

Factors influencing serum immunoglobulin E levels in Greek children

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Serum levels of immunoglobulin E (IgE) were determined by enzyme immunoassay in 414 Greek infants and children of both sexes, 1 month to 14 years old. The children were admitted to the "Aghia Sophia" Teaching Hospital for Children (Athens, Greece) for surgical corrections of minor anatomic abnormalities, but they were otherwise healthy. Statistical analysis was performed through multiple regression after logarithmic transformation of the immunoglobulin values. IgE levels increased significantly by about 80% per year up to the age of 5 years, without noticeable impact of age on these levels thereafter. History of allergic disease showed a significant positive association with serum levels of IgE in both younger (less than 5 years) and older children. History of frequent infections was positively associated with IgE levels, although the relation was statistically significant only in the older age group. IgE levels in Greek children appear to be higher than the corresponding levels of children living in northern Europe, but much lower than those of children in Southeast Asia, a fact that may reflect different exposure level during childhood to infections known to influence IgE levels.

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Serum immunoglobulin E (IgE) levels depend on a variety of genetic and environmental factors, including ethnic background, sex, age, and history of infections and allergic diseases (8, 11, 12, 17). Among them, the age of the patient is of particular importance for the interpretation of immunoglobulin levels in clinical practice (2, 3, 13, 17). Healthy infants are born with very low IgE levels of fetal origin, which increase gradually until they reach adult levels before or during adolescence (18). IgE levels are clinically useful in the diagnosis of patients with allergic diseases and parasitic infestations, mostly those caused by helminths; elevated IgE levels have also been associated with some viral and fungal infections and certain immunologic conditions (2, 7, 10, 13, 18). The aim of this study was to assess the range of serum IgE levels in a sample of apparently healthy Greek children and to investigate determinants or correlates of these levels.

Material and methods

Study population

From January to December 1992, 414 children, 1 month to 14 years old, were consecutively admitted

to the First and Second Surgical Departments of the "Aghia Sophia" Teaching Hospital for Children (Athens, Greece) for minor surgical operations. Of these children, 362 were boys and 52 were girls. A standardized interview was conducted by one of us (ML) with one of the parents of each child after informed consent was obtained. The questionnaire covered a series of sociodemographic and medical history variables, namely, age, sex, birth weight, history of breast-feeding, paternal occupation, history of atopic disease of the child, history of infections, and vaccination status with regard to DTP and Sabin vaccines. Before any medical intervention, blood was drawn for the determination of IgE levels; at that time, none of the children were found to take any medications which could affect immune homeostasis, and all children were free of infection or allergic symptoms. Ninety of the children were considered to be atopic on the basis of reported allergic disease (eczema, allergic rhinitis, and/or asthma).

Laboratory methods and materials

To determine the serum levels of IgE, blood samples were centrifuged, and the sera were stored at -70°C .

Serum IgE levels were determined by enzyme immunoassay (IgE EIA, Pharmacia, Sweden). Results were expressed in international unit per milliliter (iu/ml).

Statistical methods

Statistical analysis was undertaken after log-transformation of individual IgE values, since the frequency distribution of IgE values is positively skewed. Log-transformed IgE was then used as the dependent variable in multiple regression models with age, sex, season of birth, season of blood sampling, weight, breast-feeding, paternal occupation (manual, nonmanual), history of allergy (negative, positive), and history of frequent infections (negative, positive) as independent (predictor) variables. Vaccination status variables (none or incomplete *vs* complete) with respect to DTP and Sabin vaccines were alternatively introduced to avoid collinearity problems (1, 16). Traditionally, the immunization schedule for children in Greece follows the recommendations of the American Academy of Pediatrics; namely, three doses of DTP and oral polio vaccine (Sabin) are given during the first year of life, a first booster at 18 months, and a second at the pre-school age.

Results

Table 1 presents the frequency distribution of the 414 subjects by the predictor variables, whereas Table 2 presents, for eight consecutive age groups, the respective number of subjects without history of atopy, as well as the 10th, 50th, and 90th percentiles. Since there is random variation on account of biologic variability, as well as laboratory variability, the age-specific range should be used only as a standard for comparison. Visual inspection of the age-dependent changes of IgE levels in semilog diagrammatic representation indicates that the age pattern of the log-transformed values can be reasonably described by two straight lines: one from 1-month- to less than 5-year-old children, and another from 5- to 14-year-old children. Table 3 shows, for the eight consecutive age groups, the respective number of 90 atopic subjects (21.7% of the studied children), and the 10th, 50th (medium), and 90th percentiles of IgE levels in these currently asymptomatic atopic children.

