

Cord blood levels of immunoglobulin G subclass antibodies to food and inhalant allergens in relation to maternal atopy and the development of atopic disease during the first 8 years of life

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Summary

Background Factors that either protect from or enhance the development of atopic disease appear to be acting early in life. The gestational environment, including maternal immune responses, such as transplacentally transferred immunoglobulin (Ig) G antibodies to allergens, may be of importance in this respect, since allergen-specific immunity has been demonstrated to develop *in utero*.

Objective To evaluate the relation between cord blood IgG subclass antibodies to allergens, maternal atopy and development of atopic disease in the children.

Material and methods The study group comprised a cohort of 96 children participating in a prospective study up to 8 years of age. Cord blood IgG subclass antibodies to ovalbumin, β -lactoglobulin, Bet v 1 and cat dander were analysed by ELISA.

Results The levels of all IgG subclass antibodies to ovalbumin and rBet v 1 were higher in newborn infants with an atopic mother, as compared with babies with nonatopic mothers. IgG1 antibody levels to cat and IgG4 antibody levels to β -lactoglobulin and cat were also higher in atopic than in nonatopic mothers, whereas the other subclass antibody levels to those allergens were similar. High levels of cord blood IgG antibodies to cat and birch, but not to the food allergens, were associated with less atopic symptoms in the children during the first 8 years of life. Moreover, children who developed IgE antibodies to cat had lower levels of IgG antibodies to that allergen at birth.

Conclusions High levels of cord blood IgG subclass, especially IgG4, antibodies to food and inhalant allergens are associated with maternal atopy. High levels of IgG antibodies to inhalant, but not food, allergens are associated with less development of atopy in the children.

Keywords: allergens, atopy, childhood, cord blood, immunoglobulin G subclass antibodies

Clinical and Experimental Allergy, Vol. 30, pp. 34–40. Submitted 16 December 1998; revised 20 March 1999; accepted 24 April 1999.

Introduction

Cross-sectional [1,2] and prospective [3] studies indicate that exposure to allergens early in life may have an impact on the incidence of allergy many years later. Thus, factors that either protect from or enhance the development of

atopic disease appear to be acting early in life, i.e. during a critical period of immune development. The gestational environment may be of importance in this respect, since allergen-specific immunity has been demonstrated to develop *in utero* [4–6]. The fetus may be influenced by factors in the *in utero* environment, including maternal immune responses such as transplacentally transferred immunoglobulin (Ig) G antibodies to allergens [7]. Studies

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in rats [8] and mice [9,10] suggest that maternal IgG antibodies to ovalbumin can suppress the development of IgE antibodies in the offspring in an antigen-specific way. There are studies in humans supporting this possibility. For example, fewer positive skin prick tests to grass were seen in 3–12-year-old children whose mothers had undergone rye grass immunotherapy during pregnancy, and therefore developed high IgG antibody levels, as compared with children of untreated mothers [11]. High cord blood IgG antibody levels to food allergens have been associated with both less [12] and more [13] atopic symptoms, while other studies did not show any effect [14,15].

The aim of this study was to investigate the levels of cord blood IgG antibodies to ovalbumin, β -lactoglobulin, rBet v 1 and cat in relation to maternal atopy and development of atopic symptoms and sensitization in the children through the first 8 years of life.

