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Prediction of Atopy in the First Year of Life Using Cord Blood IgE Levels and Family History

A. J. Sybilski[1, 3], A. Doboszynska[2], B. Samolinski[1]

[1]Department of the Prevention of Environmental Hazards and Allergology, Warsaw Medical University, Warsaw, Poland;
[2]Department of Pediatric and Neonatology, Central Clinical Hospital of Ministry of Internal Affairs, Warsaw, Poland;
[3]Department of Clinical Nursing, Warsaw Medical University, Warsaw, Poland

Abstract
We assessed correlations of total and specific cord-blood IgE (cIgE) levels with allergic symptoms in the first year of life. cIgE levels were determined by an immunoassay test in full-term neonates. This is a prospective study in which a questionnaire was used after birth, and at 6 and 12 months of age. We used multiple logistic regression models to assess the association between the family history of atopy and the incidence of allergy. The infants were divided into groups based on the cIgE level (Group 1<0.1 IU/ml, n=65; Group 2 0.1-0.5 IU/ml, n=63; Group 3 >0.5 IU/ml, n=45). We found the symptoms of atopy in 26 children in Group 1 (40%), 30 (47.6%) in Group 2, and 17 (37.7%) in Group 3; the percentage of atopic diseases was insignificantly different among the three groups. No association between a high total cIgE and specific cIgE with atopy family history and the outcome of atopic diseases was discovered. We conclude that neither total nor specific cIgE level with atopy family history can be used as an indicator to single out high risk infants.

Key words: cord blood, IgE, infant, allergy

Introduction

Growing incidence of allergic diseases, particularly in highly developed countries, created a need for the precise determination of risk factors for initiation and exacerbation of allergies and, based on these premises, for the development of effective prophylactic programs. Increasingly often, first signs of allergy appear already in early infancy, necessitating implementation of prophylactic measures at the moment of birth, or even earlier – at the time of conception [1].

The process of sensitization begins as early as the 11th week of intrauterine life as a result of contact of the fetus with allergens. Elevated levels of plasma IgE predict an early outburst and greater severity of symptoms of allergy. These findings made scientists assess the level of total IgE in cord blood plasma (cIgE) as a predictive factor for subsequent development of allergy in children. Several studies suggest that an isolated assessment of cIgE is neither sensitive nor specific enough for a reliable prediction of development of allergy. Its diagnostic value increases considerably when combined with other parameters, such as family history and the total IgE level in the maternal blood [2, 3]. In recent years, sensitivity of diagnostic tools improved considerably, enabling the detection of immunoglobulins at very low concentrations.

The aim of the present study was to detect the existence of correlations between the elevation of total cord blood IgE or antigen-specific IgE and the subsequent development of clinical symptoms of atopic diseases within the first 12 months of life. The authors also wanted to evaluate the usefulness of the above outlined parameters as prognostic factors for the development of atopic diseases in early infancy and to isolate a group of children at risk of developing allergy.

Material and Methods

Our research was a prospective birth cohort study with retrospective analysis of the pregnancy. The study was approved by a local Ethics Committee. Two hundred and seven term and healthy neonates (≥37 Hbd, birth body weight ≥2500 g) born in the Department of Obstetrics of the Central Clinical Hospital MSWiA in Warsaw were included in the survey. Most of the children (92%) lived in a city. Seventy seven percent of the families settled in apartment houses (30% - concrete blocks) and 33% in single family houses. 53% of infants' mothers and 44% fathers had higher education.

Directly after delivery, 4 ml of umbilical blood were obtained by puncture of the umbilical vein; the sample was centrifuged and blood plasma thus obtained was frozen to –70°C and stored at this temperature for further analyses. Total concentration of immunoglobulin IgE was determined by a chemiluminiscence technique of the sandwich type assay (ECLIA), using an Elecsys 2010 analyzer (Roche Diagnostics, Mannheim, Germany). Allergen-specific IgE was assessed using a quantitative kit (Allergopharma, Reinbek, Germany). The study was performed using three kits of antibodies: for infant food (hen egg protein, cow milk protein, wheat flour, peanuts, and soy), grass and cereals (cocksfoot - Dactylis glomerata; meadow fescue – Festuca pratensis; perennial ryegrass – Lolium perenne; timothy – Phleum pratense; Kentucky bluegrass – Poa

Table 1. Diagnostic criteria for allergic diseases.

