

Allergic symptoms up to 4–6 years of age in children given cow milk neonatally

A prospective study

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In a previously published prospective study, we followed the development of allergic symptoms in term infants with a slightly reduced birthweight (-1 SD to -2 SD). These children received, according to local routine, early feeding with cow milk formula in order to diminish such neonatal problems as hypoglycemia and hyperbilirubinemia. Of 216 infants 207 were observed for allergic symptoms up to 18 months of age. One group (F) received cow milk formula during the first days of life *before* the mother's breastmilk production started and was then breastfed; the other (B) was not given any formula before normal breastfeeding started. Unexpectedly, we found fewer allergic symptoms, in particular allergic skin problems, in the group fed cow milk, the difference being concentrated to children with a family history of allergic symptoms. At 5 years of age 183 of the 207 children have been reinvestigated. Mild symptoms of allergy (suspected and obvious) were found in 22% (F) and 27% (B) respectively (NS). Moderate and severe symptoms of allergy (obvious) were found in 4.2% (F) and 4.5% (B). In the subgroup with a double family history of allergic symptoms, 28% (7/25, F) and 59% (10/17, B) had symptoms of allergy ($p < 0.05$). This difference was even more pronounced when laboratory tests in favour of atopic diagnosis were included, 14% (F) and 53% (B) respectively ($p < 0.05$). Thus at 5 years we still find a significantly lower frequency of allergic symptoms in the subgroup fed cow milk formula early with a family history of allergic symptoms. This difference was mainly caused by a reduced incidence of mild symptoms, some of which might not be true allergic symptoms. The incidence of moderate to severe disease was not affected, which can possibly be due to the relatively small number of children, especially in the high risk group. Thus, feeding with a high allergenic load during the first days of life seems, in the long run, to be ineffective in inhibiting the development of *significant* (moderate and severe) atopic disease.

Clinical aspects

We have not been able to prove the hypothesis that early massive exposure to foreign protein has a protective effect on the development of significant (moderate and severe) allergic disease, but a suppressive effect on mild symptoms was observed.

The development of allergic symptoms in children and the impact of different feeding regimens on the incidence of allergy have been much debated in the literature. The underlying concern has to do with the rising incidence of allergic symptoms in industrialized countries, including Sweden (19).

In a previous paper (11) we reported that feeding

babies with increasing amounts of cow milk formula before the onset of breastfeeding was associated with a lower risk of allergic symptoms up to 18 months of age compared with infants only breastfed. Remarkably, the lower risk was confined to infants with a double family history of allergic symptoms.

These findings were in conflict with other studies

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(2, 3, 7, 12, 16), supporting the theory that avoidance of such highly allergenic foods as cow milk formula during the first period of extrauterine life is vital for diminishing the incidence of allergic symptoms in children. Some support for our results was to be found in animal studies showing that an early load of large amounts of allergen was associated with a reduced propensity for high-risk individuals to produce specific IgE (6). In this study we have followed the further development of allergic disease in this group of children. We have also reevaluated and classified the severity of allergic symptoms in detail, in order to strengthen the basis for our conclusions.

Material and methods

In a previous study, 207 term but low weight (-1 to -2 SD) infants randomly assigned to one of 2 groups, F or B, were followed for 18 months (11). Of these, 109 (Group F) received cow milk formula from the first day of life until normal breastfeeding started. The other 98 infants were given only their mother's breastmilk and served as controls (Group B). Of this study group 95 (F) and 88 (B) children have now been reexamined at the age of 4–6 years.

The parents completed an extended questionnaire focusing on allergic symptoms among family members and on suspected past or present symptoms of allergy in the child, as well as on type of day care, exposure to tobacco smoke and to furred pets at home and at day care. The children were then examined by one of two senior pediatricians (L.D. and S.W.), unaware of the mode of feeding, following a standardised form. Based on the clinical examination and the questionnaire, the children were classified as having possible or probable, (combined in the results as suspected), obvious or no allergy (8). Eight children, who were not able to attend our clinic, were examined and classified by their regular pediatrician. On the basis of the new questionnaire, the family history of allergic symptoms was classified as follows. *Single heredity*: one parent or a sibling with a history of allergic symptoms. *Double heredity*: 2 parents or one parent and a sibling with such a history.

