

IgE against Food and Respiratory Allergens in Healthy and Allergic Mothers and Their Children

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ABSTRACT. IgE against mixtures of common food or respiratory allergens were determined by ELISA in healthy ($n = 38$) and allergic ($n = 62$) mothers and their children. Significantly higher level of IgE against respiratory allergens was found in sera of allergic mothers and in cord blood of their children. No correlation between antibody level in maternal and newborn's sera was found; this argues against the transfer of IgE from mother to fetus and points rather to offspring's intrauterine sensitization. Specific IgE level in cord blood was higher in children who developed later allergy than in children who did not. Specific IgE level in colostrum was low both in healthy and allergic mothers; there was no correlation between high concentration of IgE against respiratory allergens in sera of allergic mothers and their colostrum, which does not support the idea of IgE transport from blood to mammary gland. Only slightly increased colostral IgE was detected in allergic mothers whose children manifested allergy later. Allergy of the mother and high level of anti-allergen IgE in her serum and in cord blood are the main predictive factors of future occurrence of allergy in the offspring. A combination of several predictive factors could have higher prognostic value.

Allergic disorders mediated by IgE are very frequent in human population and their incidence steadily increases. The main risk factor for the development of allergy is the genetic background (Tariq *et al.* 1998; O'Connell 2004; Ruiz *et al.* 1992; Bergmann *et al.* 1997). However, the final outcome depends also on environmental factors and maternal immune system influencing the development of infant's immune system prenatally by the transfer of numerous biologically active substances *via* placenta or *via* amniotic fluid and postnatally by breast feeding (Hanson *et al.* 2002; Wijga *et al.* 2006). The effect of these factors has not yet been unambiguously elucidated. There is a constant effort to define predictive markers in newborns pointing to probable future occurrence of allergic ailment (Žižka *et al.* 2007). Another question is the comparison of milk of healthy and allergic mothers and the evaluation of the possibility of an adverse effect of allergic milk on the immune system of the child.

One of the factors followed in the above respects is maternal and fetal IgE, their concentration, specificity and mutual relationship. The total concentration of IgE (irrespective of its specificity) has usually been followed in the majority of studies and the results are rather controversial.

We tested specific IgE against common allergens in healthy and allergic mothers and their children in the effort to characterize differences between these two groups and evaluate possible predictive value of anti-allergen antibodies. Our results concern the first 2 years of life of the children.

METHODS

Subjects. Two groups of mothers and children according to mothers' clinical statement were used as donors: (1) healthy non-allergic mothers and their children ($n = 38$ at the beginning of the study) and (2) allergic mothers and their children ($n = 62$ at the beginning). Only mothers with physiological pregnancy and children delivered physiologically in full term were included. Diagnostics of allergy in mothers was based on clinical manifestation of allergy persisting for >2 years, monitoring by an allergologist, positive skin prick tests or positive specific IgE and anti-allergic treatment before pregnancy. Manifestation of allergy in

children was followed by allergologist during the whole time. The work was approved by the *Ethical Committee of the Ministry of Public Health* and was carried out with the informed consent of the mothers.

Tested samples. Maternal blood was obtained by venepuncture at the time of delivery. Cord blood was collected after careful cleaning of the cord by puncture of umbilical vein to avoid contamination with maternal blood. Colostrum and milk were collected after 2 d and in 3rd, 6th, 12th months, and in some cases even 2 years after delivery. The fat layer and cell pellet were removed by centrifugation (8000 g, 25 min, 4 °C).

Specific IgE was estimated immunoenzymically by RISA (Ring-Immuno-Sorbent-Assay) using Enzyme Allergo Sorbents Test (*Doverton*) kits and allergen rings with a mixture of the most common food allergens (FX 4) or the most common respiratory allergens (DYNX 1). The test was processed according to manufacturer's recommendation. Results were read from a calibration curve and expressed as kU/L. Specific IgE concentration <0.35 kU/L is considered negative in terms of possible sensitization.