Allergic Disease	Diagnostic Criteria (History Data)
Atopic dermatitis	Presence of erythematous, papular, desquamating lesions against a background of dry skin, typical location; itching, dry skin, lesions present for several weeks.
Atopic rhinitis	Recurrent aqueous or mucous nasal discharge, persistent sneezing and catarrh, difficult nasal breathing; signs no connected with infection.
Atopic conjunctivitis	Watery eyes, hyperemia of conjunctivae, itching eyes, rubbing of eyes. Symptoms present for at least 2 weeks, and no connection with infection.
Symptoms of asthma	Obstructive bronchiolitis, episodes of rales in the course of infection within the last 6 months, expiratory wheezes without infection.
Allergic gastro-intestinal disorders	Recurrent diarrhea (frequently with admixture of mucus and blood), vomiting and spilling, severe colic after ingestion of certain products.

pratense; rye; common velvetgrass – Holcus lanatus; oat – Avena sativa; wheat – Triticum vulgare; barley – Hordeum vulgare), house dust mites - HDM (D. pteronyssinus, D. farinae). Specific IgE in circulating blood was assessed using a non-competitive immunoenzymatic assay. Results were presented as the EAST classes, where sIgE concentration over 0.35 IU/ml was considered positive (confirming the presence of specific immunoglobulins).

Family history was obtained using a questionnaire. The questionnaire was completed by 193 parents during a period of 6 months and by 173 parents in 12 months. A self-developed questionnaire was of a filled-in type, based on an interview of the child's mother or of both parents by the investigator. Questions concerned the presence of signs and/or atopic diseases in the child's parents, siblings, or other relatives. An atopic disease was considered present if any atopic disease has been diagnosed by a physician (bronchial asthma, atopic dermatitis, hay fever, nettle-rash, atopic conjunctivitis, or signs of food allergy) and/or has been confirmed by immunologic tests (Prick test, RIST, RAST) and required continuous care by an allergist. For the sake of further analyses, children included in the study were further subdivided into 4 groups, differing in terms of inherited risk for the development of atopic disease. The risk for the development of atopic disease was defined as follows: 0 – no risk (lack of atopic diseases in the family); 1- small risk (probable or confirmed atopic disease in a distant relative); 2 - moderate risk (presence of atopy in father and/or sibling); 3 - high risk (presence of atopic disease in mother and/or father and/or sibling). Prospective monitoring of children's development during the first 12 months was accomplished by two follow-up visits (in the 6th and 12th month), whereby a questionnaire was filled by investigators and the child was examined at the out-patient clinic of the Department of Pediatrics and Infant Diseases of the Central Clinical Hospital of the Ministry of Interior and Administration in Warsaw, Poland. Physical examination was not a prerequisite for inclusion of a child in the final analysis. Data from allergic history were verified on a current basis and atopic diseases/allergic symptoms were diagnosed as based on pre-defined criteria (Table 1).

All levels of significance were calculated using tests for independence of two qualitative variables and the Mann-Whitney U test. Tests for independence of qualitative variables (Chi-square; Yates's Chi-square, V-square and Fisher test) were selected depending on the table of frequency, according to indications found in pertinent literature. For variables with no normal distribution, the Spearman rank correlation and the Kruskal-Wallis test were used. The threshold for significance was set at $P<0.05$. Relative risk (odds-ratio) was calculated according to the standard 2 x 2 table.

Table 2. Detection of specific IgE in umbilical cord blood (n = 173).

Specific IgE	Positive Results		
	Number of specimens with positive results		
grass	20		
mites	11		
foods	9		
	Number of children with positive results		
	n	% of total	% positive result
	34	19.7	100
grass	15	8.7	44.1
mites	8	4.6	23.5
foods	5	2.9	14.7
grass and mites	2	1.2	5.9
grass and foods	3	1.7	8.8
mites and foods	1	0.6	2.9

Results

The values of total cIgE ranged from 0.0 to 23.8 IU/ml, with the mean of 0.55 ±2.07 IU/ml (median 0.16 IU/ml). The infants were divided into 3 groups: Group 1 consisted of children with the total IgE level

Table 3. Total cord blood IgE and the occurrence of allergy symptoms up to 1 year of life.