Separate regression models were applied for all children in each of the two age groups (less than 5 years old; more than 5 years old) with log-transformed values of IgE as dependent variable and a series of biologically plausible factors as independent (predictor) variables. The predictor variables were introduced either continuously (age in years;

Table 1. Distribution of 414 children by study variables

Variable	Category or unit	No.	Percent (%)
Age	≤ 5 months	20	4.8
	6–11 months	16	3.9
	1–2 years	89	21.5
	3–4 years	86	20.8
	5–6 years	63	15.2
	7–8 years	48	11.6
	9–10 years	46	11.1
	11+ years	46	11.1
Sex	M	362	87.4
	F	52	12.6
Birth weight (g)	≤ 999	20	4.8
	1000–1499	4	1.0
	1500–1999	12	2.9
	2000–2499	15	3.6
	2500–2999	55	13.3
	3000–3499	136	32.9
	3500–3999	130	31.4
	4000–4499	36	8.7
	4500+	6	1.4
Breast-feeding*	None	121	31.6
	≤ 3 months	183	47.8
	4–6 months	51	13.3
	7+ months	28	7.3
History of allergies	Negative	324	78.3
	Positive	90	21.7
History of frequent infections	Negative	291	70.3
	Positive	123	29.7
Paternal occupation	Manual	168	43.1
	Nonmanual	222	56.9
DTP vaccine*	≤ 3 doses	196	50.4
	4+ doses	193	49.6
Sabin vaccine*	≤ 3 doses	173	44.5
	4+ doses	216	55.5
Season of birth	Spring	114	27.5
	Summer	107	25.8
	Autumn	92	22.2
	Winter	101	24.5
Season of interview	Spring	130	31.4
	Summer	80	19.3
	Autumn	89	21.5
	Winter	115	27.8

* There were missing values for breast-feeding (31), DTP vaccine (25), Sabin vaccine (25), and paternal occupation (24).

and birth weight in 1000 g), as ordered variables (breast-feeding, in intervals approximately equal to 3 months) or as categoric contrasts (sex; DTP and Sabin vaccines, with none or incomplete vaccination, *i.e.*, less or equal to three doses, *vs* complete vaccination, *i.e.*, four or more doses; medical history with respect to atopy; previous health status with respect to infection, *i.e.*, fewer than *vs* more than five febrile episodes during the last 2 years; paternal occupation; season of birth; and season of sampling).

Tables 4 and 5 show multiple-regression-derived

Table 2. Median and 10th and 90th percentiles of IgE (in iu/ml) levels by age in non-atopic children

Age	No.	Percentile		
		10	50	90
1-5 months	20	1	3	33
6-11 months	12	2	11	19
1-2 years	67	6	31	102
3-4 years	60	7	45	176
5-6 years	51	10	46	257
7-8 years	34	4	43	177
9-10 years	41	8	45	249
11-14 years	39	12	45	173

Table 3. Median and 10th and 90th percentiles of IgE (in iu/ml) levels by age in atopic children

Age	No.	Percentile		
		10	50	90
1-5 months	None	-	-	-
6-11 months	4	1	56	108
1-2 years	22	12	328	1016
3-4 years	26	75	352	1172
5-6 years	12	62	375	1019
7-8 years	14	151	276	590
9-10 years	5	430	950	1284
11-14 years	7	270	938	1485

Table 4. Multiple regression-derived proportional (percentage) changes of IgE levels among children 1 month to less than 5 years old by indicated changes in series of predictor variables

Predictor variable	Category or unit	Average change (%)	P value (two-tailed)	95% confidence intervals (%)
Age	1 year	+53	< 10 ⁻⁴	+31, +79
Sex	M	Baseline		
	F	-45	0.03	-68, -5
Birth weight	1000 g	-16	0.31	-40, +18
Breast-feeding	3 months	+7	0.65	-19, +41
History of allergies	Negative	Baseline		
	Positive	+649	< 10 ⁻⁴	+359, +1122
History of frequent infections	Negative	Baseline		
	Positive	+17	0.48	-24, +83
Paternal occupation	Nonmanual	Baseline		
	Manual	+6	0.78	-28, +57
DTP vaccine*	None/incomplete	Baseline		
	Complete	-1	0.97	-34, +50
Sabin vaccine*	None/incomplete	Baseline		
	Complete	+3	0.89	-32, +56
Season of birth	Spring	Baseline		
	Summer	-39	0.06	-64, +2
	Autumn	-41	0.06	-65, +1
	Winter	-52	0.1	-72, -71
Season of blood sampling	Spring	Baseline		
	Summer	+12	0.69	-36, +96
	Autumn	+25	0.40	-26, +111
	Winter	+5	0.83	-35, +72

* Alternatively used, in order to avoid collinearity problems.

