

Cord serum immunoglobulin E as a risk factor for allergic symptoms and sensitization in children and young adults

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Early markers of atopic predisposition are needed for targeting allergy preventive measures to high-risk infants. An elevated cord serum immunoglobulin E (CS-IgE) level is considered a risk factor for subsequent allergy in childhood. However, the previous studies have not assessed the predictive value of CS-IgE in a follow-up extended to adulthood. We aimed at clarifying whether CS-IgE is useful in predicting subsequent atopic manifestations up to age 20 yr. A cohort of 200 unselected, full-term newborns were prospectively followed up from birth to age 20 yr. The CS-IgE level was successfully measured in 190 subjects at birth. The subjects were re-examined at ages of 5, 11 and 20 yr with assessment of the occurrence of allergic symptoms during the preceding year, skin prick testing and measurement of serum total IgE. An elevated CS-IgE level was associated with allergic symptoms and skin prick test positivity at age 5 yr ($p = 0.03$ and 0.01), with allergic rhinoconjunctivitis at age 20 yr ($p = 0.04$) and with an elevated serum total IgE at ages of 11 and 20 yr ($p = 0.02$ and 0.01). The sensitivity of CS-IgE, i.e. the probability of an elevated CS-IgE in an infant who subsequently develops atopy, in predicting skin prick test-verified atopy at ages of 5 and 20 yr was 50% and 26%, respectively. The combination of elevated CS-IgE and positive family history of allergy was strongly associated with subsequent atopic manifestations. Nevertheless, it showed a reduced sensitivity as compared to CS-IgE or family history of allergy. We conclude that an elevated CS-IgE level predicts subsequent atopy up to age 20 yr.

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Atopic diseases such as atopic eczema, allergic rhinoconjunctivitis and allergic asthma represent a major and increasing health problem in industrialized countries (1). Therefore, strategies to prevent the development of atopic manifestations and the progression of the early atopic symptoms into persistent symptoms later in life are necessary. In order to target the preventive measures to the newborns at a high risk of developing allergic diseases, early markers of atopic predisposition are needed (2).

An elevated cord serum IgE (CS-IgE) level is considered to be a risk factor for the develop-

ment of atopic symptoms and allergen sensitization in children. Recently, CS-IgE level has been shown to be associated with polymorphisms of interleukin-13, interleukin-4 and cytotoxic T-lymphocyte antigen 4 genes (3–5). However, previous studies on the value of CS-IgE in predicting the risk of atopic manifestations have yielded conflicting findings. Several studies have reported the CS-IgE to be ineffective in predicting early atopic symptoms, i.e. those appearing during the first 2 yr of life (6–9). However, other studies indicate that CS-IgE above 0.7–0.8 kU/l may predict

the development of atopic disease by this age (10, 11). CS-IgE ≥ 0.3 kU/l may be associated with atopic dermatitis, and atopic disease combined with elevated total IgE in children at age 18 months (12, 13). In high-risk infants, CS-IgE ≥ 0.5 kU/l may also be a risk factor for urticaria due to food allergy at 12 months of age (14). There are only a few reports available on the value of CS-IgE in predicting atopic manifestations after early childhood. A high CS-IgE may be a risk factor for developing atopic disease by the age of 10–11 yr, even though the sensitivity of CS-IgE measurement in predicting atopic disease was low (15). Furthermore, an elevated CS-IgE has been shown to be associated with allergic sensitization at ages 4 and 10 and with asthma at age 10 yr (16). In the context of the present 20-yr prospective follow-up study on unselected infants, we had an opportunity to clarify whether an elevated CS-IgE has a predictive value on subsequent atopic manifestations in children and adolescents up to age 20 yr.