IgE	Group I <0.1 IU/ml		Group II 0.1–0.5 IU/ml		Group III >0.5 IU/ml	
	n=65	(%)	n=63	(%)	n=45	(%)
Atopy symptoms	26	40	30	47.6	17	37.7
Atopic dermatitis	23	35.3	26	41.2	14	31.1
Allergic rhinitis	10	15.4	9	14.2	4	8.9
Allergic conjunctivitis	1	1.5	3	4.7	1	2.2
Asthma	7	10.7	3	4.7	3	6.6
Allergic digestive symptoms	5	7.7	2	3.0	1	2.2

Table 4. Occurrence of symptoms of allergy up to 1 year of life vs. specific cord blood IgE.

sIgE	Allergy symptoms		Atopic Dermatitis		Allergy rhinitis		Allergy conjunctivitis		Asthma		Gastro-intestinal disorders	
	(-)	+	(-)	+	(-)	+	(-)	+	(-)	+	(-)	+
sIgE against food												
Present (n=9)	5	4	6	3	8	1	8	1	8	1	9	0
Not present (n=164)	95	69	104	60	142	22	160	4	152	12	156	8
sIgE against grass & cereals												
Present (n=20)	11	9	13	7	14	6	19	1	17	3	19	1
Not present (n=153)	89	64	97	56	136	17	149	4	143	10	146	7
sIgE against house dust mites												
Present (n=11)	5	6	7	4	7	4	10	1	10	1	11	0
Not present (n=162)	95	67	103	59	143	19	158	4	150	12	154	8

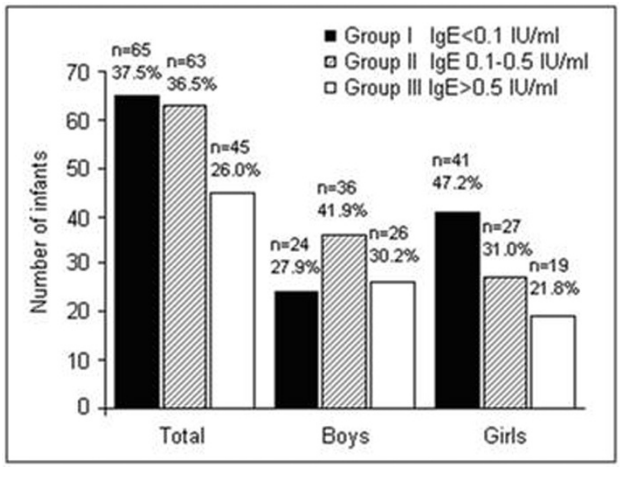

Fig. 1. Number of infants stratified according to the values of total cord blood IgE.

<0.1 IU/ml (considered as lacking cIgE), n=65, 37.5%; Group 2 - total IgE 0.1-0.5 IU/ml (n=63; 36.5%); Group 3 - total IgE >0.5 IU/ml (n=45; 26%) (Fig. 1). Overall, 519 tests for antigen-specific IgE were performed (3 kits of antibodies x 173 children). Positive results were obtained in 40 cases (6.6%) in 34 infants (Table 2). In the first 12 months of life, symptoms of allergy occurred in 73 children (42.0%). Clinical manifestation of the symptoms up to 12 months of life is presented on Fig. 2.

Each group of infants was further subdivided according to the presence of atopia in the mother, father, or in relatives. An analysis of the subdivided study population did not reveal any correlations concerning the future development of atopic diseases within the 1st year of life (Table 3). Next, infants were subdivided into two groups depending on their level of cIgE, adopting 0.5 IU/ml or 0.9 IU/ml as the cut-off values. Again, no correlations between the development of atopic diseases in infants and the presence of allergy in their mothers, fathers, or relatives were found.

The results concerning the presence of allergy symptoms vs. specific cord blood IgE are presented in Table 4. No statistically significant associations were found between the presence of this specific immunoglobulin for food and the incidence of allergic symptoms, neither for cumulated allergy symptoms (P=0.84) nor for the particular entities: atopic dermatitis (P=0.87), allergic rhinitis (P=0.83), symptoms of asthma (P=0.691), allergic conjunctivitis (P=0.14), or gastro-intestinal disorders (P=0.50). A significant

