FAMILY HISTORY AND CORD BLOOD EOSINOPHIL COUNT AS PREDICTORS FOR ATOPIC MANIFESTATIONS

Helena Tesari Crnković[1, 2], Krešo Bendelja[3], Andrea Šimić Klarić[1, 2], Marijana Tomić Rajić[1], Vlado Drkulec[1], Neda Aberle[2]

[1]General County Hospital Požega, Požega, Croatia
[2]School of Medicine, University of Osijek, Osijek, Croatia
[3]Centre for Research and Knowledge Transfer in Biotechnology, University of Zagreb, Zagreb, Croatia

SUMMARY

Objectives: The aim of our study was to investigate the correlation between several clinical parameters and the appearance of atopic manifestations (atopic eczema, food allergy, wheezing bronchitis, allergic rhinoconjunctivitis) in the first four years of life.

Methods: A total of 139 unselected full-term newborns were included in a prospective follow up from birth to age 4. Cord blood total immunoglobulin E (cIgE) and cord blood absolute eosinophil count (cEo), positive family history of allergy, maternal smoking during pregnancy, mode of delivery, and duration of exclusive and overall breastfeeding were evaluated as predictors for appearance of atopic manifestations.

Results: We found that children with a positive family history of both mother and father are 19.03 times more likely to develop atopic manifestations and those with a positive family history of only mothers are 12.55 times more likely to develop atopy compared with children with a negative family history. Neonates with cord blood eosinophilia had 5.30 times higher chances for developing atopic manifestations. No statistically significant associations were found between cIgE ($p = 0.099$), mode of delivery ($p = 0.379$), maternal smoking ($p = 0.661$), exclusive ($p = 0.867$) and overall breastfeeding duration ($p = 0.675$) and the presence of atopic manifestations up to age 4.

Conclusions: A positive medical history, especially of mothers and cEo, seem to be predictive in screening for the onset of allergic diseases.

Key words: allergy, children, family history, cord blood, eosinophils

Address for correspondence: H. Tesari Crnković, Osječka 107, 34 000 Požega, Croatia. E-mail: tesari_helena@yahoo.com

https://doi.org/10.21101/cejph.a5601

INTRODUCTION

Allergic diseases represent an increasing health problem, particularly in highly developed countries. Early markers of atopic predisposition are needed to identify high-risk infants and to target possible preventive measures. Genetic predisposition has been implicated as a major risk factor for the development of allergic diseases (1). Prenatal exposure to maternal smoking impairs child's lung function immediately after birth and later in life (2, 3). Maternal cigarette smoking can modify aspects of foetal immune function and has been linked with elevated cord blood total immunoglobulin E (cIgE) (4). It has been suggested that the delayed establishment of normal intestinal flora in infants born by caesarean section may lead to a higher risk of allergic sensitization and to the development of allergic diseases in later life (5), while others found no association of allergic diseases with mode of delivery (6). An elevated level of cIgE is considered a risk factor for development of allergy in children up to age 20 (7). Eosinophils play an important role in the pathogenesis of allergic inflammation. Blood eosinophilia is known to be associated with atopic diseases (8). There are numerous studies showing that breastfeeding protects against the development of atopy (9, 10), while others indicate a promoting effect of breastfeeding on allergic diseases. That is more likely because of reverse causation which means that infants at risk of allergic diseases might be breastfed for a longer period (11). The aim of our study was to investigate the correlation between positive family history for allergic diseases, maternal smoking during pregnancy, mode of delivery, total cIgE levels, cord blood absolute eosinophil count (cEo), duration of exclusive and overall breastfeeding and the development of clinical symptoms of atopic diseases within the first four years of life.