Table 5. Multiple regression-derived proportional (percentage) changes of IgE levels among children 5 years old to 11+ years old by indicated changes in series of predictor variables

Predictor variable	Category or unit	Average change (%)	P value (two-tailed)	95% confidence intervals (%)
Age	1 year	-0	0.94	-7, +7
Sex	M	Baseline		
	F	-9	0.75	-47, +59
Birth weight	1000 g	+28	0.12	-6, +75
Breast-feeding	3 months	+8	0.52	-15, +38
History of allergies	Negative	Baseline		
	Positive	1208	< 10 ⁻⁴	+725, +1973
History of frequent infections	Negative	Baseline		
	Positive	+78	0.01	+19, +166
Paternal occupation	Nonmanual	Baseline		
	Manual	+8	0.65	-24, +54
DTP vaccine*	None/incomplete	Baseline		
	Complete	+4	0.81	-26, +48
Sabin vaccine*	None/incomplete	Baseline		
	Complete	-2	0.89	-31, +39
Season of birth	Spring	Baseline		
	Summer	-38	0.07	-63, +4
	Autumn	-41	0.06	-66, +2
	Winter	-52	0.01	-72, -17
Season of blood sampling	Spring	Baseline		
	Summer	+9	0.76	-37, +90
	Autumn	+23	0.44	-27, +108
	Winter	+3	0.91	-37, +68

* Alternatively used, in order to avoid collinearity problems.

proportional (percentage) changes of IgE levels among infants and children by indicated changes in the predictor variables. Since the values of the dependent variable were log-transformed, the regression coefficients and the 95% confidence intervals represent proportional changes vs the baseline value (in categoric contrasts) or per unit of change (in quantitative or ordinal variables). It can be seen (Table 4) that IgE levels were increased by an average of 53% per year among children 1 month to less than 5 years old, and that the increase was statistically highly significant. In this age group, girls appear to have had significantly lower IgE levels by 45%. Birth weight, breast-feeding, vaccination, and low socioeconomic status as reflected in manual paternal occupation had no significant association with IgE serum levels. History of frequent infections in this age group had a positive but not statistically significant association with IgE levels, but if the child had a history of allergic disease, IgE levels tended to be significantly and substantially higher (6.5-fold, on average). There is no evidence for seasonal variation by date of blood sampling, but children who were born in spring had significantly higher IgE levels than those born at any other season.

Concerning the changes of IgE among children more than 5 years old (Table 5), it can be seen that IgE levels were not significantly associated with age,

sex, birth weight, breast-feeding, vaccines, or socioeconomic status. History of frequent infections in the older age group was positively associated with IgE levels, and the increase was statistically significant; so was history of allergic diseases, for which the increase was much higher (12-fold, on average). There were no seasonality patterns with respect to either time of sampling or time of birth.

Discussion

Serum IgE levels are influenced by multiple, endogenous and exogenous factors. Although new laboratory procedures for the determination of IgE are substantially more sensitive than older methods, the evaluation of these levels presents various problems, with different methods and laboratories giving variable results in different population groups (6, 11, 14). IgE levels are often used in clinical practice, but very few studies have provided information about the normal range of IgE in children and adolescents (11, 17) or in adults (3, 17). In Greece, no study has been undertaken for the determination of IgE levels in healthy children, although there is a recent publication concerning levels of IgE among adults (7). The sample of the children participating in the present study was not randomly chosen from the underlying population, but selection factors related to the catchment area of the teaching hospital are not likely to be related to immunoglobulin levels in a way that would compromise the validity of the results. Conditions that have necessitated the minor surgical operations for which the children were treated have not been associated with abnormal immunoglobulin values.

The frequency of atopy varies greatly in the literature (1, 7, 8, 15). In the present study, positive history of atopic disease was reported in one out of five children, whereas, among adults, the prevalence of atopy was found to be 32% (7). In Greek children, IgE levels approached adult levels by the age of 5 years, whereas investigators in northern Europe (11) and in the USA (3) have reported an asymptotic reach toward the end of the first decade of life. This may be due to differences in density or intensity of exposure to parasitic diseases or to some viral, mycobacterial, or fungal infections which are known to affect IgE levels (18); however, helminthic infection, which can frequently cause IgE elevations, is now rare in Greece. In our study, a positive association with history of frequent infectious episodes was found among both younger and older children, although the difference reached statistical significance only among the older age group. History of allergic disease in the child is strongly associated with IgE levels, atopic children having 6–12 times higher IgE levels in comparison to unaffected children of simi-

lar age and sex. There was an indication of lower IgE levels among younger girls; similar sex differences have been reported by other investigators (3, 7, 9, 17).

There was no evidence of seasonal variation by date of blood sampling in the present study; a small and marginally significant elevation of IgE levels among older children sampled during the autumn is likely to reflect the multiple comparison process. By contrast, children born during spring had higher IgE levels during their first 5 years of life, compared to children of similar age born during all other seasons of the year. Similar results have been reported by other investigators although the evidence is still inconclusive (4, 19).

Studies undertaken in different parts of the world using identical procedures and reagents (Pharmacia) have yielded substantially different results regarding IgE levels among healthy children. In particular, studies in northern European countries have generated lower IgE levels (11), whereas very high values have been reported from studies in Southeast Asia (14). These differences may be partly accounted for by different patterns of exposure to different microorganisms (18), although large analytic studies on this topic have not yet been reported.

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