A skin prick test (SPT) against a standard panel (birch, timothy, cow milk, egg, cod, cat, horse) (Soluprick ALK 3 hep) was done on the volar side of the forearm by an experienced nurse according to the "Nordic Guidelines". SPT was considered to be positive when the wheal was at least 50% of the area of the wheal for histamine chloride 3 mg/ml, used as a reference.

The duration of breastfeeding, alone or mixed, after the neonatal period, was similar in the total groups as well as in the subgroups based on family history of allergy, as reported in detail in our earlier study (11). The time of introduction of solid food

was between 4 and 6 months of age in all but 7 children, with a later introduction.

Blood samples were taken for analysis of serum IgE RIACT, Pharmacia Diagnostics AB, Uppsala, screening tests for IgE antibodies against airway allergens (Phadiatop, Pharmacia Diagnostics AB) and a custom-made pediatric food allergen mix (Pharmacia Diagnostics AB) containing egg, milk, wheat, peanut and soy bean.

IgE values were classified as normal when IgE was less than mean + 1 SD for age, moderately high between mean + 1 and mean + 2 SD, high when exceeding mean + 2 SD for age (10).

Statistical methods

The chi-square test with Yates' correction and Fisher's exact test were used for statistical analysis of the results. Comparisons between exposure groups were calculated as odds ratios with 95% confidence intervals (14).

The study was accepted by the Ethics Committee of Karolinska Institute. Informed parental consent was obtained.

Results

There were 24 (14 F, 10 B) dropouts after the evaluation at 18 months. Among these, one (7%) of the F and 4 (40%) of the B children were regarded as allergic at 18 months of age. The corresponding figures in the reexamined group are 20% (F) and 32% (B) respectively.

The 2 groups were similar as regards age, exposure to tobacco smoke, furred pets and type of day care (Table 1). Stratification for these confounding factors did not change the crude odds ratio for development of allergic symptoms. At follow-up, clinical allergy was obvious in 9 (F) and 9 (B) children, while 16 (F) and 18 (B) had suspected allergy. The

Table 1. Exposure to environmental factors in Group F, initially formula fed, and Group B breastfed

	Group F n=95	Group B n=88
Mean age (years)	4.8	4.7
Percentage with:		
Smoking at home	54	49
Maternal smoking		
Fur animals:		
At home	44	48
In day-care	19	22
Type of day-care:		
Day-care centre	52	56
Family day-care	29	26

majority had only mild symptoms; only 4 children in each group were considered to have moderate or severe allergic symptoms.

SPT was performed in 83% of Group F and 82% of Group B. Blood was sampled for signs of allergy in 78% of Group F and 75% of Group B. In symptomatic children, SPT and/or blood test were done in 92% (F) and 100% (B). IgE above mean + 1 SD and/or a positive SPT and/or positive Phadiatop or Pediatric Food Allergen Mix, were found in 36% of the tested children in Group F, compared to 46% in Group B (NS). In the following these findings are labeled "laboratory evidence of allergy". This evidence was found in 29% of the asymptomatic children compared to 66% of the symptomatic children. IgE above mean + 2 SD and/or a positive SPT and/or positive Phadiatop or Pediatric Food Allergen Mix, labeled "strong laboratory evidence", was found in 23% (F) and 28% (B) of the tested children. Such evidence was found in 12% of the asymptomatic and 54% of the symptomatic children.

The frequency of allergic heredity, based on history, was similar in the 2 groups (Table 2). Stratification for heredity increased the odds ratio for development of allergic symptoms from 0.8 (0.4–1.5) to 1.8 (0.8–3.5) in children with a family history of allergy. The frequency of allergy in the subgroups based on family history is also shown in Table 2. A significant difference was found in the groups with double heredity, where 28% of Group F children but 59% of Group B children were classified as having suspected or obvious allergy on clinical grounds ($p < 0.05$). This difference was even greater when

Table 3. Distribution of children with different (suspected and obvious) allergic symptoms according to: clinical judgement in relation to family history of allergy. No statistically significant differences were found between Groups F and B with similar heredity. Percentages for all children with a symptom in Groups F and B are given in parentheses.

