

Original Research

Chosen Factors and High Total Concentration of Immunoglobulin E (IgE) in Children

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Abstract

Genetic predisposition and environmental conditions are mentioned among the factors modifying the synthesis of IgE immunoglobulin. The aim of the study was to analyze chosen factors in children with high total concentration of IgE (>100 IU/ml). The study included 261 children who were divided according to the serum level of IgE into 3 groups: I - IgE 101-1000 IU/ml; II - IgE >1001 IU/ml and III (control group) with IgE 1-100 IU/ml.

The mean age was similar in the study group and equaled 8 years (± 4.4). The male sex predominated in all groups of patients with IgE >100 IU/ml, whereas the female sex only in the controls. Predominance of the families with a positive family history of an allergic disease, which usually affected mothers (statistically insignificant), was demonstrated in each group. Regardless of IgE concentration, families with more than one child predominated, even in the group of patients with allergic diseases. Similarly, no significant difference was demonstrated in IgE concentrations when comparing the time of breastfeeding or the season of child's birth in the studied children. A significant relationship between the high serum concentration of IgE, atopic status and living in the city was observed ($p < 0.05$). Another correlation on the border of statistical significance was found between exposure to tobacco smoke and high IgE concentration ($p = 0.087$).

Though numerous studies have reported the influence of environmental factors on the excessive production of IgE, our study showed only one significant correlation between high total IgE concentration, atopic status and living in the city.

Keywords: IgE, environmental factor, allergic disease, season of child's birth, family history of allergy, breast feeding, gender, place of living, number of siblings, exposure to tobacco smoke

Introduction

The concentration of IgE in the human serum depends on the individual's genetic predisposition, the appropriate immune response of an organism, age, sex, race and some environmental factors such as exposure to food and/or inhalatory allergens, viral, bacterial, fungal and parasitic infections, social and living conditions, passive and active exposure to tobacco smoke [1, 2], environmental pollution [3], and alcohol consumption [4].

Liu et al. proved the role of genetic and environmental factors in revealing a given feature in children in whom polymorphism of a gene for IL-13 (C-1055T and Arg130Gln) in association with exposure to tobacco smoke (by a smoking mother both in the prenatal and postnatal period) contributed to a higher concentration of total IgE in comparison with similar children, not exposed to tobacco smoke [5].

It has been known for a long time that atopy is inherited predominantly in the mother line, which is explained by the phenomenon of genomic imprinting and the influence of the mother's environment on the foetus during pregnancy or in the later period on the baby through breastmilk.

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A positive correlation has been found several times between the increased concentration of IgE in the cord blood and the presence of atopy in the mother [6, 7]. The importance of the diet used by a mother during pregnancy and in the first months of the baby's life has been the subject of many disputes, because the method of feeding is one environmental factor we can modify.

Interestingly, a low percentage of atopic diseases have been observed in underdeveloped countries with a low social and living status and a high risk of parasitic and infectious diseases, despite high serum concentrations of IgE in infected patients [8, 9]. Similar observations concern the population living in one country, but in the differently-developed industrial regions, or living in the city or in the country [10, 11]. Allergic disorders are also less frequently observed in families with many children. Matricardi et al., found that exposure to microbes transmitted via the alimentary way, such as HAV, *Toxoplasma gondii*, or *Helicobacter pylori*, decreased the incidence of atopy, though it had no influence on IgE concentration [12].

According to the "hygiene theory" [13], the increased predisposition to the development of an allergy in children results from the excessive activity of lymphocytes Th2 (taking part in the regulation of IgE synthesis) with the insufficient stimulation of lymphocytes Th1, because of limited or decreased exposure to pathogenic microbes in early childhood.

This study was undertaken to examine the differences of the chosen factors (sex, season of child's birth, the place of living, the number of siblings, a positive family history of allergy, duration of breastfeeding, exposure to cigarette smoke in the group of children with moderately elevated (101-1000 IU/ml) and very high (>1001 IU/ml) IgE levels compared with children with the normal serum concentration of IgE (<100 IU/ml).

Patients and Methods

The study included 215 children with high total serum concentration of IgE (> 100 IU/ml), chosen from a group of 3400 patients who were diagnosed and/or treated due to different complaints in the IIIrd Department of Pediatrics or in our outpatient clinic of the Medical University of Białystok in 2003-04. The control group consisted of 46 patients with the normal total concentration of IgE with regard to age-proper values and diagnosed because of different recurrent clinical symptoms at the same department.