Methods

Study population

This investigation is part of a follow-up study of 200 unselected newborns and their mothers initiated in 1981 (17). Healthy, non-smoking mothers with an uncomplicated pregnancy and delivery and a full-term healthy newborn with a birth weight appropriate for gestational age were invited to participate. The mothers were encouraged to breastfeed exclusively for as long as possible. During the exclusive breastfeeding, the infants received human milk without any supplementary formula or solid foods; only water and routine vitamins were allowed. The infants and the mothers were seen frequently during the first year of life; consequently, the duration of exclusive breastfeeding was reliably recorded. The number of infants on strictly exclusive breastfeeding was 167 at 2, 116 at 6, 36 at 9 and 7 at 12 months of age. When exclusive breastfeeding became insufficient for the infant, the infant was gradually weaned to a cow's-milk-based formula (Tutteli®; Valio, Helsinki, Finland) and after 3 months of age to solid foods.

Of the 200 subjects, 84 (42%) had a family history of allergy, defined as the presence of at least one first grade relative with allergic symptoms. Two of the 200 infants were lost to follow-up during the first year. Of the remaining 198 children, 163 (82%) were re-assessed at age 5 yr,

150 (76%) at 11 age yr and 164 (83%) at age 20 yr with skin prick testing, a clinical examination, and parental (at ages 5 and 11) and personal (at age 20) structured interviews by a physician unaware of the early feeding history or laboratory parameters (17).

Definitions of allergic symptoms

Atopic dermatitis was defined as a chronic or relapsing itchy dermatitis with a characteristic morphology and distribution (18). Atopic dermatitis was recorded if it was present at a follow-up examination, or if it had been diagnosed by a physician and there was a history of relapsing eczema with typical features and localization during the preceding year.

Allergic rhinoconjunctivitis was defined as recurrent non-infectious rhinitis at pollen seasons or on aeroallergen exposure, and/or itching and watery discharge of the eyes at pollen seasons or on aeroallergen exposure.

Recurrent wheezing was recorded if the subject had a diagnosis of bronchial asthma, or two or more separate episodes of respiratory distress and wheezing.

Symptoms of food hypersensitivity were defined as a repeated history of itching or swelling of the lips, the oral mucosa or the throat, urticarial eruption, or severe vomiting after ingestion of a specific food. As performing double-blind placebo-controlled food challenges were not feasible, we chose to rely on the history of food hypersensitivity, which was recorded in a personal interview by a physician and based on reports of typical symptoms appearing after ingestion of a specific food. At age 20 yr, symptoms of food hypersensitivity were no longer taken into account.

Verified atopy was recorded if the subject had one or several allergic symptoms and a positive skin prick test (SPT) to at least one of the common allergens tested.

Skin prick testing

We performed SPTs at ages of 5, 11 and 20 yr with standardized allergen extracts (ALK, Copenhagen, Denmark) of birch, alder, timothy, Kentucky blue, mugwort, cat, dog, *Der-matophagoides pteronyssinus*, cow's milk, egg and codfish; histamine hydrochloride (10 mg/ml) and a diluent control were included. A positive SPT was defined as at least one test reaction with a mean diameter equal to or greater than half the diameter of the histamine wheal.

Determination of serum immunoglobulin E (IgE) and plasma retinol concentrations

CS-IgE was determined in 190 of the 200 newborns from undiluted samples by a paper radioimmunoabsorbent test (Phadebas IgE PRIST®, Pharmacia, Uppsala, Sweden). Based on the lower analytical limit of the method, the CS-IgE values were dichotomized into <0.5 and ≥ 0.5 kU/l (16, 19).

Total serum IgE at ages 5 and 20 yr was determined by the Pharmacia ImmunoCAP System IgE FEIA® (Pharmacia Diagnostics, Uppsala, Sweden). The samples were stored at -20°C until analysed in 2004. The samples at age 11 yr were analysed by Pharmacia CAP System IgE FEIA® in 1993. The cut-off for an elevated total IgE was set to 130 kU/l at ages of 11 and 20 yr, and to 48 kU/l at the age of 5 yr (20).

The plasma concentration of retinol was determined in cord blood in every other infant entering the study. Thus, it was measured in 97 infants (21). Blood plasma was separated and frozen within 30 min, stored at -18°C and transported in dry ice by air to the Department of Human Nutrition and Health, F. Hoffmann-La Roche & Co. Ltd. (Switzerland), where the vitamin A concentration in plasma was determined by high-performance liquid chromatography (22).