Materials and methods

Study group

From November 1987 to January 1989 pregnant women and their families were asked by the midwives of the maternity clinics in the Linköping area, County of Östergötland, Sweden, to participate in the study. Participation was accepted by 96 families. Umbilical cord blood was collected at birth and the sera were frozen and stored at -20°C . The children were followed with mailed questionnaires at 3, 6, 9 and 12 months and then yearly up to 8 years. At 6 and 18 months and 8 years, a medical examination focusing on signs of atopic disease, an interview with one or both parents, and skin prick tests were performed. In addition, a venous blood sample was obtained. For this study, 78 children were selected based on availability of cord blood samples from the original cohort, which has been described in detail previously [16]. Thirty-three of those children had an atopic mother, 17 had an atopic father and 28 had no parental atopic history. The atopic status of the parents was established by a typical clinical history, e.g. allergic rhinoconjunctivitis, allergic asthma or flexural itchy dermatitis. Presence of IgE antibodies to inhalant allergens was demonstrated in all but five of the atopic mothers and two of the atopic fathers by Phadiatop[®] (Pharmacia, Uppsala, Sweden) or skin prick tests. All but three of the 78 children were born at term. Serum samples from 43 of the mothers were collected, mostly within a month of the delivery.

Atopic dermatitis was defined as pruritic, chronic or chronically relapsing noninfectious dermatitis with typical features and distribution, as suggested by Hanifin and Rajka [17]. Asthma was defined as three or more episodes of bronchial obstruction, at least once verified by a physician. Allergic rhinoconjunctivitis was defined as rhinitis and

conjunctivitis appearing at least twice after exposure to a particular allergen and not related to infection. Urticaria was defined as allergic if it appeared at least twice within 1 h of exposure to a particular allergen. Probable atopy was used when some, but not all of the diagnostic features described above were present.

Skin prick tests were performed in duplicate on the volar aspects of the forearms with egg white extract (Dome/Hollister-Stier/Bayer, Spokane, WA, USA) and skimmed cows' milk (lipid concentration 0.5%) at 6 and 18 months. At 8 years, the children were tested with standardized birch, timothy and cat extracts (Soluprick[®], ALK, Hørsholm, Denmark). Histamine hydrochloride (10 mg/mL) was used as a positive control and albumin diluent was included as a negative control. The test was regarded as positive if the mean diameter was ≥ 3 mm.

Detection of IgG subclass antibodies

The determination of IgG subclass antibodies to ovalbumin, β -lactoglobulin, rBet v 1 and cat dander was performed by ELISA as described in detail elsewhere [18].

Detection of IgE antibodies

Levels of IgE antibodies to birch, cat, egg white and β -lactoglobulin were analysed with Magic Lite (a commercial chemoluminometric method, according to the recommendations of the manufacturer (ALK, Hørsholm, Denmark). At 6 months, the sera were tested for the presence of IgE antibodies to the food allergens only, at 18 months to all allergens and at 8 years to the inhalant allergens only.

Statistics

As the levels of IgG subclass antibodies to the allergens were not normally distributed, even after logarithmic transformation, groups were compared with Mann–Whitney *U*-test, and correlations with Spearman's rank order correlation coefficient test. The chi-square test was employed for categorical variables, and Fisher's exact test was used when the expected frequency for any cell was less than five. A probability level of $<5\%$ was considered to be statistically significant. Calculations were performed with a statistical package StatView 4.5 for Macintosh (Abacus Concepts Inc, Berkeley, CA, USA).

Ethics

The study was approved by the Regional Ethics Committee for Human Research at the University Hospital of Linköping.

