

Distribution of serum IgE in children and adolescents aged 7 to 16 years in Copenhagen, in relation to factors of importance

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The distribution of total serum-IgE and factors of importance for the level of IgE was studied in a random sample of 508 children and adolescents, aged 7-16 years, from Copenhagen. A detailed history about asthma, rhinitis, dermatitis and urticaria was obtained, and a physical examination, skin prick test with 9 common allergens, lung function test, bronchial challenge with inhaled histamine and exercise, and measurement of IgE (kU/l) were performed. The distribution of IgE among children and adolescents was found to exhibit a log normal distribution and a positive skin prick test, allergic symptoms, a family history of allergic diseases, age and smoking were found to be significantly related to an increased level of IgE. No relationship was found between increased bronchial responsiveness and IgE. The geometric mean of "normal" values of IgE (*1 SD and *2 SD) of the Danish children and adolescents was 18 kU/l (*4.7, *18.2), suggesting that normal IgE values were within 330 kU/l. Measurement of IgE as the only screening for allergic disease is unreliable, as the predictive value of an elevated IgE in population samples was found to be 50%, whereas misclassification (1-specificity) of asymptomatic subjects as allergic because of an increased IgE was low (4%). In conclusion, total IgE is highly influenced by allergen skin reactivity. Further, this study suggests that normal IgE values were within 330 kU/l, although the range was wide.

Clinical aspects

This study showed that a total serum level of IgE which is within normal values is a good predictor of non-allergy, whereas measurement of IgE as the only screening for allergy is unreliable. We found no separation between normal and abnormal levels of IgE because of the wide range of normal IgE values in asymptomatic children. The IgE level was found to be related to positive skin prick test, whereas no relationship was found between IgE and bronchial responsiveness to non-specific agents.

Key words: children; IgE; allergy; population sample; factors of importance.

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Ever since Ishizaka (15) and Johansson (17) and their colleagues identified immunoglobulin E (IgE) as the antibody responsible for the immediate type of immune response, a number of studies noted marked elevations of IgE in young subjects with allergic asthma (16, 28) and other allergic (atopic) diseases (30).

Circulating IgE is found to exhibit a unimodal distribution (18, 21) with a considerable overlap be-

tween the IgE levels in atopic and non-atopic individuals (19, 21). The levels of IgE are remarkable because of the wide scatter with values from < 2 to > 5000 kU/l among normal children (19, 22). The reason for this wide scatter might be that the "normal" levels of serum IgE in children and adolescents may be altered by various factors of importance (3, 18, 19). These differences in circulating IgE are probably caused by differences in both specific

and unspecific factors, such as parasitic infestations (12), smoking (4, 27), pollution (5), aeroallergens (20), local diet (13) and different genetic background (5, 24).

The purpose of this study has been to investigate the distribution of serum-IgE in a random sample of children and adolescents; and, moreover, to examine the influence of different factors of importance on the distribution of IgE.

Material

A random sample of 983 children and adolescents living in the area surrounding the State University Hospital in Copenhagen was drawn from the citizen registry and invited to participate in the study in 1986. All invited subjects were born in the first week of each month; were aged between 7–16 years; and were all Caucasian. A total of 508 (52%) (253 boys and 255 girls) accepted the invitation and were examined. A sample of 100 non-responders (families who did not respond when contacted by letter) was contacted by telephone. A description of the non-responders has been presented in a previous paper (2).

All participants and their parents were interviewed by one of the authors (V.B.) and completed a questionnaire about allergic (atopic) symptoms: asthmatic symptoms (14) and other allergic symptoms, i.e. rhinitis (sneezing, running or blocked nose not associated with colds), atopic dermatitis (an itchy dry rash on face, arms or legs), and urticaria (itchy, generalized irregular wheal-like lesions) in themselves, their siblings and their parents (2). Nineteen subjects were not willing to undergo venous puncture and were excluded.

The material ($n = 508$) was divided into 2 groups, those with allergic symptoms ($n = 115$) and those without, i.e. the non-allergic subjects ($n = 393$).

Group 1. Allergic subjects. Twelve subjects fulfilled the criteria for having bronchial asthma, 44 had rhinitis, 25 atopic dermatitis, and 12 urticaria; additionally, 22 individuals had more than one allergic symptom. Fifty-eight of 115 (50%) subjects had near relations who had allergic symptoms.