MATERIALS AND METHODS

Our research was a prospective birth cohort study with a retrospective pregnancy analysis. A total of 139 unselected full-term newborn babies born at the maternity department of General County Hospital Požega from December 2009 till September 2010 were prospectively followed up from birth to age 4. Informed consent from their mothers was obtained. Immediately after delivery, 4 mL of umbilical cord blood was acquired by puncturing the cord vein. Total concentration of cIgE was determined by electro-chemiluminescence immunoassay (Cobas, e411, Roche diagnostics, Tokyo, Japan). The concentration of immunoglobulin

A (IgA) in the cord blood was measured to rule out maternal contamination of the cord blood specimen. The cEo was determined with an automated blood cell analyser (Abbott Cell Dyn Ruby, Abbott Park, North Chicago, USA). Although highly variable in neonates, eosinophilia was defined as cEo > 700/mm^3. Neonates with perinatal infections were excluded from analysis of cord blood eosinophilia. Family history was obtained using a questionnaire and structured interview of the child's mother by a clinician. Question concerned whether there were signs and/or atopic diseases in the child's parents and siblings. Allergy symptoms were considered present if an atopic disease had been diagnosed by a physician. Of the 139 subjects, 83 had a positive family history of allergy, defined as the presence of at least one first grade relative with allergic symptoms. At the age of 1 and 2 years the children were re-assessed with clinical examination and structured parental interviews by a physician. At the age of 4 (3 years and 8 months to 4 years and 1 month) interviews with parents were undertaken. The subjects' history of allergy symptoms or physician diagnosed atopic eczema, wheezing bronchitis, food allergy and allergic rhinitis during the first 4 years of life was recorded. The age of each subject at the onset of allergy symptoms was determined. Mother's smoking during pregnancy and the duration of exclusive and overall breastfeeding was recorded. Atopic dermatitis was recorded if it was present at follow-up examination, or if it had been diagnosed by a physician. Diagnostic criteria included presence of typically localised chronic or relapsing erythematous, papular or desquamating lesions on the skin. Wheezing bronchitis was recorded if the subject had episodes of wheezing in the course of infection or episodes of respiratory distress and wheezing in the absence of infection. Symptoms of food allergy were defined as a repeated history of typical symptoms appearing after ingestion of a specific food. Allergic rhinoconjunctivitis was defined as recurrent non-infectious rhinitis and/or itching and watery discharge of the nose or eyes at pollen seasons or on aeroallergen exposure. This study was approved by the local ethics committee.

Data is shown in tables. Kolmogorov-Smirnov test was used to assess data normality and according to findings, appropriate non-parametric test was used in statistical analyses. Chi-square test was used to analyse differences between investigated groups (with and without allergic manifestations) regarding categorical variables (Table 1). Differences in quantitative variables were assessed with Mann-Whitney U test (Table 2). Binary logistic regression model has been made to assess the likelihood of belonging to a group with at least one allergic manifestation (Table 3). Binary logistic regression was the most appropriate solution for this kind of analysis since we had binary outcome as a dependent variable combined with non-parametric distribution of included predictor variables. All p-values below 0.05 were considered significant. Statistical software STATISTICA version 10.0 (StatSoft, Inc. 2011) was used in all statistical procedures.

Table 1. *Differences between investigated groups (with and without allergy symptoms) in categorical variables: chi-square test*

		Allergy symptoms				Test results
		Without N = 102		Positive N = 37		
		n	%	n	%	
Gender	Male	49	48.0	18	48.6	$\chi^2 = 0.004$ df = 1 p = 0.949
	Female	53	52.0	19	51.4	
Family history	Negative	56	54.9	10	27.0	Fisher's exact test p = 0.001
	Mother	12	11.8	4	10.8	
	Father	14	13.7	5	13.5	
	Brother or sister	14	13.7	5	13.5	
	Mother and father	1	1.0	4	10.8	
	Mother and brother/sister	1	1.0	5	13.5	
	Father and brother/sister	2	2.0	2	5.4	
	Mother and father + brother/sister	2	2.0	2	5.4	
Family history: groups	Negative	56	54.9	10	27.0	$\chi^2 = 8.460$ df = 1 p = 0.004
	Positive	46	45.1	27	73.0	
Smoking	Negative	59	57.8	21	56.8	$\chi^2 = 1.593$ df = 3 p = 0.661
	Mother	6	5.9	4	10.8	
	Others	20	19.6	8	21.6	
	Mother and others	17	16.7	4	10.8	
Mode of delivery	Vaginal	84	82.4	28	75.7	$\chi^2 = 0.773$ df = 1 p = 0.379
	Caesarean	18	17.6	9	24.3	