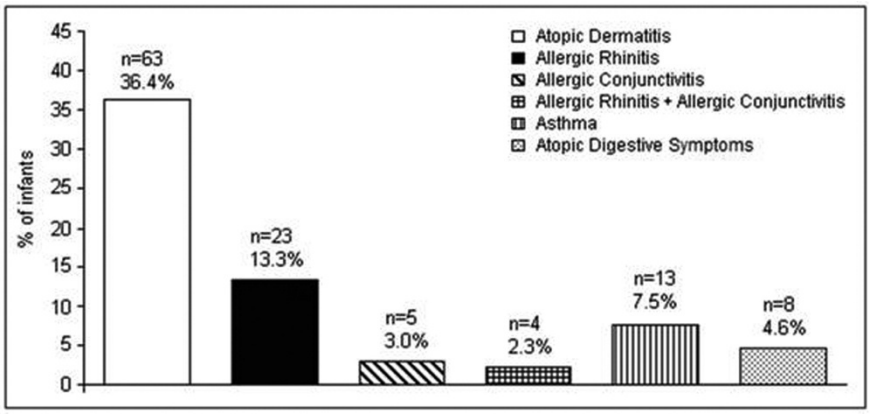

Fig. 2. Number of infants with allergy symptoms up to 12 months of life.

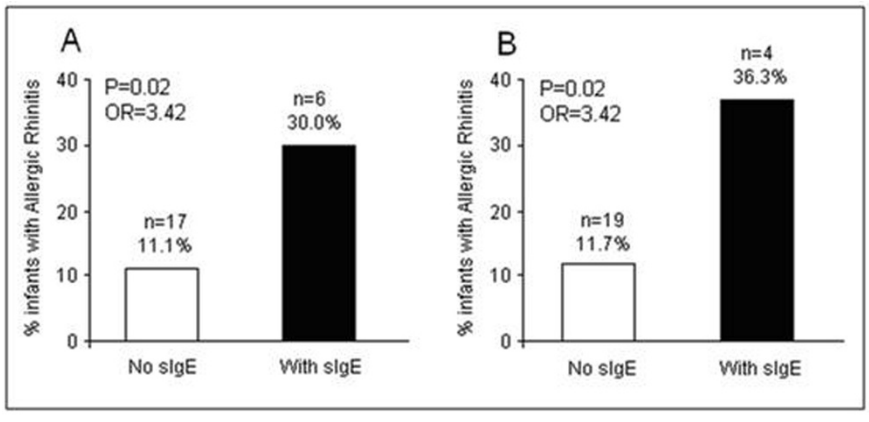

Fig. 3. Panel A - Infants with symptoms of allergic rhinitis and the presence or lack of specific IgE against grass and cereals; Panel B - Infants with symptoms of allergic rhinitis and the presence or lack of of specific IgE against house dust mites.

correlation was noted between the presence of sIgE against grass and cereals and allergic rhinitis (OR=3.42; P=0.02) (Fig. 3A). There was no association of this specific immunoglobulin with symptoms of allergy (P=0.79), asthma (P=0.19), atopic dermatitis (P=0.84), allergic conjunctivitis (P=0.57), or gastrointestinal disorders (P=0.63).

A significant correlation also was found between the presence of specific IgE for HDM and allergic rhinitis (P=0.02; OR=3.42) (Fig. 3B). Further analysis, however, did not reveal any correlations between the presence of this specific IgE and the development of signs of allergy (P=0.38), atopic dermatitis (P=0.75), atopic conjunctivitis (P=21), symptoms of asthma (P=0.70), or gastro-intestinal disorders (P=0.45).

Discussion

Studies concerning the measurement of antigen-specific immunoglobulins of the IgE class in cord blood are sparse. Taking into account continuously increasing availability of these assays, confirmation of usefulness of assessing the total and specific cord blood IgE might contribute to the selection of a group of infants at risk for the development of allergic diseases.

Geographic allocation of a study has an influence on the selection of patients, and thus may influence the results obtained. In the Warsaw region of Poland, there is a high incidence of allergy, which probably has to do with increasing environmental pollution, lifestyle, hygienic and nutritional habits [4, 5].

Most studies on the relation between total umbilical cord blood IgE and the subsequent development of atopic diseases divide the children population samples into two groups: those with IgE levels below 0.5 IU/ml and those with IgE levels equal or above 0.5 IU/ml [6, 7]. In the present study, we adopted a three-tiered stratification scheme, based on our belief that newer and more precise diagnostic techniques enable a better detection of low IgE concentrations. Another important issue is that there is no generally agreed 'normal' level of IgE in the umbilical blood. Every author relies on his own experience. It is particularly difficult to define which IgE level should be considered as unambiguously elevated. A review of pertinent literature indicates that most authors adopt a cut-off value within the 0.5-1.0 IU/ml range [6, 7]. In our opinion, due to the present more sensitive diagnostic techniques, the cut-off value may be set at 0.1 IU/ml, while the 0.5 IU/ml level may become an arbitrary borderline.