	Group F n=95			Group B n=88		
	no	single	double	no	single	double
Heredity Number	42	28	25	32	39	17
Eczema	9	2	5 (17)	5	9	8 (25)
Asthma	3	4	2 (9)	1	3	4 (9)
Rhino-conj.	2	4	3 (9*)	1	1	0 (2*)
Gastro-intest. allergy	2	0	0 (2)	0	0	1 (1)
> one symptom	4	2	2 (8)	1	2	3 (17)

laboratory evidence was added, 14% vs 53% ($p < 0.05$). In the subgroups with no or single heredity no significant difference was found even when laboratory evidence was included (Table 2).

No statistical differences were found in the distribution of different allergic symptoms (Table 3), with the exception of rhinoconjunctivitis, where more cases were found in Group F, 9/95, compared to 2/88 in Group B. A tendency towards more cases of atopic eczema was found in Group B.

We also studied specific allergy, indicated by a positive prick test (Table 4). The only cases with a positive SPT to milk were found in Group F, including one case with severe multiple allergy and without a family history of allergy. However, positive prick tests to airway allergens were more frequent in Group B. These differences were not statistically different.

Discussion

In our first study (11) we followed 207 of originally 216 newborn infants to the age of 18 months. They

Table 2. Distribution of children with suspected or obvious allergic symptoms according to clinical judgement and different degrees of laboratory evidence in relation to family history of allergy in Group F (initially formula-fed), and Group B (breastfed). The statistical comparison has been made between F and B subgroups with similar heredity. Percentages are given in parentheses

	Group F n=95			Group B n=88		
	no	single	double	no	single	double
Heredity Number	42	28	25	32	39	17
Allergic: suspected	5	7	4	4	8	6
obvious	5	1	3	2	3	4
Total	10 (24) NS	8 (29) NS	7 (28) *	6 (19) NS	11 (28) NS	10 (59) *
Tested children n	34	24	22	27	32	15
Laboratory evidence	5 (15) NS	5 (21) NS	3 (14) *	5 (19) NS	7 (22) NS	8 (53) *
strong evidence	5 (15) NS	4 (17) NS	1 (5) *	4 (15) NS	7 (22) NS	6 (40) *

* $p < 0.05$.

Table 4. Presence of specific IgE antibodies, indicated by a positive skin prick test, in Group F (initially formula-fed) and Group B (breastfed)

	Group F n=80	Group B n=74
SPT positive to:		
cow milk	3	0
egg	1	1
cod	1	1
any food	3	2 NS
birch	3	5
timothy	2	4
dog	0	3
cat	3	4
horse	0	4
any airway allergen	6	11 NS

were fullterm with a slightly low birthweight (-1 to -2 SD) and without major neonatal problems. The infants in one group (F) were supplemented with cow milk formula from the first day of life, according to a local routine at that time to diminish certain neonatal problems (e.g. hypoglycemia, hyperbilirubinemia), the other group was taken off this routine and did not receive formula initially. Both groups were breastfed as soon as the mother's lactation started. The time of introduction of solid food uniformly followed the present recommendation from the Swedish Pediatric Association, i.e. at 4 to 6 months of age. The frequency of smoking at home and domestic furred animals were comparable to that in a recent Swedish study (20), with no difference in the 2 groups.

Symptoms of allergy, according to criteria from earlier Swedish studies (8), before 18 months of age developed in 18% of the children in the early formula fed group (F), compared to 33% in the other group (B). The difference in frequency of allergic symptoms was confined to the children with a double family history of allergy, and was concentrated to allergic skin disease. The study thus raised the hypothesis that early feeding with cow milk formula *before* breast milk feeding might reduce the incidence of allergic symptoms before 18 months of age in a high-risk group for allergy. Criticism has been raised regarding the limited number of children in the high risk group, the numbers of investigators involved, and diagnosis based on clinical criteria solely, all factors weakening the basis of the conclusion in the first paper.

In the present study, the overall frequency of allergic symptoms, compared to a contemporary Swedish study in the same age group (9), was for obvious allergy 9.8% vs 18.2%, and for total allergic symptoms 28.5% vs 36.7%. This could possibly indicate a tendency of underdiagnosis in our study.