Group 2. Non-allergic subjects. These were individuals who had no symptoms which could be classified as definite allergic symptoms. Of the 393 subjects 137 (35%) had near relations who had allergic symptoms.

The protocol was evaluated and approved by the local ethics committee and informed consent was obtained from all participating subjects and their parents.

Methods

Determination of total IgE

Blood samples were drawn and kept at -20°C for approximately 30 days (19); total serum IgE levels were determined by direct paper radioimmunosorbent test (PRIST, Pharmacia, Copenhagen) (22).

Allergen skin prick test

A skin prick test (SPT) with 9 common aeroallergens was performed in 524 (99%) of the participating subjects (10). The allergens used were birch, grass, mugwort, horse, dog, cat, house-dust mite (*Dermatophagoides pteronyssinus*), *Alternaria iridis* and *Cladosporium herbarum*. The strength of the allergens was equivalent to 100 000 BU/ml (Pharmacia), and histamine HCl 10 mg/ml in 50% glycerol was used as a reference for recording the skin prick test results. The urticaria reactions were read after 15–20 min. The size of the skin reactivity was recorded as the sum of the longest and the midpoint orthogonal diameters divided by two ($(D + d)/2$). The diluent was used as negative reference (negative control). Wheal area (WA) was compared with histamine wheal (HW) and classified as true positive if WA was at least the same size as HW ($\geq 100\%$, grade 3), and negative if the wheal was similar to the negative control (grade 0) (10). Moderate skin reactivity was recorded as grade 2 (50%) if WA was more than half the size of the HW but not the full size, whereas grade 1 (25%) was WA less than half the HW size although not negative. Three subjects, of whom one was allergic, were not willing to undergo an allergen skin prick test.

Lung function and bronchial challenge test

All subjects were asked not to smoke for 2 h before the tests and to avoid anti-asthmatic medication in accordance with the recommendations by Eiser et al. (11). In the case of a recent respiratory infection, all tests were postponed for at least 6 weeks. The forced expiratory volume in 1 s (FEV_1) (Vitalograph®), the forced vital capacity (FVC) and the FEV_1/FVC ratio were measured in all participants. Predicted values (% pred.) based on sex and height of the subjects were calculated according to Zapletal (31).

Bronchial responsiveness to inhaled histamine was measured according to the method described by Cockcroft et al. (8). The percent reduction in FEV_1 per μmol of the last inhaled concentration of histamine, i.e. the dose-response slope (DRS), was calculated and used in the analysis (25). Bronchial response to exercise, i.e. exercise-induced bronchoconstriction (EIB), was measured under standard

circumstances after a 6-min run in a climate chamber (1).

Statistical analysis

To compensate for the positively skewed distribution of the IgE values, the statistical calculations were made after log transformation of the IgE results. The distribution of log-IgE was analysed using a probit plot. A univariate correlation between log-IgE and background variables of possible importance was performed, and the correlation coefficient of each variable was noted in Table 1. Background variables of possible importance for the distribution of log-IgE were entered into a multiple regression model and non-significant variables were deleted by backward elimination. Geometric mean, standard deviation (SD) and the range of log-IgE within 2 SD (i.e. mean multiplied with 2 SD (mean * 2 SD)) were calculated and 2 sample t-tests were used when analysing differences. Further, one-way analysis of variance on IgE was used analysing the influence of age and results of SPT. The sensitivity, specificity, predictive value of a positive test (PV +) and predictive value of a negative test (PV -) of IgE in relation to the diagnosis of atopy were calculated as follows:

Sensitivity	$\frac{\text{allergics with increased IgE}}{\text{all allergics}}$
Specificity	$\frac{\text{non-allergics with normal IgE}}{\text{all non-allergics}}$
PV +	$\frac{\text{allergics with increased IgE}}{\text{all individuals with increased IgE}}$
PV -	$\frac{\text{non-allergics with normal IgE}}{\text{all individuals with normal IgE}}$

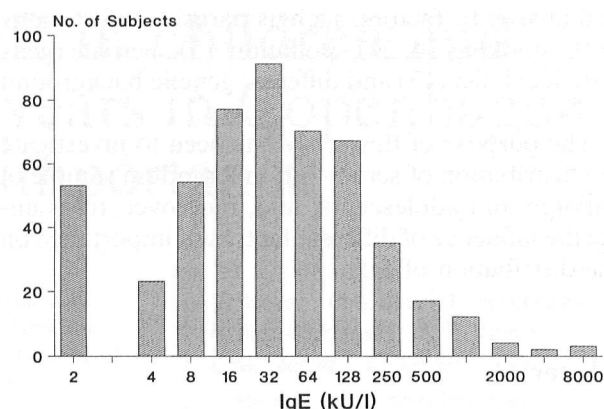


Fig. 1. Density distribution of serum-IgE in children and adolescents.