Statistics. Data are presented as medians and 25th and 75th percentiles. Difference between groups was evaluated using non-parametric Mann–Whitney test. Correlation among specific IgE level in maternal sera, milk and cord blood sera was determined using Spearman's rank correlation test. The probability level $p < 0.05$ was considered significant.

RESULTS

Specific IgE against the most common food and respiratory allergens (FX 4 and DYNX 1 allergen mixtures, respectively) were tested in maternal blood taken at the time of delivery, in cord blood, in children's blood and in maternal colostrum and/or milk of healthy mothers and their children, and allergic mothers and their children. Possible manifestation of allergy in children was followed regularly by clinical examination.

Newborn children and their mothers. Groups of 38 healthy mothers and their children and 62 allergic mothers and their children were compared (Table I). The majority of allergic mothers were sensitized

Table I. IgE antibodies against food and respiratory allergens in healthy and allergic mothers and their children^a

Allergen	Sample ^b	Healthy mothers and their children			Allergic mothers and their children			<i>p</i>
		<i>n</i>	median	25–75	<i>n</i>	median	25–75	
FX 4 ^c	CBS	34	0.23	0.14–0.34	47	0.20	0.17–0.28	0.752
	MS	37	0.18	0.14–0.22	62	0.13	0.07–0.27	0.041
	COL	38	0.16	0.12–0.21	59	0.16	0.06–0.32	0.919
DYNX 1 ^d	CBS	34	0.22	0.14–0.24	47	0.25	0.22–0.37	0.003
	MS	37	0.21	0.16–0.28	62	2.93	0.74–7.46	<0.0001
	COL	38	0.17	0.14–0.22	59	0.15	0.08–0.28	0.516

^aMedian: detected by ELISA (kU/L); 25–75 – 25th–75th percentile; *p* – *p* value (two-tailed).

^bCBS – cord blood serum, MS – maternal serum, COL – colostrum.

^cMixture of food allergens. ^dMixture of respiratory allergens.

against respiratory allergens, which was reflected in increased levels of anti-DYNX 1 IgE in their sera. This difference was not accompanied by any difference in colostral levels of IgE. Anti-DYNX 1 antibodies in cord blood were very low, but their concentration in children of allergic mothers was significantly higher ($p = 0.003$) than in children of healthy mothers. For correlations of IgE levels in maternal sera, colostrum and cord blood see Table II. The low increase of anti-DYNX 1 IgE in cord blood of children of allergic mothers is caused rather by fetus sensitization (materno–fetal transfer of allergens) than by materno–fetal transfer of IgE since there is no correlation between anti-DYNX 1 IgE in maternal sera and cord blood; there is no correlation between high anti-DYNX 1 level in sera of allergic mothers and very low level of these antibodies in corresponding colostrum; this argues against the transfer of IgE from serum to colostrum.

One-year-old children and their mothers. Thirty-four healthy mothers and their children and 47 allergic mothers and their children have been followed for 1 year. In the healthy group, onset of allergy was diagnosed in one child (2.9 %), in the allergic group in 8 children (17 %). Specific IgE concentration of healthy mothers with healthy children was in all samples <0.35 kU/L. The only child with clinical manifestation of allergy had markedly increased IgE against food allergens at 6 months; after 1 year IgE was already lower but still increased (Table III *left*).

Table II. IgE antibodies against food and respiratory allergens; correlation of antibodies in maternal sera (MS) and cord blood sera (CBS) and in maternal sera and colostrum (COL)^a

Allergen	Compared samples	Healthy mothers and their children; <i>n</i> = 30			Allergic mothers and their children; <i>n</i> = 41		
		<i>r</i>	<i>p</i>	correlation	<i>r</i>	<i>p</i>	correlation
FX 4	MS vs. CBS	-0.066	0.730	—	0.394	0.011	*
	MS vs. COL	0.644	0.0001	***	0.653	<0.0001	***
DYNX 1	MS vs. CBS	0.072	0.706	—	-0.044	0.786	—
	MS vs. COL	0.468	0.009	**	0.122	0.448	—

^aSpearman's rank correlation test: *r* – correlation coefficient (positive correlation: *r* > 0; negative correlation: *r* < 0); *p* – *p* value (two-tailed).