Statistical analyses

Statistical analyses were performed with StatView 5.0 (SAS Institute; Cary, NC, USA). Chi-square and Fisher's exact tests were used to measure statistical significance, and $p < 0.05$ was considered indicative of statistical significance. Multivariate logistic regression analyses were performed in order to control for the effect of potential covariates. As potential covariates, gender, maternal atopy, sibship size, i.e. the number of elder siblings, duration of exclusive breastfeeding (<6 or ≥ 6 months) and smoking in the household during the infant's first year were taken into account. For the outcomes at age 20 yr, personal smoking status of the subject was added.

Sensitivity (SE), specificity (SP) and positive predictive value (PPV) were calculated according to standard procedures (8). Positive likelihood ratio (LR+) was calculated as $\text{SE}/1 - \text{SP}$.

Ethical considerations

The Ethical Review Board of the Hospital for Children and Adolescents and the Ethical

Review Board for Internal Medicine of Helsinki University Hospital have approved the study. Written informed consent was obtained from the parents at the beginning of the study, and from the participants of the 20-yr re-examination.

Results

Of the 190 infants, 38 (20%) presented with an elevated CS-IgE (≥ 0.5 kU/l). The values were within the range of 0.5–9.1 kU/l in 37 newborns. One newborn had a value of 44.4 kU/l. Because an exceptionally high CS-IgE value might be due to contamination with maternal blood, we excluded this infant from further analyses. The incidence of an elevated CS-IgE was similar in boys and in girls, and in those with and without a history of smoking in the household. Of the 79 infants with a family history of allergy, 23% had an elevated CS-IgE, whereas 17% of the 110 infants without a family history of allergy had an elevated CS-IgE.

An elevated CS-IgE was associated with subsequent allergic symptoms and SPT positivity at age 5 yr (Fig. 1). As we have previously reported, atopic dermatitis and food hypersensitivity were the most frequent allergic symptoms recorded at age 5 yr (17). Of the children with an elevated CS-IgE, 33% had atopic dermatitis at age 5 yr, whereas it was recorded in 15% of the children without an elevated CS-IgE ($p = 0.02$).

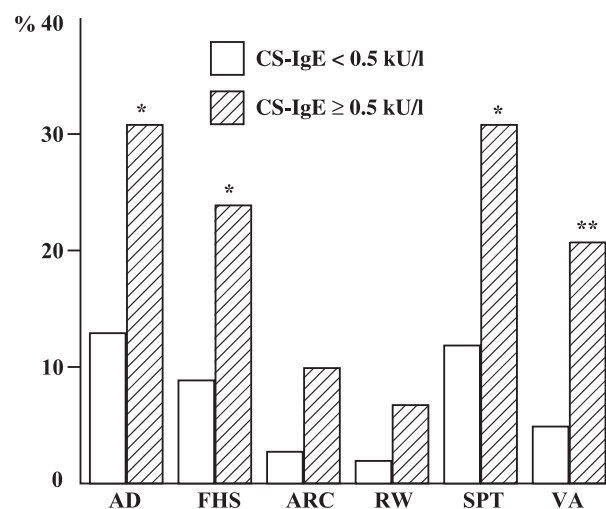


Fig. 1. Prevalence of allergic symptoms, skin prick test (SPT) positivity and verified atopy (i.e. allergic symptoms and SPT positivity) at age 5 yr in children with and without an elevated CS-IgE. AD, atopic dermatitis; FHS, food hypersensitivity symptoms; ARC, allergic rhinoconjunctivitis; RW, recurrent wheezing; SPT, skin prick test positivity; VA, verified atopy. Significant differences marked with asterisks (* $p < 0.02$, ** $p < 0.01$).