Table 2. *Differences between investigated groups (with and without allergic disease) in quantitative variables: Mann-Whitney U test*

Allergy manifestations		N	Minimum	Maximum	Percentiles			p-value
					25th	50th (Median)	75th	
Age (years)	Without	102	3.70	4.11	3.85	3.96	4.03	0.353
	Positive	37	3.73	4.07	3.80	3.91	4.02	
Gestational age (days)	Without	102	261.00	292.00	271.00	274.00	279.25	0.457
	Positive	37	259.00	287.00	271.00	276.00	280.00	
Birth weight (g)	Without	102	2,510.00	4,600.00	3,140.00	3,380.00	3,650.00	0.777
	Positive	37	2,500.00	4,130.00	3,140.00	3,380.00	3,695.00	
Birth length (cm)	Without	102	45.00	55.00	48.00	50.00	50.00	0.932
	Positive	37	45.00	53.00	48.00	49.00	50.00	
Head circumference (cm)	Without	102	31.00	41.00	33.50	34.00	35.00	0.486
	Positive	37	32.00	38.50	33.00	35.00	36.00	
cIgE (IU/mL)	Without	102	0.00	16.20	0.00	0.00	0.33	0.099
	Positive	37	0.00	2.20	0.00	0.20	0.30	
cIgE* (IU/mL)	Without	84	0.00	10.70	0.00	0.00	0.32	0.132
	Positive	29	0.00	2.20	0.00	0.20	0.41	
cEo (mm^3)	Without	90	0.20	2,500.00	345.00	479.00	633.00	0.143
	Positive	36	141.00	1,920.00	357.00	568.50	867.50	
cEo* (mm^3)	Without	73	0.20	1,610.00	331.00	421.00	634.00	0.035
	Positive	28	205.00	1,920.00	381.75	598.50	931.50	
Breastfeeding duration in months (exclusively)	Without	101	0.00	8.00	1.00	4.00	6.00	0.867
	Positive	37	0.00	7.00	1.00	4.50	6.00	
Breastfeeding duration in months (overall)	Without	100	0.00	48.00	2.00	7.00	12.00	0.675
	Positive	37	0.00	30.00	2.00	5.00	13.00	

*cEo – cord blood eosinophil count among patients without perinatal infection
*cIgE – cord blood total IgE level among patients without perinatal infection