In allergic mothers whose children developed allergy during the first year were anti-DYNX 1 antibodies at the time of parturition much higher than in mothers with healthy children (8.9 against 3.2 kU/L; Table III *right*). In both healthy and allergic children's groups, specific IgE in cord blood was higher than that of children's blood at 3 months. There was a small increase of anti-FX 4 and anti-DYNX 1 in cord blood of children who later developed allergy (Tables III and IV).

Table IV. Allergic mothers and their children till 2 years of age^a

Allergen	Sample ^b		Months	Healthy children, <i>n</i> = 11			Allergic children, <i>n</i> = 6				
				<i>n</i>	median	25–75	<i>n</i>	median	25–75		
FX 4 ^c	child	CBS serum		11	0.20	0.19– 0.30	6	0.41	0.16– 1.94		
			3	11	0.17	0.07– 0.21	5	0.19	0.16– 0.27		
			6	11	0.28	0.08– 0.31	6	0.26	0.19– 0.39		
			12	10	0.23	0.10– 0.29	5	0.23	0.13– 0.26		
			24	10	0.10	0.02– 0.25	5	0.12	0.06– 0.44		
	mother	serum		10	0.16	0.08– 0.19	6	0.24	0.18– 0.72		
				10	0.15	0.06– 0.23	6	0.34	0.17– 0.51		
		COL milk	3	9	0.08	0.05– 0.17	1	0.32	–		
			6	7	0.16	0.02– 0.19	1	0.34	–		
			12	4	0.15	0.07– 0.20	–	–	–		
		DYNX 1 ^d	child	CBS serum		11	0.22	0.00– 0.35	6	0.59	0.23– 6.18
					3	11	0.17	0.08– 0.19	5	0.20	0.17– 0.29
6	11				0.20	0.08– 0.23	6	0.22	0.16– 0.46		
12	10				0.18	0.09– 0.27	5	0.25	0.18– 0.26		
24	10				0.12	0.05– 0.19	5	0.17	0.07– 0.24		
mother	serum			10	4.05	1.26–10.97	6	10.9	0.99–35.7		
				10	0.14	0.10– 0.42	6	0.28	0.18– 0.38		
	COL milk		3	9	0.13	0.06– 0.19	1	0.35	–		
			6	7	0.15	0.04– 0.17	1	0.34	–		
			12	4	0.20	0.14– 0.27	–	–	–		

^aMedian: detected by ELISA (kU/L); 25–75 – 25th–75th percentile.

^bCBS – cord blood serum, COL – colostrum.

^cMixture of food allergens;

^dMixture of respiratory allergens

Two-year-old children and their mothers. These groups comprised 14 healthy mothers and their children and 17 allergic mothers and their children. Allergy manifestation was diagnosed in 3 children (21 %) of the healthy group and in 6 children (35 %) of the allergic group (Table IV). In the group of healthy mothers and their children, specific IgE level in cord blood, children's sera, maternal sera and colostrum and/or milk was in the physiological range in spite of a clinical manifestation of allergy in 3 children.