Table 1. Association of an elevated CS-IgE and atopic manifestations at ages of 5, 11 and 20 yr as calculated with logistic regression*

	OR (95% CI)	p value
Outcomes at age 5 yr		
Atopic dermatitis (n = 26)	3.9 (1.3–11.3)	0.01
Food hypersensitivity symptoms (n = 18)	4.3 (1.2–14.8)	0.02
Any allergic symptom (n = 37)	2.8 (1.1–7.3)	0.04
SPT† positivity (n = 24)	4.6 (1.7–12.7)	0.003
Outcomes at age 11 yr		
Food hypersensitivity symptoms (n = 16)	3.9 (0.9–16.9)	0.06
Allergic rhinoconjunctivitis (n = 40)	2.6 (1.0–6.9)	0.05
Elevated total IgE (≥ 130 kU/l) (n = 27)	3.2 (1.2–8.7)	0.02
Outcomes at age 20 yr		
Allergic rhinoconjunctivitis (n = 65)	2.7 (1.1–6.4)	0.02
Any allergic symptom (n = 81)	2.4 (1.0–5.7)	0.04
Elevated total IgE (≥ 130 kU/l) (n = 41)	3.7 (1.6–8.8)	0.01

*Independent variables used in the model: CS-IgE (<0.5 kU/l or ≥ 0.5 kU/l), gender, maternal atopy, sibship size, smoking in the household during the infant's first year, duration of exclusive breastfeeding. Smoking status at age 20 yr was added for the outcomes at age 20 yr.

†Skin prick test.

Furthermore, food hypersensitivity symptoms were more frequent among the children with an elevated CS-IgE (28%) than in those without (10%, $p = 0.02$). In addition, SPT positivity (n = 24) and verified atopy (n = 12) at age 5 yr were associated with an elevated CS-IgE ($p = 0.02$ and 0.01 , respectively).

We observed an association between the elevated CS-IgE and the occurrence of allergic rhinoconjunctivitis. It was significant at ages of 11 and 20 yr ($p = 0.04$ and 0.02 , respectively; Table 1). Of the children with an elevated CS-IgE, 41% had allergic rhinoconjunctivitis at age 11 yr, whereas it was recorded in 25% of those without an elevated CS-IgE. The similar percentages were 58% and 37% at age 20 yr. Moreover,

an elevated CS-IgE was associated with an elevated serum total IgE at ages of 11 and 20 yr ($p = 0.02$ and 0.01 , respectively).

As we have previously reported from the present follow-up cohort, prolonged exclusive breastfeeding was associated with an increased prevalence of atopic dermatitis at age 5 yr, and food hypersensitivity symptoms at ages of 5 and 11 yr. Therefore, the duration of exclusive breastfeeding was considered a potential confounder and included as one of the covariates in the analyses presented in Table 1. However, the CS-IgE level was not associated with the duration of exclusive breastfeeding, i.e. children with an elevated CS-IgE and those with CS-IgE ≤ 0.5 kU/l were equally likely to receive a prolonged exclusive breastfeeding (Fisher's exact test, $p = 0.8$).

A combination of elevated CS-IgE and positive family history of allergy predicted subsequent atopic manifestations more accurately than CS-IgE or family history of allergy alone, as is indicated by the higher likelihood ratios (Table 2). The combination of elevated CS-IgE and positive family history of allergy was associated with SPT positivity, allergic symptoms and verified atopy at age 20 yr (Fig. 2) as well as with SPT positivity at age 11 yr ($p = 0.05$) and SPT positivity, allergic symptoms and verified atopy at age 5 yr ($p = 0.001$, 0.01 and 0.001 , respectively). Whereas the specificities and positive predictive values were increased, the sensitivities of the combination of CS-IgE and family history of allergy were decreased as compared with those of CS-IgE or family history of allergy (Table 2).

We have recently reported from this cohort an inverse association of plasma retinol level at age 2 months and subsequent atopic manifestations (21). Therefore, we examined the possible association of cord blood retinol and CS-IgE levels.