Allergen Subclass	Atopic mother	n	Nonatopic mother	n	P
<i>Ovalbumin</i>					
IgG	1389 (180–4870)	34	704 (63.2–2108)	44	<0.01
IgG1	139 (53.4–872)	2	70.6 (43.0–352)	42	<0.01
IgG2	169 (ND–575)	32	30.5 (ND–391)	37	<0.05
IgG3	5.1 (ND–19.1)	32	1.8 (ND–9.4)	37	<0.001
IgG4	488 (ND–3374)	34	106 (ND–899)	40	<0.001
<i>β-lactoglobulin</i>					
IgG	399 (25.0–2830)	33	233 (ND–752)	41	NS
IgG1	93.3 (ND–499)	33	88.0 (ND–266)	41	NS
IgG2	27.2 (ND–212)	32	9.3 (ND–277)	37	NS
IgG3	4.2 (ND–19.7)	32	3.0 (ND–10.4)	37	NS
IgG4	190 (ND–920)	32	30.1 (ND–660)	39	<0.05
<i>rBet v 1</i>					
IgG	81.8 (11.5–730.9)	34	28.1 (ND–64.9)	41	<0.001
IgG1	51.2 (10.7–364.7)	33	11.0 (ND–40.5)	40	<0.001
IgG2	2.5 (ND–48.2)	33	ND (ND–ND)	40	<0.001
IgG3	ND (ND–0.8)	33	ND (ND–ND)	40	<0.01
IgG4	4.2 (ND–270.1)	32	ND (ND –4.6)	39	<0.001
<i>Cat</i>					
IgG	40.5 (ND–127.7)	31	ND (ND–84.0)	39	<0.01
IgG1	26.6 (ND–79.2)	31	ND (ND–59.3)	38	<0.05
IgG2	4.3 (1.9–25.4)	31	4.7 (ND–10.6)	38	NS
IgG3	ND (ND–0.6)	31	ND (ND–ND)	38	NS
IgG4	3.7 (ND–16.5)	31	ND (ND–13.6)	38	<0.01

ND, not detectable. NS, not significant.

Results

Antibody levels in relation to maternal atopic disease

The levels of all IgG subclass antibodies to ovalbumin and rBet v 1 were higher in newborn infants with an atopic mother as compared with babies with nonatopic mothers (Table 1). The IgG1 antibody levels to cat and the IgG4 antibody levels to β-lactoglobulin and cat were also higher in babies of atopic than in babies of nonatopic mothers, whereas the other subclass antibody levels to those allergens were similar. The IgG subclass antibody levels in maternal serum were strongly correlated with the cord blood levels (Spearman's rank order correlation coefficient test, $Rho = 0.62–0.95$, $P < 0.001$). There was a trend towards a seasonal variation of the IgG subclass antibody levels to rBet v 1 in cord serum from infants of atopic mothers. Thus, the levels tended to be higher in infants born during the spring and summer, i.e. from the end of March to August (data not shown). This trend was not seen in infants of nonatopic mothers. Similarly, newborns of atopic mothers who had a cat at home had higher IgG and IgG1 subclass antibody levels to cat than newborns of atopic

mothers without a cat, whereas these differences were not seen in newborns of nonatopic mothers (data not shown). There was a similar trend for IgG2 antibodies in atopic mothers, whereas IgG3 and IgG4 antibody levels were similar.

Antibody levels in relation to the development of atopic disease

The cumulative incidence of atopic disease during the 8-year follow-up period was 42% (33/78). Thirty-seven children (47%) did not develop any allergic manifestations and eight (10%) were classified as probably atopic. Fifteen of the 33 children with maternal atopy developed atopic symptoms. The corresponding rates for the various clinical features of atopic disease were for atopic dermatitis 27%, asthma 15%, allergic rhino-conjunctivitis 4% and urticaria 1%. Four children had both atopic dermatitis and asthma, one both allergic rhinoconjunctivitis and urticaria and one both eczema and allergic rhinoconjunctivitis.

The cord blood levels of IgG subclass antibodies to β-lactoglobulin and ovalbumin were similar in children

Table 1. Cord blood IgG subclass antibodies to ovalbumin, β-lactoglobulin, rBet v 1 and cat in relation to maternal atopic disease. Median levels (AU) and the 10th and 90th percentiles are indicated. The levels in atopic and nonatopic mothers were compared with Mann–Whitney *U*-test