In the group of allergic mothers and their children, the main difference in IgE level was again among the maternal sera at the time of parturition; their IgE against respiratory allergens was much increased, mainly in mothers in whose children allergy occurred during the first 2 years (4 kU/L mothers with healthy children vs. 11 kU/L mothers with allergic ones), colostral and/or milk antibodies being low in both groups. The only difference among children was in cord blood: the children who developed allergy had a higher level of specific IgE (both against food and respiratory allergens). After birth, the IgE decreased in all children, even in

Table III. Healthy mothers and their children, and allergic mothers and their children till 1 year of age^a

Allergen	Sample ^b	Months	Healthy mothers			Allergic mothers		
			Healthy children, n = 33			Healthy children, n = 39		
			n	median	25–75	n	median	25–75
FX 4 ^c	child	CBS	28	0.26	0.14–0.34	0	–	–
		serum	29	0.16	0.10–0.20	1	0.25	–
			28	0.19	0.13–0.24	1	4.10	–
			32	0.15	0.09–0.20	1	1.13	–
	mother	serum	31	0.18	0.14–0.23	1	0.17	–
		COL	31	0.16	0.12–0.21	1	0.21	–
		milk	25	0.15	0.09–0.19	1	0.12	–
			22	0.16	0.09–0.21	1	0.07	–
	DYNX 1 ^d	child	13	0.08	0.07–0.22	1	0.12	–
		serum	28	0.22	0.19–0.24	0	–	–
			29	0.16	0.12–0.21	1	0.15	–
			28	0.16	0.12–0.21	1	0.23	–
	child	CBS	32	0.12	0.08–0.17	1	0.10	–
		serum	31	0.21	0.16–0.26	1	0.44	–
		COL	31	0.18	0.15–0.22	1	0.22	–
		milk	25	0.15	0.11–0.18	1	0.21	–
	mother	serum	22	0.13	0.10–0.17	1	0.09	–
		COL	13	0.12	0.10–0.20	1	0.17	–
	allergic children, n = 8	child	31	0.20	0.17–0.28	31	0.20	0.17–0.28
		serum	37	0.13	0.05–0.23	37	0.13	0.05–0.23
			33	0.16	0.06–0.27	33	0.16	0.06–0.27
			36	0.13	0.05–0.23	36	0.13	0.05–0.23
	allergic children, n = 8	mother	37	0.14	0.08–0.23	37	0.14	0.08–0.23
		COL	36	0.15	0.06–0.22	36	0.15	0.06–0.22
		milk	31	0.11	0.05–0.18	31	0.11	0.05–0.18
			27	0.16	0.02–0.19	27	0.16	0.02–0.19
	allergic children, n = 8	child	13	0.11	0.02–0.14	13	0.11	0.02–0.14
		serum	31	0.26	0.21–0.37	31	0.26	0.21–0.37
			37	0.12	0.06–0.19	37	0.12	0.06–0.19
			33	0.15	0.06–0.25	33	0.15	0.06–0.25
	allergic children, n = 8	mother	36	0.11	0.05–0.20	36	0.11	0.05–0.20
		serum	37	3.16	0.96–7.9	37	3.16	0.96–7.9
		COL	36	0.14	0.08–0.22	36	0.14	0.08–0.22
		milk	31	0.13	0.06–0.20	31	0.13	0.06–0.20
	allergic children, n = 8	child	27	0.15	0.04–0.21	27	0.15	0.04–0.21
		serum	13	0.12	0.10–0.20	13	0.12	0.10–0.20

^aMedian: detected by ELISA (kU/L); 25–75 – 25th–75th percentile.^bCBS – cord blood serum, COL – colostrum.^cMixture of food allergens.^dMixture of respiratory allergens.

children with future allergy, and were comparable with those of healthy children at 3, 6, 12 and 24 months (Table III *right*, Table IV).

We can suggest that the main prognostic signs from the point of view of the development of future allergy are anti-allergen IgE levels in maternal and cord blood sera.