Table 2. Comparison of the predictive value of CS-IgE ≥ 0.5 kU/l (CS-IgE+), positive family history of allergy (FHA+), and a combination of CS-IgE ≥ 0.5 kU/l and a positive family history of allergy (CS-IgE+ and FHA+) on atopic manifestations at ages of 5 and 20 yr

	CS-IgE+				FHA+				CS-IgE+ and FHA+			
	SE	SP	PPV	LR+	SE	SP	PPV	LR+	SE	SP	PPV	LR+
Outcomes at 5 yr												
Allergic symptoms	30	85	38	2.0	62	61	35	1.6	22	94	53	3.7
SPT* positivity	38	84	30	2.4	63	58	21	1.5	29	94	47	4.8
Verified atopy†	50	83	20	2.9	75	61	13	1.9	42	93	33	6
Outcomes at 20 yr												
Allergic symptoms	26	84	64	1.6	48	68	62	1.5	15	95	75	3
SPT* positivity	24	82	61	1.3	48	68	62	1.5	16	96	81	4
Verified atopy†	26	82	48	1.4	55	69	55	1.8	18	95	69	3.6

Sensitivity (SE), specificity (SP) and positive predictive values (PPV) given as percentages. LR+, Positive likelihood ratio.

*Skin prick test (SPT).

†Allergic symptoms and SPT positivity.

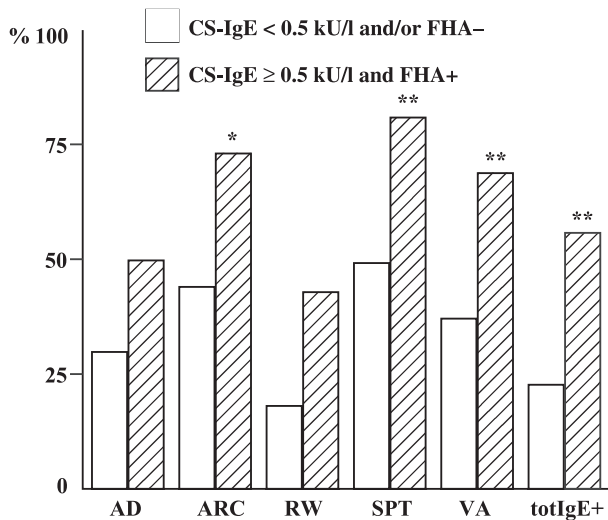


Fig. 2. Prevalence of atopic manifestations at age 20 yr in subjects with CS-IgE ≥ 0.5 kU/l and positive family history of allergy (FHA+) as compared with subjects with CS-IgE < 0.5 kU/l and/or negative family history of allergy (FHA-). AD, atopic dermatitis; ARC, allergic rhinoconjunctivitis; RW, recurrent wheezing; SPT, skin prick test positivity; VA, verified atopy (i.e. allergic symptoms and SPT positivity), totIgE+, an elevated total IgE (≥ 130 kU/l). Significant differences marked with asterisks (* $p < 0.03$, ** $p < 0.01$).

The infants with an elevated CS-IgE had a lower mean plasma retinol in cord blood than the infants with CS-IgE below 0.5 kU/l, though the difference was not statistically significant.

Discussion

Our study cohort consists of healthy, randomly selected full-term newborns prospectively followed-up from birth to age 20 yr. This setting enabled us to examine the possible association of CS-IgE level and subsequent allergic symptoms, SPT reactivity and serum total IgE in children and young adults.

We observed that an elevated CS-IgE was associated with atopic dermatitis, food hypersensitivity symptoms and SPT reactivity in children at age 5 yr. Furthermore, an elevated CS-IgE was associated with allergic rhinoconjunctivitis at age 20 yr and with a high serum total IgE at ages of 11 and 20 yr. Using a combination of a family history of allergy and an elevated CS-IgE in predicting subsequent atopic manifestations resulted in improved specificity and positive likelihood ratio, and a reduced sensitivity as compared with an elevated CS-IgE or a family history of allergy alone. In the context of the present study, the high specificity indicates that very few of the subjects who did not develop

atopic manifestations had a combination of an elevated CS-IgE and a positive family history of allergy. The modest level of sensitivity signifies that by using the combination of a positive family history of allergy and an elevated CS-IgE as a criterion, we were able to recognize only a subgroup of the subjects who subsequently developed atopic manifestations.

