

Serum IgE in healthy infants fed breast milk or cow's milk-based formulas

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Summary

A group of ninety-five infants was followed from birth to one year of age, and the total serum IgE concentration was studied. The infants were fed on breast milk, home-prepared cow's milk formula, or proprietary infant milk formula. Solid foods were introduced at 3.5 months of age. The breast milk group had lower IgE than the cow's milk group up to 4 months of age, i.e. until the end of exclusive milk feeding. The formula group had intermediate IgE values. The difference was not due to the presence of IgE antibodies to cow's milk in the bottle-fed infants, since no such antibodies could be detected. After the introduction of solid foods the differences between the groups disappeared. Our data suggest that exclusive breast milk feeding can reduce total serum IgE concentration in early infancy. Reference values for unselected infants and for infants with no atopic manifestations are reported.

Introduction

Many factors of both genetic and environmental origin appear to contribute to the development of immediate hypersensitivity (Type I allergy, atopic allergy). Cow's milk-based formulas and other potentially allergenic foods may be among the causative factors, especially if introduced early in life (Johnstone & Dutton, 1966; Halpern *et al.*, 1973; Gerrard *et al.*, 1973; Koivikko, 1974; Matthew *et al.*, 1977; Björkstén & Saarinen, 1978). Prolonged breast feeding may postpone the development of food allergies. However, the information on relationships between infant feeding and immediate hypersensitivity is scarce and even controversial (May & Bock, 1978).

The level of serum IgE is low at birth, and the rise through the first year of life is documented in follow-up studies on infants with asthmatoïd bronchitis (Foucard, 1974), infants with a positive family history of immediate hypersensitivity (Kjellman & Johansson, 1976; Soothill *et al.*, 1976; Matthew *et al.*, 1977) infants with no such risk factors (Berg & Johansson, 1969; Bazaraï, Orgel & Hamburger, 1971; Kjellman, 1976), infants on an allergen-avoidance regimen (Matthew *et al.*, 1977), and a mixed group of

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infants (Orgel *et al.*, 1975). A high concentration of serum total IgE in infants and young children is related to an increased risk of the appearance of overt immediate hypersensitivity (Kjellman, 1976; Dannaeus, Johansson & Foucard, 1978).

The purpose of the present study was to evaluate the effect of three different milk regimens, including breast feeding, on the concentration of serum total IgE in healthy infants during their first year of life. Multivariate analyses were performed in order to examine separately the effects of the milk feeding regimen, age, sex, atopic heredity, and observed atopic symptoms.

Subjects

A group of 238 healthy term infants with birth weights over 3 kg were followed from birth to 1 year of age. The infants were born at the Helsinki University Central Hospital during the first 3 months of 1975. Every healthy newborn, whose parents agreed to join the programme, was included. The infants were seen at the Children's Hospital at the ages of 2 weeks, and 1, 2, 4, 6, 9 and 12 months for dietary instructions and blood sampling.

Dietary regimens

Breast milk was initially recommended for every infant. At the time of weaning, every second infant, determined randomly at the time of birth, was started on an industrial proprietary milk formula, and the others on a home-prepared cow's milk formula (Table 1). For infants under 6 months of age the latter formula was prepared as follows: 600 ml of commercially available pasteurized and homogenized dairy milk and 400 ml of water were mixed and brought to the boiling point, after which 50 g of lactose was added. After 6 months of age, commercially available cow's milk as such was used.

Solid foods were introduced to all infants after 3.5 months of age according to a strict protocol. Cooked vegetables and fruit were given after 3.5 months, cereals after 5 months, meat and eggs after 6 months, dairy products after 8 months, and a free diet after 9 months of age. The use of fish and citrus fruits was avoided until one year of age.

Study groups

Out of the 238 infants, three study groups with a total of ninety-five infants were selected for the present study as follows:

Table 1. Composition of milks used in the study. In the proprietary formula also vitamins and minerals were added

	Breast milk	Proprietary formula	Home-prepared cow's milk formula
Energy (Kcal/l)	680	675	620
Lactose (g/l)	70	72	80
Proteins (g/l)	11	15	20
Casein (%)	40	40	80
Whey (%)	60	60	20
Fats (g/l)	36	35	23
Saturated fatty acids (%)	50	36	73
Unsaturated fatty acids (%)	50	64	27

(i) *Breast milk group* (twenty-three boys and eighteen girls). Breast milk was the only source of milk until 6 months of age, after which the infants were gradually weaned either to proprietary milk formula, or cow's milk. Until 6 months of age we tried to exclude cow's milk-containing foods from the diet as far as this was possible through parent counselling.

(ii) *Cow's milk group* (twelve boys and fourteen girls). Cow's milk formula prepared at home was started prior to one month of age and continued until 6 months of age, after which commercial cow's milk was consumed. Partial breast feeding continued on an average until 2.5 months of age.

(iii) *Formula group* (fourteen boys and fourteen girls). Proprietary industrial milk formula was started prior to one month of age and continued until one year of age. Partial breast feeding was continued on an average until 3 months of age.