Studies performed to-date do not provide a clear answer to the question: Is there a correlation between the cord blood total IgE level and the development of allergy in the first 18 months of life? In a paper by Lopez et al. [8], total IgE level was significantly higher in neonates who developed allergy in their first year of life. However, Kaan et al. [6] analyzed 384 neonates born to high-risk mothers with asthma. They noted that in those children an elevated total IgE level was associated with a 4-fold increase of risk for the development of urticaria when exposed to food allergens in the first 12 months of life. Those authors suggest that the determination of total cord blood IgE level might play a role in selecting the high-risk children for IgE-dependent allergy and qualifying them for prophylactic

measures aimed at prevention of food allergy. Other recent reports, encompassing large numbers of patients, seem to confirm the theory advanced many years ago that the determination of total cord blood IgE, combined with a detailed medical history and also ancillary tests (specific IgE, maternal IgE), is a fairly specific and sensitive prognostic factor for the future development of allergy [9, 10, 11]. Nevertheless, other investigators represent an entirely different point of view, as they negate the predictive role of the total IgE.

The present study conforms to the latter view. The results obtained in the particular subgroups of neonates did not reveal any association of a high or moderate concentration of cord blood IgE with the appearance and exacerbation of allergic symptoms. When considering allergic diseases separately, no clear-cut trend could be noted. An analysis of the non-stratified children's population failed to unravel any influence of a higher IgE level on the incidence of atopic diseases or on the course of allergy in infants either. Neither isolated total IgE concentration nor its combination with a positive maternal allergic history seem sufficient to predict the future development of atopic diseases within the first 12 months of life [2, 3]. Subdivision of infants into two groups, with the cut-off IgE levels of 0.5 and 0.9 IU/ml, did not show any correlations either. No correlations were observed concerning allergy in fathers, siblings, and distant relatives. Therefore, we failed to identify a group of children at risk of developing allergic disease on the basis of medical history and total cord blood IgE level.

A role of antigen-specific IgE a prognostic factor for developing allergic conditions in infancy seems doubtful as well. In an Italian study, a positive result for specific IgE was obtained only in 5.4% of patients [12]. In a later study by Furuhashi et al. [13], the percentage of positive results for sIgE to egg and milk amounted to 20.5% and 43.0%, respectively. In the present study, the use of combined kits (of grass and grain pollen, house dust mites, and food) was intended to increase the chance of discovering the particular allergens. Most of positive determinations, as many as 20, concerned the presence of specific IgE for grass and grain pollen. This is in accord with expectations – the test of sIgE indicated the highest sensitivity to aeroallergens. Almost half of the other positive determinations were associated with other sIgE and the rarest were sIgE against selected items of food. We found an association between the presence of sIgE for house dust mites and grass and grain pollens and the appearance of allergic rhinitis. This seems an interesting observation, as manifestation of allergic rhinitis in infants is relatively rare.

The importance of combining the presence of sIgE in cord blood with a past history of allergic diseases remains unclear. There are several studies which emphasize the prognostic value of such a combination, particularly for house dust mites and food allergens [9, 14, 15, 16]. In the present study, a small number of positive IgE results did not allow to carry out a reliable statistical analysis.

In conclusion, the present study failed to demonstrate that elevated concentration of umbilical cord blood total IgE and the presence of antigen-specific IgE in neonates, even combined with a positive allergic family history correlated with the development of atopic diseases in the 1st year of life. Such measures are, therefore, insufficient to single out infants at high risk of allergy. In the end, the best and most effective method for the identification of such infants seems a meticulous collection of medical history.

Conflicts of interest: The authors reported no conflicts of interest in relation to this article.

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Address for correspondence:
Adam J. Sybilski
Department of Pediatric and Neonatology
Central Clinical Hospital of Ministry of Internal Affairs
137 Woloska St.
02-507 Warsaw, Poland
Phone: +48 22 5081221
Fax: +48 22 5081220
E-mail: Adam.sybilski@cskmswia.pl