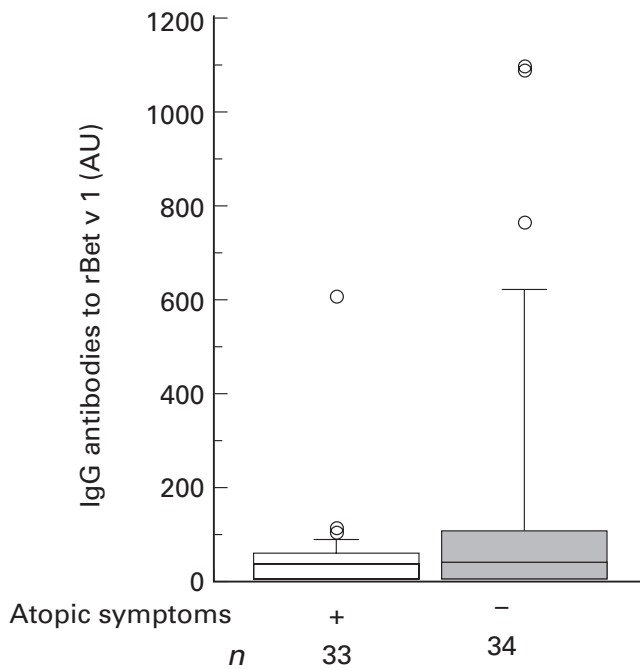


Fig. 1. Levels of IgG antibodies to rBet v 1 in cord serum of children who did or did not develop atopic symptoms. The 10th, 25th, 50th, 75th and 90th percentiles are indicated, as well as outliers.

who did or did not develop atopic disease, and were not correlated with the skin prick test results.

In contrast, children who did not develop atopic disease more often had high levels of IgG (>150 AU; see Fig. 1), IgG1 (>90 AU), IgG2 (>1 AU) and IgG4 antibodies (>25 AU) to rBet v 1 in cord blood than children with atopic symptoms (Fisher's exact test, $P < 0.05$ for IgG, IgG1 and IgG4 and $P < 0.01$ for IgG2). When absolute levels were compared with Mann-Whitney U -test, however, only non-significant trends were observed, except for IgG2 ($P < 0.01$), and then only in children of atopic mothers. Only one of seven children with positive skin prick tests to birch had high levels of IgG antibodies to rBet v 1, as compared with 22 of 63 children with negative skin prick tests (not significant). Similarly, two of eight children with IgE antibodies to birch had high levels of IgG antibodies to rBet v 1, as compared with 20 of 56 children with no circulating IgE antibodies (not significant).

Low levels of IgG (Fig. 2a) and IgG1 ($P < 0.05$), but not IgG4 antibodies, to cat in cord blood were associated with the development of atopic symptoms. Similar trends were seen in children with and without atopic mothers and in children with and without a cat at home. Furthermore, children who had developed IgE antibodies at 8 years of age had lower levels of IgG antibodies to cat in cord blood than children without IgE antibodies to cat (Fig. 2b),