Definitions of atopic heredity and of suspected immediate hypersensitivity

Family history of immediate hypersensitivity (atopy) was defined as the occurrence of allergic asthma, allergic rhinitis, atopic dermatitis, or food allergy in at least one parent or sibling. As possible symptoms of immediate hypersensitivity in infants we included typical or suspected atopic dermatitis, food allergy causing skin reactions or heavy vomiting after ingestion, or typical asthmatoïd bronchitis at least once before one year of age.

The medical care of the infants was handled almost completely and the atopic symptoms registered by one of the authors (U.M.S.) during the study.

The proportion of infants with a positive family history of immediate hypersensitivity was highest in the breast milk group (44%) and lowest in the formula group (36%), but the differences were not statistically significant.

Methods

At every visit of the infants, venous blood was drawn. The sera were stored at -20° until analysed.

Laboratory determinations

Serum total IgE was determined with the Phadebas IgE PRIST kit (Pharmacia Diagnostics, Uppsala, Sweden). After all samples had been collected, they were randomly allocated to analysis series. In 6.8% of the cases, an insufficient amount of sample was available. A control serum pool was analysed in duplicate in every series, and the results indicated a variation coefficient of 11%. Concentrations below 0.5 u/ml could not be accurately measured, and in the statistical analyses these low concentrations were assumed to be 0.4 u/ml.

Serum milk-specific IgE was determined with the Phadebas RAST kit.

Statistical methods

Serum IgE values have a log-normal distribution (Kjellman, Johansson & Roth, 1976), and logarithmic values were therefore used in the statistical analyses. The effects of different factors on serum IgE concentration, e.g. sex, heredity, or type of milk feeding, were studied separately by the analysis of variance with unbalanced data (Searle, 1971). The method estimated the dependence between serum IgE and the parameter under analysis when adjusted by the confounding factors in the model. Statistical significances were tested with the F-test.

Results

A number of factors seem to affect the concentration of serum total IgE in infancy. These include age, atopic disease, possibly sex, and also the quality of milk feeding.

The adjusted values of serum total IgE were higher in cow's milk-fed infants than in breast-fed infants at the ages of 1, 2 and 4 months ($P < 0.01$, $P < 0.01$, and $P < 0.05$, respectively) (Fig. 1). There was a small, although not significant difference between the values already at the beginning of the study at 2 weeks of age. The interpretation of this result is somewhat difficult since in more than half of the bottle-fed infants the respective formula was started before the first IgE determination at 2 weeks of age, and the starting levels unmodified by feeding effects remain thus unknown. When the results were adjusted for this difference in starting level, the breast milk group and the cows' milk group still had different values at 1 and 2 months of age ($P < 0.05$). The formula group had intermediate values in the 0.5–4 month period. At 6 months of age and later, no significant differences could be noted between the three study groups.

Milk-specific IgE was, surprisingly, only found in a few infants of the breast milk group, but not at all in infants of the cow's milk or formula groups when these studies were performed at 6 and 12 months of age (Björkstén & Saarinen, 1978).

Twenty-two out of the ninety-five infants fulfilled our criteria of suspected immediate hypersensitivity. These individuals had a higher average concentration of serum total IgE than those without symptoms (Fig. 2). This difference was evident after about 2 months of age but reached a statistical significance ($P < 0.05$) only at the age of 6 months. It is of interest that the magnitude of this, more or less predicted difference, was not greater than the difference between the breast milk and cow's milk groups. Atopic heredity, found in 40% of the infants, did not affect the serum IgE concentration in any obvious manner.

Wide individual variations were found in the concentrations of serum total IgE. The average IgE level was low at 2 weeks of age, increased greatly until 6–9 months of age, and then remained relatively stable (Table 2). Boys had higher mean values than girls in all age groups, but this difference never reached statistical significance.

In order to determine reference values for healthy non-atopic infants, those with

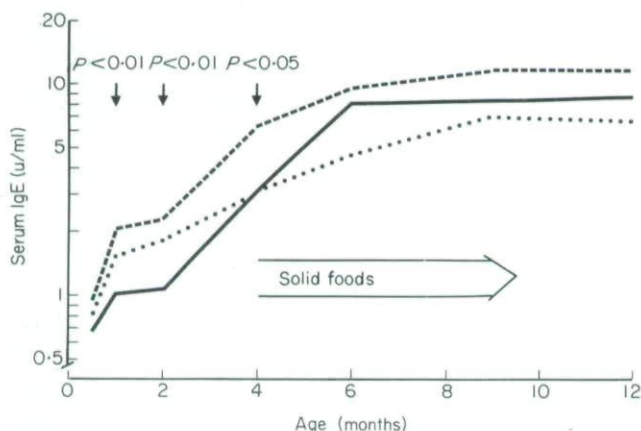


Fig. 1. The concentration of serum total IgE in the three study groups at different ages. Geometric means statistically adjusted for sex and inheritance are shown. The P -values indicate significant differences between the breast milk group and the cow's milk group. (- - -), Cow's milk; (—), breast milk; (· · ·) formula.