RESULTS

Thirty seven of the 139 children included in our study (26.6%) developed atopic manifestations during the 4 year follow up period. Atopic dermatitis was diagnosed in 10.07% (14/139) of the children, 23% (23/139) had wheezing bronchitis, 2.88% (4/139) had food allergy, and 3.60% (5/139) had allergic rhinitis. Most of the children with atopy (73%) had a positive family history. The values of cIgE ranged from 0.0 to 16.20 IU/mL. Twenty seven of the 139 neonates (19.4%) presented with an elevated cIgE (≥0.5 kU/L). The values of cEo ranged from 0.20 to 1,920/mm^3 after exclusion of neonates with perinatal infections. Thirty one of the 139 neonates (22.3%) presented with an elevated cEo. Atopic manifestations developed in 14 of the 31 neonates with pronounced eosinophilia. Table 1 shows differences between groups with and without allergic manifestations. The only significant difference was regarding family history. Participants who had positive family history for allergy are more frequently in a group with at least one atopic manifestation ($p=0.004$). In Table 2 differences in quantitative variables between groups with and without allergic symptoms are presented. The only significant difference was in cEo, after excluding patients with a perinatal infection, significantly higher cEo counts were in the group positive to at least one atopic manifestation ($p=0.035$). Binary logistic regression as a multivariate model has been made to ascertain the effects of all relevant clinical variables on the likelihood that participants have at least one atopic manifestation (Table 3). The logistic regression model was statistically significant ($\chi^2=29.89$; $df=16$; $p=0.019$). The model explained 30.4% of the variance in atopic manifestations and correctly classified 80.0% of included cases. Several predictor variables are significant: positive family history for allergic diseases and cEo. Children with a positive family history of both mother and father are 19.03 times more likely to develop atopy, and those with a positive family history of only mothers are 12.55 times more likely to develop atopic manifestations compared to children with a negative family history. Cord blood eosinophil count >700/mm^3 had significant prediction: OR=5.30 which means that patients with cEo of more than 700/mm^3 had 5.30 times higher chances of having at least one allergic manifestation, controlled for all other variables used in the model. Neonatal complications (hypoxia at birth, perinatal infection and hyperbilirubinemia) are at the borderline of statistical significance ($p=0.062$). No statistically significant associations were found between development of atopic symptoms and

Table 3. *Predictors of having at least one atopic manifestation: binary logistic regression*

	OR	95% CI		p-value
		Lower	Upper	
Age (years)	0.04	0.00	2.72	0.133
Female gender	0.93	0.35	2.42	0.875
Negative family history (ref.)	–	–	–	0.003
Positive family history: mother	12.55	2.88	54.63	0.001
Positive family history: father	2.34	0.63	8.73	0.204
Positive family history: brother/sister	2.71	0.65	11.18	0.169
Positive family history: mother and father	19.03	3.02	119.96	0.002
Smoking	1.49	0.56	3.92	0.423
Medications during pregnancy	1.20	0.47	3.06	0.701
Gestational age (weeks)	0.99	0.91	1.07	0.730
Birth weight (g)	1.00	1.00	1.00	0.909
Birth length (cm)	0.86	0.51	1.46	0.585
Caesarean section	1.15	0.36	3.76	0.811
cIgE level > 0.5	0.93	0.29	3.03	0.904
cEo > 700/mm^3	5.30	1.83	15.34	0.002
Positive neonatal complications	2.66	0.95	7.44	0.062
Breastfeeding duration in months (exclusively)	0.99	0.82	1.20	0.914

cEo – cord blood eosinophil count
cIgE – cord blood total IgE level

cIgE levels (p = 0.099). We found no association between mode of delivery (p = 0.379), maternal smoking (p = 0.661), exclusive (p = 0.867) and overall breastfeeding duration (p = 0.675) and the presence of atopic manifestations in the first 4 years of life (Tables 1–3).

