow's milk (n = 14), (B) egg white (n = 24), (C) *Dermatophagoides pteronyssinus* (n = 39), and (D) *Dermatophagoides farinae* (n = 41) from baseline (diamonds) to follow-up (squares) in subjects sensitized at baseline or at follow-up.

eTable 1

Comparison of clinical manifestation of allergy in polysymptomatic group

	2003	2008	P values
AR + asthma	9/77 (11.7%)	8/77 (10.4%)	NS
Total serum IgE (IU/mL), mean (range)	1,439.9	548.8	<.05
Increased		1/8	
Unchanged		0/8	
Decreased		7/8	
Persistence of symptoms		5/9	
Total serum IgE (IU/mL), mean (range)	1,314.6	619	<.05
New cases		3/77 (3.9%)	
Total serum IgE (IU/mL), mean (range)	552.3	431.7	NS
Relief of symptoms		1/9	
Total serum IgE (IU/mL), mean (range)	692	567	—
AR + AD	5/77 (6.5%)	8/77 (10.4%)	NS
Total serum IgE (IU/mL), mean (range)	1,135.4	654.9	NS
Increased		2/8	
Unchanged		1/8	
Decreased		5/8	
Persistence of symptoms		2/5	
Total serum IgE (IU/mL), mean (range)	1,029.5	1,117	—
New cases		6/77 (7.8%)	
Total serum IgE (IU/mL), mean (range)	1,118.8	500.8	NS
Relief of symptoms		1/5	
Total serum IgE (IU/mL), mean (range)	1,004	102	—
AD + asthma	1/77 (1.3%)	2/77 (2.6%)	NS
Total serum IgE (IU/mL), mean (range)	799	2,853	—
Increased		1/2	
Unchanged		1/2	
Decreased		0/2	
Persistence of symptoms		0	
Total serum IgE (IU/mL), mean (range)	0	0	—
New cases		2/77 (2.6%)	
Total serum IgE (IU/mL), mean (range)	2,597.5	2,853	—
Relief of symptoms		0	
Total serum IgE (IU/mL), mean (range)	0	0	
AR + AD + asthma	2/77 (2.6%)	9/77 (11.7%)	NS
Total serum IgE (IU/mL), mean (range)	1,181.5	1,048.4	NS
Increased		4/9	
Unchanged		1/9	
Decreased		4/9	
Persistence of symptoms		2/2	
Total serum IgE (IU/mL), mean (range)	1,181.5	503	—
New cases (previously monosymptomatic)		4/77 (5.2%)	
Total serum IgE (IU/mL), mean (range)	1,734.8	1,532.3	NS
New cases (previously bisymptomatic)		3/77 (3.9%)	
Total serum IgE (IU/mL), mean (range)	1,813.3	767	NS
Relief of symptoms			
Total serum IgE (IU/mL), mean (range)	0	0	

Abbreviations: AD, atopic dermatitis; AR, allergic rhinitis; NS, not significant.