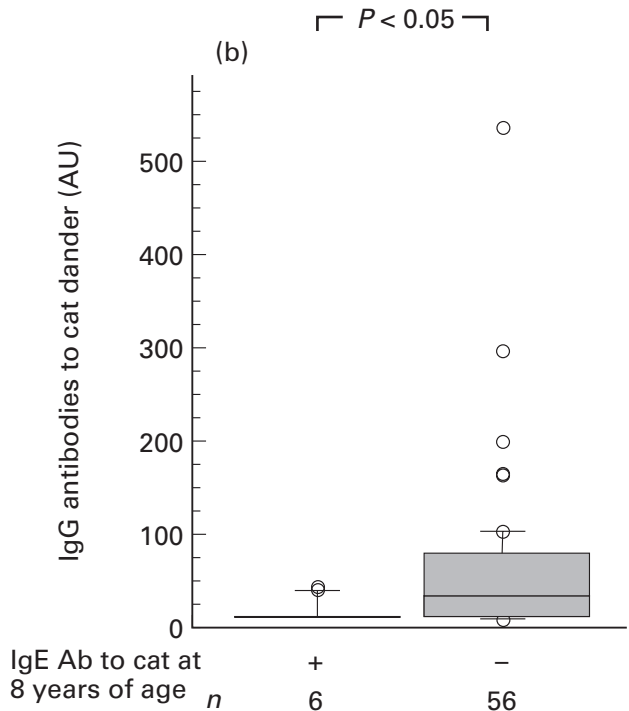
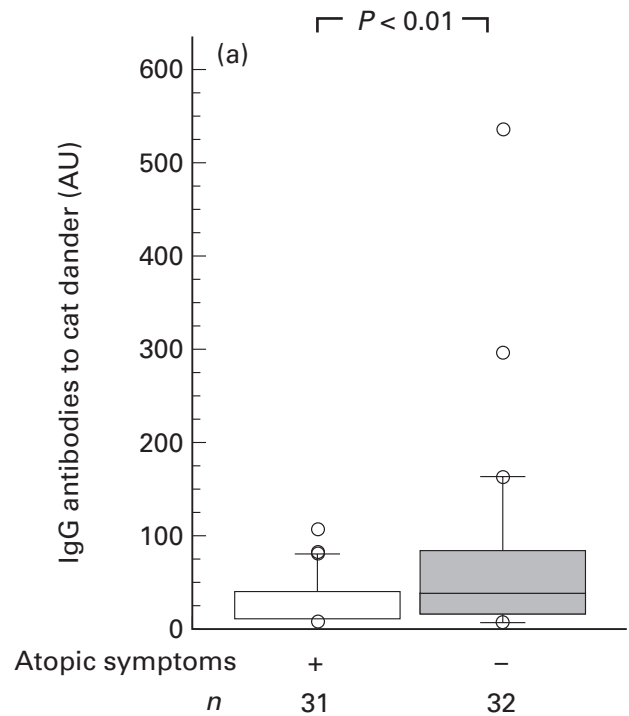


Fig. 2. Levels of IgG antibodies to cat dander in cord serum of children who did or did not develop atopic symptoms (a) or IgE antibodies at 8 years of age (b). The 10th, 25th, 50th, 75th and 90th percentiles are indicated, as well as outliers.

whereas only a similar non-significant trend was observed for IgG1 antibodies to cat in cord blood (data not shown). Similar trends were seen in children with and without atopic mothers and in children with and without a cat at home. There was also a non-significant trend towards an association between low IgG antibodies to cat in cord blood and development of positive skin prick tests to cat at 8 years of age (data not shown).

Discussion

The levels of food and inhalant allergen-specific IgG antibodies of most subclasses were higher in cord serum from infants of atopic mothers, as compared with babies of nonatopic mothers. This was most obvious for the IgG4 subclass. High cord blood levels of IgG antibodies to ovalbumin, with a similar tendency for β -lactoglobulin, have previously been reported to be associated with maternal atopy [19], while IgG antibodies to inhalant allergens in cord blood have not been studied by other groups. It has been reported, however, that the levels of IgG [20,21] and IgG4 [22,23] antibodies to *Dermatophagoides pteronyssinus* are higher in atopic individuals, while the IgG1 antibody titres are similar to those found in nonatopic individuals [22]. Furthermore, grass pollen-specific IgG4 antibody titres are higher in atopic than nonatopic individuals [22–24], whereas the levels of IgG1 antibodies have been reported to be similar [22] or higher [24]. Higher IgG4 binding activity to cat dander has also been reported in atopic as compared with nonatopic individuals [23]. Furthermore, Bet v 1-specific IgG1 and IgG4 responses were detected by immunoblotting more frequently in birch pollen-allergic than in normal individuals [25], supporting our findings in cord serum. These findings may reflect qualitatively different immune responses in atopic and nonatopic individuals, with a bias towards a production of type 2 cytokines in the former [26,27]. Enhanced humoral responsiveness in atopic individuals could be caused by increased immunoglobulin synthesis inducing efficiency of human TH2, as compared with TH1 cells, which are limited by their cytolytic activity [28]. As IgG4 switching is selectively stimulated by TH2-type cytokines [29], the higher antibody levels of this subclass in atopic individuals were expected.