The study was carried out dividing conventionally the group of 261 patients aged from 8 months to 18 years (mean age 8 years and 3 months) into 3 subgroups with regard to the value of IgE concentration (group I with moderately elevated IgE: 101-1000 IU/ml, group II with very high IgE >1001 IU/ml and group III with normal IgE 1-100 IU/ml), which is presented in Table 1. Total IgE concentration was determined at one-time in the blood serum by the fluoroenzymological method - FEIA (of Pharmacia & Upjohn Diagnostics AB firm) during hospitalization and/or after consulting a patient in the outpatient clinic.

Retrospective clinical analysis was carried out in the study group to find out the causes of the high total IgE concentration. The detailed family history was taken searching for allergic disorders such as asthma, hay fever or eczema and chosen environmental factors, probably influencing excessive IgE production. Allergic sensitization (atopic status) in the study children was defined as showing positive SPT (reaction size >3mm) or the specific IgE level above the detection limit (>0.35 kU/L) to at least one common aeroallergen and/or nutritional allergen. If it was necessary, the appropriate laboratory tests were performed, for example stool examination when parasitic infestation was suspected. The seasons of birth included spring (21 March-22 June), summer (23 June-22 September), autumn (23 September-22 December) and winter (23 December-20 March). For the purposes of this study, "city" means a large town with about 10,000 residents and "village"- a village with fewer residents. To evaluate the effect of breastfeeding on the concentration of IgE, we assumed that 6 months were the optimal period of exclusive breastfeeding of infants in our study.

For the analysis of relationships between the concentration of IgE and exposure to cigarette smoke, subjects of each group were categorized as those who lived with at least one smoking member of the family and those without any smokers at home.

Data were analyzed with the Statistical Package for Social Science programs (version 8.0; StatSoft Inc.). Differences concerning quality features were evaluated with the independence test χ^2 . $p < 0.05$ was considered statistically significant, qualifying to reject zero hypothesis.

Results

Table 1 presents the description of subgroups including all examined factors. The participation of males was significant in all groups of patients with IgE >100 IU/ml; whereas females predominated in controls with IgE values below 100 IU/ml.

In the whole group, children born in autumn predominated (N = 78/261; 29.8%). However, taking into consideration patients with an allergy - the most numerous group consisted of individuals born in summer (45/129; 34.9%).

Regardless of the IgE level, most of the children lived in the city. No relation was found between the incidence of parasite disorders in children with high concentrations of IgE and a different place of living (a city or village) (Table 2). But predominance of allergic diseases in the group with IgE >101 IU/ml and living in the city in comparison with the control group, was statistically significant ($p < 0.05$) in our study (Table 2).

More than one child was found in the predominant number of families, even in the group of patients diagnosed with an allergic disease.

The percentage range of parents reporting the habit of cigarette smoking was almost the same in all groups. Any significant smoking-related effect was not observed even in the group of children with atopy. The positive relation on

Table 1. Description of study groups and total serum concentration of IgE.