In order to reverse the trend of increasing atopic diseases, effective allergy preventive measures are warranted (2, 23). Along with dietary allergen avoidance measures (24), some new primary and secondary allergy preventive strategies involving the administration of probiotics (25), oral antihistamines (26) and specific immunotherapy (27) have been suggested. To be cost-efficient, the allergy preventive measures should be directed to subjects at a high risk for developing atopic diseases. Therefore, markers for screening of the atopic predisposition are needed. Our results suggest that by using the combination of family history of allergy and CS-IgE as a criterion, it is possible to identify a group of infants who are very likely to develop allergic symptoms later in life.

To our knowledge, this is the first study evaluating the predictive value of CS-IgE on atopic manifestations not only in childhood but also in young adults, i.e. at age 20 yr. Most of the previous studies have focused on the atopic manifestations in infancy or early childhood with the exception of two studies with a follow-up extended to 10–11 yr of age (15, 16). Comparisons of the results of the previous studies are complicated by the various cut-offs for an elevated CS-IgE and the different definitions of allergic outcomes. The cut-off level we used, 0.5 kU/l, has been found optimal in predicting atopic outcomes in two previous studies (16, 19). In a study by Hansen et al. (28), the similar CS-IgE determination method (PRIST®) was used as in our study, and the predictive values of CS-IgE ≥ 0.5 kU/l, and the combination of CS-IgE ≥ 0.5 kU/l and a positive family history of allergy on atopic outcomes at age 5 yr were reported. The specificities we found are very close to those reported by Hansen et al., whereas the sensitivities are higher in our study (sensitivity of CS-IgE was 50% in our study and 25% in the study Hansen et al.; and the sensitivity of the combination of CS-IgE and family history of allergy was 42% in our study and 10% in the study of Hansen et al. These differences may be due to the fact that Hansen et al. defined 'allergy' at age 5 yr as the presence of atopic symptoms and a high serum IgE, whereas we defined 'verified atopy' as the presence of atopic symptoms and a positive SPT.

Recently, we reported from the same cohort that the subjects with allergic symptoms or a positive skin prick test in childhood or adolescence had lower retinol concentrations in infancy and childhood than symptom-free subjects (21). The difference in the retinol levels was most pronounced at the age of 2 months. Therefore, we chose to test whether the CS-IgE and cord blood retinol levels were associated. We found that the infants with an elevated CS-IgE to have a lower mean plasma retinol in cord blood than the infants with CS-IgE below 0.5 kU/l; however, the difference was not statistically significant.

Maternal atopy is more strongly associated with high CS-IgE than paternal atopy (16, 29, 30). Therefore, we chose to adjust our results for the maternal atopy. In addition, we performed the logistic regression analyses with family history of allergy, instead of maternal atopy, as a covariate. This approach yielded essentially similar results.

According to some studies, maternal smoking during pregnancy is associated with increased CS-IgE (31), though others were not able to confirm this (29). In our study, only non-smoking mothers were included, and smoking in the household during the infant's first year was taken into account as a potential confounder.

All the mothers of our study cohort were encouraged to start and to maintain exclusive breastfeeding as long as it was nutritionally sufficient for the infant. As we have previously reported, prolonged exclusive breastfeeding was associated with an increased frequency of subsequent atopic dermatitis and food hypersensitivity symptoms (17). Therefore, we included the duration of exclusive breastfeeding as one of the covariates in the adjusted analyses of the present study.

The present 20-yr prospective follow-up study was begun and the CS-IgE concentrations were measured in 1981. Later on, IgA determination on cord blood samples with an elevated IgE concentration has been recommended in order to exclude the possibility of contamination with maternal blood (32). In order to avoid the effect of possible maternal contamination, we excluded one infant with an exceptionally high CS-IgE from further analyses. Therefore, only infants with CS-IgE lower than 10 kU/l were included (14).

In conclusion, we found an elevated CS-IgE in newborns to be associated with subsequent allergic symptoms, SPT positivity and an elevated total IgE in children and up to age 20 yr. A combination of an elevated CS-IgE and a positive family history of allergy predicted atopic

manifestations with a higher positive likelihood ratio and specificity than the CS-IgE level or the family history of allergy alone.

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