High levels of cord blood IgG antibodies to cat and birch were associated with less development of atopic symptoms in the children. Moreover, children who developed IgE antibodies to cat had lower levels of IgG antibodies to that allergen at birth. This relationship seemed to be independent of maternal atopy and the presence of a cat at home, whereas the association with IgG antibodies to birch was seen only in children with maternal atopy. High levels of IgG antibodies to birch were only found in atopic mothers, whereas this was not the case for antibodies to the perennial cat allergen.

The effects of maternal IgG antibodies on immune responses in their offspring could be explained by antigen neutralization. Maternal allergen-specific antibodies may also actively suppress humoral immune responses to allergens in the children. Thus, inhibitory signals and even apoptosis [30] are transferred via immunoreceptor tyrosine-based inhibition motives when receptors for the Fc portion of IgG are cross-linked by antigen with the membrane immunoglobulin on B lymphocytes [31]. These inhibitory signals would be strongest for antibodies of the IgG1 and IgG3 subclass, since those subclasses bind the regulatory Fc γ RIIb receptors on B cells with higher affinity than IgG2 and IgG4 [31]. The IgG3 antibody levels to allergens were very low, however. High levels of all IgG subclass antibodies to birch, except the rarely found IgG3, were associated with less development of atopic symptoms. It may be difficult to distinguish the effect of the different subclasses, though, since the levels correlate. For antibodies to cat, an effect could only be demonstrated for the IgG1 subclass.

One may also speculate that maternal IgG antibodies affect the cytokine production of the child, as suggested by the observation that intravenous immunoglobulin therapy increases the plasma levels of IFN γ [32].

Studies in rats [8] and mice [9,10] suggest that maternal IgG antibodies to allergen can suppress the development of IgE antibodies in the offspring in an antigen-specific way. There are studies in humans supporting this possibility, e.g. fewer positive skin prick tests to grass in children whose mothers had undergone rye grass immunotherapy during pregnancy, and therefore developed high IgG antibody levels, as compared with children of untreated mothers [11]. Furthermore, symptoms of allergic bronchial asthma [33], rhinitis [34] and atopic dermatitis [35] may be relieved by the injection of complexes of IgG antibodies and allergens. This treatment downregulates allergen-specific IgE and IgG antibodies [36]. If maternal inhalant allergen-specific IgG antibodies are indeed protective, this may be an alternative explanation to the observations in several epidemiological studies showing an increased risk for allergy to seasonal allergens in children born before the relevant pollen season [1,2]. Birth at this time of the year would provide low levels of cord serum IgG antibodies.

Similar to previous Swedish studies [14,15], we were unable to confirm an association between high [12] or low [13] cord blood IgG antibodies to food allergens and development of atopic symptoms. Possibly, the exposure to high doses of food allergens decreases the importance of maternally-derived antibodies.

In conclusion, high levels of cord blood IgG subclass, especially IgG4, antibodies to food and inhalant allergens are associated with maternal atopy. High levels of IgG

antibodies to inhalant, but not food, allergens are associated with less development of atopy in the children during the first 8 years of life.

Acknowledgements

We thank Professor Dietrich Kraft, Institute of General and Experimental Pathology, AKH, University of Vienna, Austria, for providing the rBet v 1, and Dr Carsten Schou, ALK, Hørsholm, Denmark, for providing the cat dander extract.

We also wish to thank Lena Lindell, Ing-Marie Sandberg, Kristina Warstedt, Kerstin Hagersten and Lena Berglert for excellent technical assistance and Professor Max Kjellman, Department of Environment and Health, Division of Paediatrics, University of Linköping, for examining some of the children.

The Swedish Medical Research Council (grant #7510), the Vårdal Foundation, the National Swedish Association against Allergic Diseases, the National Heart and Lung Association and the First of May Flower Annual Campaign for Children's Health and Glaxo-Wellcome are acknowledged for financial support.

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