Results

We found that the distribution function of log-IgE was approximately a straight line in the probit plot, indicating that log-IgE has normal distribution (Fig. 1).

Positive SPT, allergic symptoms, family history of allergic diseases, passive smoking and bronchial response to inhaled histamine (DRS) and exercise (EIB) were found to be important factors for the level of IgE, whereas age, sex, height, smoking (active), lung function and month of examination had no significant influence (Table 1). However, the final multiple regression analysis showed that only the results of the SPT, allergic symptoms (active), family history of allergic diseases, age and smoking influenced the level of IgE, and of these factors positive SPT was the most important (Table 2).

A significant correlation was found between increasing SPT reactivity (size of the wheals 0, 1, 2 and 3) and IgE levels as IgE increased from 19, 27, 83,

Table 1. Results of an univariate correlation (*r* values) between log-IgE and 13 background variables

	IgE	Sex	Age	All	SPT	FEV ₁	FEV ₁ /FVC	Height	Disp	Active	Passive	DRS	EIB	Month
IgE	*													
Sex	0.05	*												
Age	-0.05	-0.05	*											
Allergy	0.29	-0.01	0.08	*										
SPT	0.43	0.07	0.13	0.38	*									
FEV ₁ %pred	0.03	-0.18	0.25	-0.04	0.00	*								
FEV ₁ /FVC	-0.05	0.09	0.01	0.03	-0.02	-0.11	*							
Height	-0.05	0.06	0.88	0.08	0.13	0.14	0.03	*						
Disposition	0.15	0.03	0.06	0.16	0.19	0.08	0.07	0.05	*					
Active	0.07	-0.06	0.29	0.10	0.00	0.13	0.01	0.22	-0.04	*				
Passive	-0.11	0.02	-0.06	-0.11	-0.05	-0.05	-0.04	-0.07	-0.05	-0.01	*			
DRS	0.17	0.02	-0.16	0.20	0.30	-0.13	-0.19	-0.18	0.10	-0.03	-0.01	*		
EIB	0.12	0.03	-0.12	0.13	0.20	-0.17	0.00	-0.16	0.04	-0.04	0.02	0.42	*	
Month	0.02	0.04	0.05	0.08	0.08	-0.11	0.80	0.05	0.06	0.05	0.01	-0.06	0.07	*

Allergy (all); skin prick test (SPT); active smoking (active); passive smoking (passive); disposition (disp); dose response-slope (DRS); exercise-induced bronchoconstriction (EIB).

Table 2. Final multiple regression model of background variables, only showing those factors which proved to be significantly related to the log-IgE (kU/l)

Background variable	Regression coefficient	Percentage of variation explained	Significance level
Level	-0.036	0.2	$p < 0.01$
Family history of allergy	0.078	2.5	$p = 0.09$
Results of skin prick test	0.236	17.3	$p < 0.0001$
Symptoms of allergy	0.129	1.9	$p < 0.001$
Active smoker	0.029	0.9	$p < 0.05$
Residual variation		77.2	

152 kU/l, respectively ($p < 0.001$, Fig. 2). No differences in mean (geometric) level of IgE were found between symptomatic (197 kU/l) and asymptomatic subjects (85 kU/l) with a positive SPT, whereas IgE both with moderate SPT (95 kU/l and 28 kU/l, respectively) ($p < 0.001$) and with negative SPT (31 kU/l and 17 kU/l, respectively) ($p < 0.05$) was found to be significantly different in symptomatic compared with asymptomatic subjects (Fig. 3).

A total of 309 subjects were found to have at least one of the factors suggested to influence the level of IgE (Table 2), whereas 199 subjects had a negative skin prick test, no allergic symptoms, no predisposition to allergic disease and were non-smokers. Further, a significant correlation was found between age and level of IgE among the 199 children and adolescents (Fig. 4, $p < 0.01$), whereas no such correlation was found among the remaining 309 subjects ($p = 0.9$).