Chosen factors		Range of total IgE concentration (IU/ml) No. of group			
		101-1000 group I	>1001 group II	1-100 group III	>101 group I+II
N / %		120 / 46	95 / 36.4	46 / 17.6	215 / 82.4
<i>IgE concentration median</i>		559	1950	22	900
<i>Age arithmetical mean SD ±</i>		8 ±4.0	8 ±4.7	8.6 ± 4.7	8.3 ± 4.4
Female sex N / %		49 / 40.8	35 / 36.8	26 / 56.5	85 / 39.6
<i>IgE concentration (median)</i>		731	1725	22	886
Male sex N / %		71 / 59.2	60 / 63.2	20 / 43.4	131 / 60.4
<i>IgE concentration (median)</i>		558	2322	22.5	929
Season of child's birth (N/%)	Spring (21.III-22.VI)	24/ 20.0	22/ 23.1	10/ 21.7	46/ 21.4
	Summer (23.VI-22.IX)	32/ 26.7	25/ 26.3	12/ 26.1	57/ 26.5
	Autumn (23.IX-21.XII)	40/ 33.3	24/ 25.3	14/ 30.4	64/ 29.8
	Winter (22.XII-20.III)	24/ 20.0	24/ 25.3	10/ 21.7	48/ 22.3
The place of living (N/%)	city	79/ 65.8	62/ 65.3	31/ 67.4	141/ 65.5
	village	41/ 34.2	33/ 34.7	15/ 32.6	74/ 34.5
Exposure to tobacco smoke (N / %)	Yes	44/ 36.7	46/ 48.4	14/ 30.4	90/ 41.9
	No	76/ 63.3	49/ 51.6	32/ 69.6	125/ 58.1
Number of children in the family (N/%)	1	29/ 24.2	22/ 23.2	14/ 30.4	51/ 23.7
	2	50/ 41.7	34/ 35.8	22/ 47.9	84/ 39.1
	≥ 3	41/ 34.2	39/ 41.0	10/ 21.7	80/ 37.2
Breastfeeding period					
All subjects (N/%)	> 6 month	67/ 58.3	54/ 58.0	25/54.35	121/ 58.2
	< 6 month	48/ 41.7	39/ 41.9	21/ 45.65	87/ 41.8
Allergy children (N/%)	> 6 month	37/ 54.4	28/ 59.6	22/ 57.9	65/ 57.0
	< 6 month	28/ 41.8	19/ 40.4	16/ 42.1	47/ 41.2
The positive family history of allergy					
Parents (N/%)		52/ 43.7	36/ 37.9	18/ 39.1	75/ 35.2
Grandparents (N/%)		31/ 26.5	24/ 26.1	15/ 33.3	54/ 25.7
Siblings (N/%)		34/ 35.4	26/ 34.2	14/ 36.8	59/ 34.3
Allergy present in a family (N/%)		73/ 66.4	57/ 67.1	28/ 63.6	127/ 59.1
Subject with atopic status (N/%)		67/ 55.8 *	47/ 49.5	15/ 32.0 *	114 / 53.0 *

*p< 0.05

Table 2. Casual conditioning and the place of living of children with total concentration of IgE > 100 IU/ml.

The kind of diseases	High IgE concentration > 100 IU/ml				Normal IgE concentration > 100 IU/ml			
	City		Village		City		Village	
	N	%	N	%	N	%	N	%
Allergic	77 / 141*	54.6	37 / 74	50.0	9/31*	29.0	6/15	40.0
Parasitic	22 / 141	15.6	18/74	24.3	3/31	9.7	1/15	6.7

*p <0.005

the border of statistical significance was found between exposure to smoke and elevated total IgE concentration ($p = 0.07$).

Most of the children were breastfed for a period longer than 6 months. After having analyzed the data and taking allergies into account, it was found that the period of breastfeeding exceeded 6 months in more than half of the examined in each group.

It is worth mentioning that the predominance of the families with a positive family history of an allergy was observed in all groups. Contribution of allergic diseases referred mainly to mothers; however, these results were not statistically significant.

The multiple regression analyses could not be used in this study because any of the examined factors had no significant influence on the level of IgE. Also, the analysis of variance could not be used because of lack of normality of IgE distribution.

Discussion

A number of studies have emphasized that IgE levels are dependent on the variety of factors. It is known that in physiological conditions, the significant age-IgE relationship exists. Peak levels are reached between 8 and 12 years with a fairly rapid decline afterwards. Hattving considers that IgE concentration depends more on the sexual maturity and reduction of the lymphatic tissue, especially in maturation, which stimulates a decrease in the IgE concentration, but not on the age of a child [14].

In our study, the range of age was similar in each group and fluctuated between 1-18 years, mean age was 8 years old (± 4.4) (Table 1).

Some authors reported sex-related IgE differences, showing that levels for male subjects were higher than for female subjects. In the studies carried out in our region, Oldak more frequently observed higher cord blood concentrations of IgE in male newborns than in newborn girls, though these results were not statistically significant [15]. However, in the studies of Shirakawa et al., and Sears et al., no correlation was found between the sex and the level of IgE [16, 17]. Similar results were obtained in our study, though there were more boys among the children with IgE > 100 IU/ml in comparison with controls. Their IgE levels did not differ from the girls' values.

Observations carried out by many researchers all over the world to compare the prevalence of an allergy and living conditions, revealed that both atopy and allergic disorders were less frequent in the country environment, which may be caused by less air pollution, or a different life style [11, 18, 19]. The causes of this phenomenon should be looked for in the development of immunotolerance or excessive stimulation of lymphocytes Th1 and suppression of Th2, induced by the larger exposure to various antigens of microbes, coming from animals kept on the farm [19]. Similar to other findings on diagnostics of allergic diseases carried out in our region, our study demonstrated the predominance of the children living in the city, which is probably the result of better access to health care services [20].