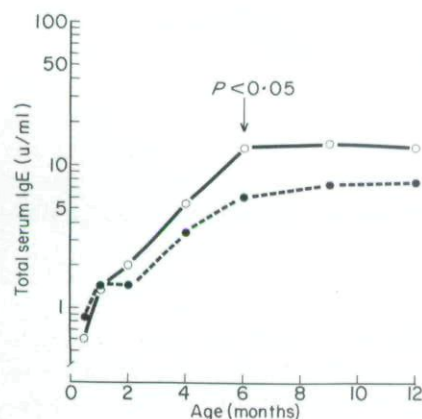


Fig. 2. The concentration of serum total IgE in infants with and without symptoms of immediate hypersensitivity. The geometric means have been statistically adjusted for sex, heredity, and type of milk feeding. The number of samples available varied between seventy-three and ninety-four in the age groups. ○, with atopic symptoms, ●, without atopic symptoms.

Table 2. The concentration of total serum IgE (u/ml) in unselected infants at different ages. No exclusions of adjustments have been made

Age (months)	n	geometric mean	± 2 s.d.
0.5	73	0.78	0.12-5.05
1	84	1.42	0.17-11.93
2	93	1.53	0.16-15.00
4	88	3.77	0.27-52.76
6	94	7.26	0.43-122.35
9	90	8.57	0.50-146.89
12	91	8.92	0.50-159.06

Table 3. Serum total IgE (u/ml) of 'healthy' infants found in the present study, compared with two other studies. Data are for subjects without symptoms of immediate hypersensitivity. In the other two studies subjects with a positive inheritance were excluded also.

Age (months)	Present study			Bazara <i>et al.</i> (1971)			Kjellman <i>et al.</i> (1976)		
	n	Geometric mean	± 2 s.d.	n	Geometric mean	± 2 s.d.	n	Geometric mean	± 2 s.d.
0				18	1.35	0.10-19.21	24	0.22	0.04-1.28
0.5	54	0.85	0.12-6.00						
1	63	1.43	0.16-13.06						
1.5				15	1.84	0.08-42.14	17	0.69	0.08-6.12
2	72	1.41	0.14-14.61						
3							15	0.82	0.18-3.76
4	68	3.38	0.26-43.96						
6	72	6.16	0.43-88.14	10	24.00	5.47-105.27	15	2.68	0.44-16.26
9	69	7.39	0.50-109.01				16	2.36	0.76-7.31
12	70	7.88	0.46-134.80				12	3.49	0.80-15.22

suspected atopic symptoms were excluded (Table 3). The additional exclusion of infants with only a positive atopic inheritance did not result in lower IgE values.

The starting IgE level appeared to have some prognostic value. The concentration tended to remain low in infants with low starting levels and high in infants with high starting levels. Significant differences were maintained at 1, 2 and 4 months of age ($P < 0.01$, $P < 0.001$, and $P < 0.05$, respectively), when the infants, who at 2 weeks of age had an IgE level less than or equal to 0.5 u/ml, were compared with infants with a level initially above 0.5 u/ml.

Discussion

Our data indicate that milk feeding has an influence on the serum IgE concentration in early infancy. The breast-fed infants had lower total IgE levels during the time of exclusive milk feeding, but after the introduction of solid foods the difference disappeared. Milk feeding is a factor which could be manipulated externally, and it might be worthwhile to study whether a longer-lasting effect on serum IgE could be obtained by postponing further the introduction of other foods except breast milk.

The higher total IgE levels in bottle-fed infants were not due to milk-specific IgE; such antibodies could not be detected in any of them (Björkstén & Saarinen, 1978). It appears that early weaning tends to raise serum total IgE through some non-specific effect, e.g. through adjuvant-like action. The response of serum IgE to early weaning was similar to that of serum IgA (Saarinen, Pelkonen & Sumes, 1977). It seems that some healthy infants synthesize IgE and some IgA as an unphysiological response to early weaning, giving a possible basis to the variable symptoms and signs which can be induced by feeding on cows' milk (May & Bock, 1978). Between the IgE and IgA values in individual infants we did not find any correlation.

The proprietary formula-fed infants tended to have intermediate IgE values during the exclusive milk feeding, when compared with the breast milk group and the cow's milk group. Milk-specific IgE was not found. We cannot conclude whether the proprietary formula had effects different from those of the home-prepared cow's milk formula.

It is difficult to obtain useful reference values for the total serum IgE concentration in infants or small children. It is not obvious whether individuals with a positive family history of immediate hypersensitivity should be excluded, or which criteria of 'health' should be used. Our 95% ranges for infants with no symptoms of atopy extend to higher values than the ranges found by Kjellman *et al.* (1976) for children selected by stricter criteria (Table 3). Still, we rejected 23% of the infants as atopic. Statistics recalculated from the data of Bazara *et al.* (1971) are more similar to ours (Table 3). The differences may in part be due to variable accuracy (bias). We also include data for unselected infants (Table 2).

An elevated level of IgE in infancy has been associated with an increased risk of subsequent allergic disease (Kjellman, 1976; Kjellman *et al.*, 1976). This finding, together with the present data provide circumstantial evidence in favour of breast feeding as a method of reducing the prevalence of allergic disease.

Acknowledgments

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