The geometric mean of IgE (± 2 SD) among the 199 asymptomatic subjects was significantly reduced, as compared with that in the remaining 309 subjects, 17 kU/l (± 22 , i.e. 374 kU/l) and 36 kU/l (± 27 , i.e. 972 kU/l), respectively ($p < 0.001$). The youngest (7 years) of the 199 children had very high IgE levels

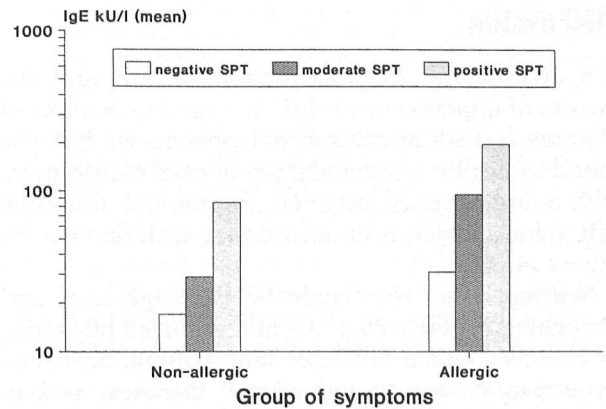


Fig. 3. Geometric mean of IgE and results of the skin prick test in asymptomatic and symptomatic subjects.

(2 SD: 1859 kU/l) and the oldest (16 years) had very low values (2 SD: 62 kU/l) (Fig. 4). After exclusion of those 2 groups no significant correlation between IgE and age was found. The geometric mean of the "normal" values of IgE (± 2 SD) in Danish children and adolescents (age 8 to 15 years) was 18 kU/l (± 18 , i.e. 327 kU/l). The value of IgE measurements, the sensitivity of IgE values in allergic subjects, i.e. number of allergic subjects with abnormal IgE (≥ 327 kU/l), was found to be low (14%). Further, the clinically important predictive value of an abnormal IgE test (PV +) in a random sample, i.e. number of subjects with abnormal IgE who have allergic symptoms, was found to be 50%, indicating that only half of the subjects with pathological findings of IgE were symptomatic. In contrast, the number of asymptomatic individuals who were misclassified as allergic because of an IgE > 327 kU/l, i.e. 1-specificity, was low (4%).

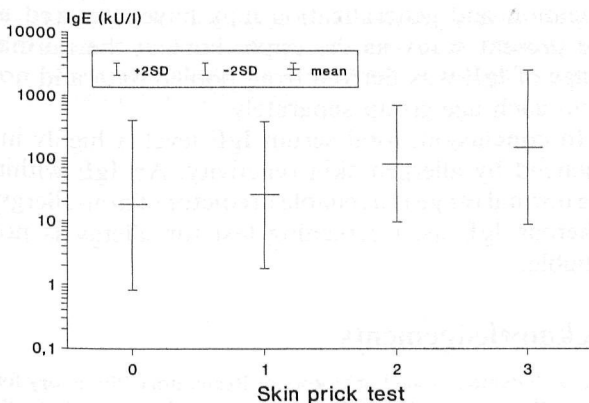


Fig. 2. Geometric mean (± 2 SD) of IgE and the results of skin prick test grade 0 (negative), grades 1 and 2 (moderate), and grade 3 (positive).

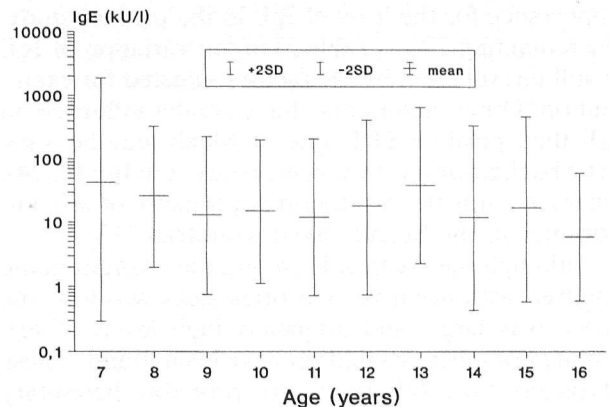


Fig. 4. "Reference" values of IgE (geometric mean (± 2 SD)) in individuals with no allergic symptoms, no family history of allergy, a negative allergen skin reactivity (grade 0) and who do not smoke.