Similar to other authors' findings about the protective influence of the village environment on the development of allergic disorders, we also confirmed a significant role of high serum IgE levels and living in the city in the atopic status, compared to children with normal values of IgE in this study. However, when we compared the results in the group with high IgE level (>100 IU/ml) the similar percentage of allergic disorders was found in children living in the city or in the country (54.6% v 50.0%), which can be associated with a comparatively low grade of environmental pollution in our region, which is called Poland's green lungs. (Table 2). No relations were found between the place of living, concentrations of IgE and parasitic infestations.

As mentioned before, one of the assumptions in the theory of hygiene is a negative correlation between the number of siblings and the prevalence of allergic diseases, which was proved in numerous population studies [12, 21, 22]. Though no such relation was found in the case of total IgE concentration [21]. Our study also did not confirm this observation, since most of the study children regardless of IgE level, had at least one sibling, even in children with a diagnosed allergy.

It has been suggested that an additional factor that may affect IgE levels is cigarette smoking. The higher concentration of IgE was observed in smokers, especially in men [7, 23]. Kjellman also proved a significant increase in IgE level in children of parents smoking cigarettes, whereas Kulig showed higher predisposition to developing oversensitivity in the clinical understanding [24, 25]. Similar results were obtained in our study, demonstrating a positive correlation (on the border of statistical significance) between children's exposure to tobacco smoke in the

household environment and high serum levels of IgE. Other authors did not find any relations between cord blood and the serum IgE concentration in infants from the risk group developing atopic diseases and exposure to tobacco smoke during pregnancy and childhood [15].

A positive family history of an allergy is important in prognosis of the disease development in a child. It was also emphasized that a high concentration of IgE was more often revealed in both the serum and cord blood in children of parents, especially mothers with an allergy [5, 6]. Koppelman in the studies carried out to search for the gene of atopy, evaluated the hereditary susceptibility of a high concentration of IgE for 55%, specific IgE for 41%, and positive skin tests for 25% [26]. In the study children, a high percentage of families, especially mothers with a positive family history of an allergy, did not depend on the level of IgE in particular groups of children with a high IgE concentration (>100 IU/ml) (Table 1). Similar observations were made by Laske et al., who compared children with an extremely high IgE concentration (>10000 IU/ml) to the group with a moderate level of IgE (400-1000 IU/ml) [27]. After 6-year-studies Oldak et al., revealed a significant difference in the level of IgE concentration between children with a positive family history of allergies and controls [28].

In search for the possible factors, triggering the symptoms of an allergy, the attention was focused on the season of the year and a child's birth. Numerous authors found such a relation, though the results of published findings were not explicit. Oldak, similar to Croner et al., proved a higher concentration of IgE in the cord blood in children born in the winter and autumn [15, 29]. In our study, children born in autumn predominated in the whole group. Summer was the most common season of birth for children with an allergy (34.9%). However, the highest level of mean IgE concentration was revealed in patients born between December and March, both in all children with IgE > 100 IU/ml and in patients with an allergy. This phenomenon may be connected with the predominance of oversensitivity to allergens of mite, which was observed (regardless of the date of a child's birth) and confirmed by positive skin tests or/and present specific IgE. These findings were contrary to Saitoh et al., who proved the lower total IgE concentration in patients born between February and April, and less frequent incidence of specific IgE against the allergen of mite in children born between January and March [30].

The importance of the diet used by a mother during pregnancy and in the first months of the baby's life has been the subject of many disputes. Many authors confirm this approach, explaining it (after long-termed observations) by a decrease in the prevalence of allergic diseases or by their delayed onset in comparison with the control group. [31-33]. Additionally, Siltanen observed that in children up to 4 years old, fed with formulas and with a negative family history of atopy, the percentage of allergic diseases increased as well as the total IgE concentration [32]. In other findings, no correlation was found between the period of breastfeeding and the enhanced level of IgE in 6-month-old infants [5]. Similarly, in our study no relationship was proved

between the high concentration of IgE and an allergy disease and the period of breastfeeding.

Conclusions

Despite other authors' suggestions that some environmental factors can be more responsible for the development of allergic disorders, especially affecting the respiratory system, than genetic ones, we only found a significant relation between the high serum concentration of IgE, atopic status and living in the city ($p<0.05$). No other significant relations could be found between chosen factors (season of birth, number of siblings, period of breastfeeding and exposure to tobacco smoke) and the enhanced concentration of IgE in the study group. We cannot exclude that our findings might be affected by too small a number of examined subjects.

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