DISCUSSION

We conducted a prospective study in which we evaluated the usefulness of several parameters as prognostic factors for the development of atopic diseases. Identifying children at high risk may facilitate their earlier diagnosis and treatment, or even provide possibility to conduct appropriate early preventive measures. We assessed correlations of family history, maternal smoking during pregnancy, mode of delivery, cIgE, cEo, and exclusive and overall breastfeeding duration with allergy symptoms within the first 4 years of life. There is increasing evidence that the mother plays a crucial role in mediating development of foetal-infant immune response to allergens. Various studies have reported that children born from allergic mothers are more likely to develop atopy than children who have allergic fathers (12, 13). The exact nature of this maternal influence is not known. Normally, the maternal environment during pregnancy promotes an initial Th2 skewed immune response in the offspring and transition to non-allergic Th1 type response after birth (14). In children of allergic mothers the transition can be delayed thus increasing the risk for the development of allergic sensitization (15). Our findings corroborated that family history is one of several important tools that identify the children at risk. Our results affirmed that maternal influences have a stronger association with childhood allergic diseases. In earlier studies the cord blood eosinophil ratio is shown to be predictive and suitable in the screening for the onset of infantile eczema and eczema was associated with the development of allergic symptoms before the age of 24 months (16). In their one year follow up study, Haus et al. found that raised cord blood eosinophil count does not seem to be an inherited factor in terms of a predisposition for atopic disease (17). Borres et al. found that elevated eosinophil count in peripheral blood of apparently healthy infants at 3 months of age is associated with a subsequent diagnosis of atopic disease during the 18-month follow up period (18). Eosinophilia at 3 days and 3 to18 months of age was found to be associated with the development of atopic symptoms until 72 months of age (19). Rossberg et al. reported that early eosinophil count at 4 weeks of life may be helpful for counselling parents to provide preventive measures (20). In our study elevated cEo was associated with subsequent atopic manifestations up to age 4. Also 46% (13/28) of neonates with cord blood eosinophilia (after exclusion of those with perinatal infections) subsequently manifested allergy manifestations until 4 years of age. This could indicate that cord blood eosinophilia is an early sign of atopic disease so it may be helpful to identify children at risk who may benefit from early prevention measures (20). We found that neonatal complications such as hypoxia at birth, perinatal infections and hyperbilirubinemia were at the borderline of statistical significance for the future development of an allergic disease. It has been suggested that complications during the first weeks of life may influence the development of asthma in the offspring (21). Previous studies on the value of cIgE in predicting the risk of allergic sensitization and atopic manifestations have given conflicting results (22). Several studies suggest that its diagnostic value increases when combined with family history (23). Our study did not reveal any association between

the maternal smoking during pregnancy, mode of delivery, cIgE, and exclusive and overall breastfeeding with the appearance of atopic manifestations in the first 4 years of life.

CONCLUSIONS

Several clinical markers for predicting the development of allergic diseases have been studied to date. The cord blood eosinophil count seems to be predictive in screening for the onset of allergic diseases. The best method for identification of high risk infants will remain a medical history, especially a positive family history of the mother. Our results emphasized the possible early intervention or prevention strategies against the development of allergy.

Acknowledgements

We acknowledge assistant professor Milan Milošević for providing valuable service in statistical analysis and Sanja Škorvaga for supervising laboratory staff.