DISCUSSION

Because of high incidence of allergic disorders in human population, there is an effort to predict the future onset of allergy already in the perinatal period to be able to make some preventive measures. The allergy of the mother is currently the most reliable predictive factor but not all children of allergic mothers become allergic. Increased levels of some cytokines are pro-allergic (Boettcher *et al.* 2000a,b) and increased proliferative response after stimulation of cord blood cells by some allergens was described in newborns at higher risk (Kobayashi *et al.* 1994). Another marker of impending allergy can be increased levels of IgE. Increased IgE levels can precede clinical manifestation of allergy and can be supposed to have a predictive value (Croneret *et al.* 1982; Wahn *et al.* 1998; Kaan *et al.* 2000; Warner 2004). Anti-allergen IgA and IgG (mainly IgG₂ and IgG₄) are described as well but their role in allergy manifestation is rather controversial – they are referred to on the one hand as blocking antibodies and on the other hand as antibodies participating in allergy pathogenesis (Pilette *et al.* 2004; Allam *et al.* 2005; Thórarinsdúottir *et al.* 2005; Taylor *et al.* 2006).

Significant difference in IgE levels we found between the healthy and the allergic group in maternal sera and in cord blood sera: differences in colostrum and milk were very low and there were not significant when the whole groups of healthy and allergic mothers were compared. A slight increase in specific IgE in colostrum and milk was evident in mothers whose children developed later allergy in comparison with mothers whose children remained healthy during the whole time. IgE level in cord blood is generally low, and its physiological level against various environmental antigens is not well defined. Kerkhof *et al.* (2005) consider specific IgE level 0.35 kU/L in the first week of life as a proof of sensitization. Such level was not always achieved in our children with clinical manifestation of allergy during the first two years of life. Several authors mention total cord blood IgE level signaling the future allergy (Businco *et al.* 1983: 1.06 ± 1.02 kU/L; Strimas and Chi 1988: 0.5; Magnusson 1988: 1.2; Kobayashi *et al.* 1994: 1; Kuiper *et al.* 2006: 0.6–0.9). High IgE level in maternal sera is of a larger predictive value. Many other authors did not find total IgE level reliable for allergy prediction (Hansen *et al.* 1992; Chang *et al.* 2005). Specific IgE has been followed very rarely in this respect.

To evaluate the possible interrelationship between maternal and fetal IgE, we analyzed the correlation among specific IgE level in maternal serum, colostrum and cord blood. These questions have been addressed several times but with different results: There was no correlation between maternal blood and cord blood IgE (Businco *et al.* 1983; Shirakawa *et al.* 1997; Shah and Bapat 2006 – only with healthy mothers); there was a correlation between maternal blood and cord blood IgE (Shah and Bapat 2006 – only with allergic mothers; Sverremark *et al.* 2002); there was only weak correlation between maternal blood and colostrum IgE pointing to local production of IgE in mammary gland (Bahna *et al.* 1982); there was a correlation between maternal blood and colostrum IgE (Duchén and Bjorksten 1996; Thornton *et al.* 2003). We did not find any convincing correlation between maternal blood and colostrum IgE. It is plausible, on the basis of these analyses, that there is no significant transfer of IgE from maternal serum to the colostrum. High level of IgE in sera of allergic mothers was not reflected in colostrum. Generally, IgE level is very low in colostrum of both healthy and allergic mothers. As contribution to the current discussion concerning possible adverse effect of milk of allergic mothers on the tuning of newborn's immune system (Boettcher *et al.* 2003; Kull *et al.* 2004) we can say that we do not assume any danger in colostrum IgE because of its low level and negligible difference between healthy and allergic mothers. Likewise, the possibility of IgE transfer from maternal blood to cord blood is not supported by our correlation tests. It is probable that IgE is produced by the fetus as a consequence of intrauterine sensitization. The decrease of IgE level in children's sera after birth could imply that the contact with allergens is more limited in the early postnatal period than during intrauterine life.

Much effort was devoted to finding some predictive factors in cord blood for the future development of allergy and some candidates were proposed: IgE level, cytokines, chemokines, soluble receptors, soluble CD14, oligounsaturated fatty acids, or the character of antigen-presenting cells (Allam *et al.* 2005). Nevertheless, maternal allergy and high anti-allergen IgE in maternal sera and cord blood still remains the most important predictive factor for the future allergy onset in a child. Simultaneous presence of several predictive factors could provide a more reliable prognosis.

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