Whereas our earlier study showed a significantly lower incidence of allergic symptoms in the formula-fed group, the difference in this study was found to have diminished. This could partly be explained by the limited number of dropouts where a higher frequency of allergic symptoms was found in Group B, 4/14, compared to 1/10 in Group F. Another possibility is that the criteria for diagnosis have been more strictly used in the present paper with its limited number of investigators. However, the frequency of children with allergic symptoms is still significantly lower in the F subgroup with a double family history of allergy.

We found a relatively high overall frequency of a family history of allergy, 59.5% vs 30–50% in other Swedish studies (9, 20). The distribution of children with allergic symptoms between subgroups with different hereditary allergic loads follows the expected

pattern in the breastfed group. In this group we found the highest frequency in the subgroup with a double family history of allergy. In the initially formula-fed group, however, we found much the same frequency of allergic symptoms regardless of family history of allergy. Thus the difference in the frequency of allergic symptoms between the subgroups with a double family history of allergy might be due to a suppressive effect of the mode of feeding.

In this 4 to 6 year follow-up, we find a diminishing difference in the frequency of allergic symptoms between the 2 feeding regimens, even when laboratory evidence is taken into account. However, in the subgroups with a double family history of allergic symptoms, the significantly higher frequency of suspected and obvious allergic symptoms, mainly from the skin, in the exclusively breastfed group, was augmented when laboratory tests were included. This difference was, however, mainly caused by a lower frequency of mild allergic symptoms in the "high-risk" subgroup of formula-fed children, while the incidence of children with moderate or severe allergic disease was similar.

Other studies have stressed the importance to allergic symptoms of smoking, exposure to animal dander, type of day-care and time of introduction of solid foods. These factors were similar in the 2 groups of children, and did not change the risk of developing allergic symptoms in this study.

When examining specific allergy by SPT, we found a positive reaction to cow milk only in the group fed formula initially. This is in accordance with earlier studies showing an increased incidence of cow milk allergy during the first year in children exposed to cow milk during the first week of life (5, 15). Specific allergy to airborne allergens tended to be more frequent in the breastfed group. This might indicate that some children in Group B may develop allergic rhinitis or even asthma later on and may reduce the difference in the incidence of rhinoconjunctivitis found in this 5-year follow-up.

In each group we found 4 children with moderate to severe disease, including one child with severe symptoms in the formula fed group without a family history of allergy. We thus still find a lower incidence of allergic symptoms, suspected and obvious, in the formula-fed subgroup with a double family history of allergy.

The earlier suggestion (1), that lymphokines in breastmilk from atopic mothers could increase IgE synthesis, has been refuted (17). However, direct cell- to -cell interaction between lymphocytes in breastmilk and the newborn's lymphocytes in cord blood or in the gastrointestinal tract has not been studied as regards IgE production. A suppressive effect on IgE production in a high-risk population when exposed to large amounts of allergen, as spec-

ulated by Jarrett on the basis of animal studies (6), could still be an explanation for our finding, though it is contradicted by the finding of positive SPT to cow milk in the initially formula-fed group. One possibility is that this suppressive effect exists but that occasional triggering of allergy can not be excluded. This would make massive exposure to foreign protein in the first days of life an unreliable method for suppressing the future development of allergic symptoms.

In conclusion, the difference in the frequency of allergic symptoms at the age of 18 months within this group of children is no longer pronounced at 4 to 6 years of age, and cannot be shown regarding obvious allergic symptoms. We still find, though, when including suspected and obvious allergic symptoms, even when laboratory support is taken into account, a reduced incidence among the small number of children with the presumed highest risk, i.e. those with a family history of allergy. This might indicate a possible IgE-suppressive effect of early massive exposure to foreign protein of insignificant clinical importance. However, the incidence of children with moderate to severe disease is similar in the 2 groups. We also find indirect signs of specific allergy, i.e. positive SPT, against cow milk only in the initially formula-fed group.

As in several other recent studies, our experience also suggests that, in the long run, the influence of different diets on the development of atopic disease appears to be limited (4, 13, 18).

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