Conflict of Interests

None declared

REFERENCES

1. Liu T, Valdez R, Yoon PW, Crocker D, Moonesinghe R, Khoury MJ. The association between family history of asthma and the prevalence of asthma among US adults: National Health and Nutrition Examination Survey, 1999-2004. Genet Med. 2009;11(5):323-8.
2. Stick SM, Burton PR, Gurrin L, Sly PD, Le Souef PN. Effect of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. Lancet. 1996;348(9034):1060-4.
3. Svanes C, Omenaas E, Jarvis D, Chinn S, Gulsvik A, Burney P. Parental smoking in childhood and adult obstructive lung disease: results from The European Community Respiratory Health Survey. Thorax. 2004;59(4):295-302.
4. Noakes PS, Holt PG, Prescott SL. Maternal smoking in pregnancy alters neonatal cytokine responses. Allergy. 2003;58(10):1053-8.
5. Renz-Polster H, David MR, Buist AS, Vollmer WM, O'Connoor EA, Frazier EA, et al. Caesarean section delivery and the risk of allergic disorders in childhood. Clin Exp Allergy. 2005;35(11):1466-72.
6. McKeever TM, Lewis SA, Smith C, Hubbard R. Mode of delivery and risk of developing allergic disease. J Allergy Clin Immunol. 2002;109(5):800-2.
7. Pesonen M, Kallio MJT, Siimes MA, Elg P, Björksten F, Ranki A. Cord serum Immunoglobulin E as a risk factor for allergic symptoms and sensitization in children and young adults. Pediatr Allergy Immunol. 2009;20(1):12-8.
8. Gleich GJ, Adolphson CR, Leiferman KM. The biology of the eosinophilic leukocyte. Annu Rev Med. 1993;44:85-101.
9. Schoetzau A, Filipiak-Pittroff B, Franke K, Koletzko S, Von Berg A, Gruebl A, et al. Effect of exclusive breast-feeding and early solid food avoidance on the incidence of atopic dermatitis in high-risk infants at 1 year of age. Pediatr Allergy Immunol. 2002:13(4):234-42.
10. Van Odijk J, Kull I, Borres MP, Brandtzaeg P, Edberg U, Hanson LÅ. Breastfeeding and allergic disease: a multidisciplinary review of the literature (1966-2001) on the mode of early feeding in infancy and its impact of later atopic manifestations. Allergy. 2003:58(9):833-43.
11. Kusunoki T, Morimoto T, Nishikomori R, Yasumi T, Heike T, Mukaida K, et al. Breastfeeding and the prevalence of allergic diseases in schoolchildren: Does reverse causation matter? Pediatr Allergy Immunol. 2010;21(1 Pt 1):60-6.
12. Hagendorens MM, Bridts CH, Lauwers K, van Nuijs S, Ebo DG, Vellinga A, et al. Perinatal risk factors for sensitization, atopic dermatitis and wheezing during the first year of life (PIPO study). Clin Exp Allergy. 2005;35(6):773-40.
13. Litonjua AA, Carey VJ, Burge HA, Weiss ST, Gold DR. Parental history and the risk for childhood asthma. Does mother confer more risk than father? Am J Respir Crit Care Med. 1998;158(1):176-81.
14. Saito S. Cytokine network at the feto-maternal interface. J Reprod Immunol. 2000;47(2):87-103.
15. Holt PG, Macaubas C. Development of long-term tolerance versus sensitisation to environmental allergens during the perinatal period. Curr Opin Immunol. 1997;9(6):782-7.
16. Matsumoto K, Shimanouchi Y, Kawakubo K, Oishi N, Wakiguchi H, Futamura K, et al. Infantile eczema at one month of age is associated with cord blood eosinophilia and subsequent development of atopic dermatitis and wheezing illness until two years of age. Int Arch Allergy Immunol. 2005;137 Suppl l:69-76.
17. Haus M, Hall JM, Heese H de V, Weinberg EG, Berman D. Cord blood and maternal total eosinophil counts in relation to infant allergy. Pediatr Allergy Clin Immunol. 1992;3:23-7.
18. Borres MP, Olderam H, Irander K, Kjellman NI, Björksten B. Peripheral blood eosinophilia in infants at 3 months of age is associated with subsequent development of atopic disease in early childhood. J Allergy Clin Immunol. 1995;95(3):694-8.
19. Borres MP, Björksten B: Peripheral blood eosinophils and IL-4 in infancy in relation to the appearance of allergic disease during the first 6 years of life. Pediatr Allergy Immunol. 2004;15(3):216-20.
20. Rossberg S, Gerhold K, Geske T, Zimmermann K, Menke G, Zaino M, et all. Elevated blood eosinophils in early infancy are predictive of atopic dermatitis in children with risk for atopy. Pediatr Allergy Immunol. 2016;27(7):702-8.
21. Annesi-Maesano I, Moreau D, Strachan D. In utero and perinatal complications preceding asthma. Allergy. 2001;56(6):491-7.
22. Lødrup Carlsen KC, Carlsen KH, Nafstad P, Bakketeig L. Perinatal risk factors for recurrent wheeze in early life. Pediatr Allergy Immunol. 1999;10(2):89-95.
23. Høst A, Andrae S, Charkin S, Diaz-Vázquez C, Dreborg S, Eingenmann PA, et al. Allergy testing in children: why, who, when and how? Allergy. 2003;58(7):559-69.

Received November 13, 2018
Accepted in revised form October 20, 2019