Discussion

We investigated the distribution of IgE and the factors of importance for IgE in a random sample of children and adolescents from Copenhagen. IgE was found to exhibit a unimodal log normal distribution, with a large overlap between normal and abnormal IgE values, which is in accordance with findings by others (4, 18, 21).

We found no association between IgE level and bronchial responsiveness to either inhaled histamine or exercise, which indicates that asthma, bronchial hyperresponsiveness and allergic diseases, as suggested by IgE, may be different abnormalities. Earlier studies have shown a close association between asthma and bronchial hyperresponsiveness (26), between allergy and bronchial hyperresponsiveness in adults (30), and between atopy (i.e. significant reactivity to SPT) and bronchial hyperresponsiveness (30). However, the final multivariate regression analysis, in the present study, showed that bronchial hyperresponsiveness is only of minor importance, if any, for the level of IgE, whereas a strong association still exists between asthma, atopy and elevated IgE. This study would suggest that an overlap between the 3 conditions exists, although they may not be identical.

Five factors examined were found to be markedly related to the level of IgE; atopy (positive skin prick test), allergic symptoms, family history of allergic diseases, age, and smoking. This close association is in accordance with other studies (4, 5, 16, 20, 28, 30). We found that SPT reactivity was of major importance for the IgE level, which agrees with findings by others (3, 10). Further, individuals with asthma, rhinitis and skin lesions were generally found to have high IgE levels; however, many subjects with atopic dermatitis had normal levels (7). These observations show that atopic dermatitis may be caused by both allergic and non-allergic disorders. Although skin prick test reactivity was of major importance for the level of IgE in the present study, the remaining 77% (Table 2) in the variation of IgE is still unexplained by the factors selected for examination. Other factors may have greater influence on IgE than positive SPT, one of which may be a genetic background with specific relation to IgE (5, 24), whereas parasitic infestation is probably of less importance in the Scandinavian countries (12).

Although the mean IgE among the asymptomatic children with negative skin prick tests was low, the range was large, and atypically high levels of IgE among non-allergic children have been found. These atypically high IgE levels are probably hereditary (23) and make separation between allergic and non-allergic difficult. However, Marsh et al. (23) have found that intraindividual variation with time of IgE

above 10% is suggestive for certain allergic disorders independent of the actual level of IgE.

The IgE level increases rapidly during the first year of life (19), followed by a more gradual increase up to the age of 10 years (6). We found an association between age and IgE, although the decrease in serum IgE was initiated before the age of 10. The decrease in IgE continued until the age of 16 years, which is in agreement with other studies (6).

The question of the true "reference values of IgE", is unsolved, this study suggests that IgE values below 330 kU/l should be regarded as normal for the age group 8 to 15 years in Denmark. However, as the distribution of IgE is log-normal, minor changes, e.g. 10% of log-IgE caused by the test variability, result in relatively larger changes in absolute values. In the present study a 10% change in IgE would lead to IgE values of 576 kU/l, which is close to the upper limits of 550 kU/l earlier recommended for the same age group (18). Therefore, our results indicate that, at least in the Scandinavian countries, the upper reference limit of IgE is similar (15) and factors of importance may be similar too. However, some of the differences in upper limit of "normal IgE values" could also have appeared because we excluded subjects with measurable SPT reactivity from our group of "normal" subjects.

Measurement of IgE as the only screening for allergic diseases is unreliable, as we found it to have a low predictive value (PV+). A low PV+ of 50% was found because some asymptomatic subjects have relatively high IgE levels and symptomatic subjects can have low levels. Thus, the value of IgE measurements in a clinical situation seems unsatisfactory. However, this study showed that the risk of asymptomatic subjects being misclassified (1-specificity) as allergics because of an increased IgE was low. The clinical implication of this finding is that an IgE within the normal range is a reliable predictor of non-allergy, whereas an increased level is not diagnostic of allergy (3, 4). A minor misclassification and generalization may have occurred in the present study as the upper limit of the normal range of IgE was derived from pooled data and not from each age group separately.

In conclusion, total serum IgE level is highly influenced by allergen skin reactivity. An IgE within the normal range is a reliable predictor of non-allergy, whereas IgE as a screening test for allergy is not reliable.

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