

Serum IgE in infants and influence of type of feeding

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Summary

Serum IgE in healthy infants was followed longitudinally during the first year of life and was related to heredity for allergy and type of feeding. During the first 6 months of life there were no significant differences of serum IgE levels in relation to presence or absence of heredity for allergy and type of feeding. IgE levels determined at the age of 12 months in infants who were weaned after the age of 6 months were significantly higher than in infants weaned before that age ($P < 0.05$). When the time periods had passed, following onset of cow's milk-feeding and complete cessation of breast-feeding, and were correlated to IgE at the age of 12 months, there were inverse significant correlations; i.e. the earlier the onset of cow's milk-feeding the lower the IgE and the later the cessation of breast-feeding the higher the IgE. This was particularly obvious as regards infants with heredity for allergy and a long duration of breast-feeding ($r = -0.43$; $P < 0.01$). Infants with heredity for allergy subjected to a hypoallergenic diet adhered to for 6 months had significantly higher IgE at the age of 12 months than infants with similar heredity but a normal diet ($P < 0.05$). The results indicate that serum IgE during late infancy is influenced by both genetic factors and the time of introduction of cow's milk formula in the diet and the time of cessation of breast-feeding.

Introduction

Several studies have demonstrated an association between atopic allergy and elevated levels of serum IgE (Johansson, 1967; Berg & Johansson, 1969; Havne *et al.*, 1973; Church, Kleban & Bellanti, 1976). Elevated IgE levels in parents are accompanied by elevated levels in offsprings (Gerrard *et al.*, 1974). High serum IgE often predicts the occurrence of atopic disease (Orgel *et al.*, 1975; Kjellman, 1976). Other clinical studies indicate an association between the type of feeding during infancy and subsequent

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development of atopy (Glaser & Jonstone, 1953; Jonstone & Dutton, 1966; Blair, 1977; Koivikko, 1974; Chandra, 1979; Saarinen *et al.*, 1979). These reports prompted us to study longitudinally serum IgE in infants with respect to type of feeding; particularly with regard to breast feeding and formulas with cow's milk.

Materials and methods

Subjects

The parents of all infants born in April–May and July–September 1977 at the Obstetric Clinic of University Hospital, Umeå, were requested to participate with their babies in a longitudinal study for one year. During that time period there were about 400 deliveries. The parents of sixty-eight infants gave their informed consent to participate in the study. Another two infants joined the study from the age of 3 months. The infants were admitted to the Out-Patient Clinic of Paediatrics four times during the study period; i.e. at the ages of 1 month, 3 months (mean 3.1 months, range 2.5–3.75 months), 6 months (mean 6.3 months, range 5.75–8 months) and 12 months (mean 12.5 months, range 11.5–14.5 months). Based on data given in the questionnaire and on the first visit to the Out-Patient Clinic the infants were assigned into either a group with heredity for allergy (forty infants) or a group without this heredity (30 infants). Criteria for heredity for allergy were history of asthma, seasonal rhino-conjunctivitis, atopic eczema and/or recurrent urticaria in parents or elder siblings.

Laboratory studies

The infants were capillary-bled by a finger-puncture. In fifty infants T lymphocytes and blood eosinophils were determined at the age of 1 month, the results of which are presented in detail elsewhere (Juto & Strannegård, 1979). Serum IgE was determined at the ages of 3, 6 and 12 months using Phadebas IgE PRIST® test kit (Pharmacia Diagnostics AB, Uppsala, Sweden). Cow's milk-specific IgE antibodies were analysed at the age of 12 months using Phadebas RAST® (Pharmacia Diagnostics AB, Uppsala, Sweden). Sera were stored at –25°C until analysed. All samples in each group were analysed on the same occasion.

Type of feeding

All but one of the infants were initially breast-fed. The time for introduction of formula and weaning (defined in the following as complete cessation of breast-feeding) were carefully recorded. The formulas were based on cow's milk with one exception; one infant was given a soy-bean based formula from the age of 2 weeks to 8 months. At the age of 2 months fruit-juices were added to the diet of the infants. From the age of 3 months fruits and potatoes were introduced. Cereals, meat, fish and egg were added to the diet from 5 months of age. Mothers who were breast-feeding their infants at the age of 3 months without addition of formula were advised to feed their baby with, in addition to breast milk, a modified diet in which cow's milk, cereals, fish and egg were completely excluded. This hypoallergenic diet was recommended up to the age of 6 months. The hypoallergenic diet was adhered to by seventeen infants (12 infants with heredity for allergy and 5 lacking this heredity). The median time for weaning was at the age of 5 months for infants with heredity for allergy and 5.5 months for infants without this heredity. Six infants were breast-fed for less than a week and four for more than 12 months.

Statistical analyses

The Mann-Whitney U test was used for analyses of IgE between different groups. Comparison between the duration of mixed-feeding in groups with and without cow's milk-specific IgE-antibodies was made using Student's *t*-test. For calculation of correlations between different durations of feeding with breast milk or cow's milk Pearson's correlation coefficient was used. In the following serum IgE values are given as geometric means $\pm$ 1 s.d.

Results

The serum IgE levels in different age groups are shown in Table 1. As shown in the

Table 1. Serum IgE levels (u/ml) at different ages in infants in relation to heredity for allergy.

Atopic allergy in parents and/or siblings	Age groups					
	3 months			6 months		12 months
	<i>n</i>	g.m.	$\pm$ 1 s.d.	<i>n</i>	g.m.	$\pm$ 1 s.d.
Present	39	1.8	0.6-5.3	33	5.8	1.4-23.5*
Absent	29	1.5	0.5-4.6	23	2.8	1.1-6.8
Total	68	1.7	0.6-5.0	56	4.3	1.2-15.2
	65	4.4	1.1-17.4			

g.m. = Geometric mean; $\pm$ 1 s.d. = range of $\pm$ 1 standard deviation.

n = numbers of subjects.

* $P=0.07$ when compared to infants without heredity for allergy.

Table IgE was higher, although not statistically significant in infants with heredity for allergy than in infants without this heredity.

In Table 2 serum IgE values were related to feeding with breast milk or formula. There was a tendency to higher values in the mixed-fed groups at all ages compared to the solely breast-fed or formula-fed groups, although the differences never reached statistically significant levels. In Fig. 1 serum IgE levels at the age of 12 months were related to cessation of breast-feeding before or at the age of 6 months and after that age. As shown in Fig. 1 IgE was significantly higher in babies who were weaned after the age of 6 months ($P<0.05$).

The results shown in Fig. 1 are, in Table 3, given as coefficients of correlation; i.e. serum IgE at the age of 12 months was correlated to the time periods passed in weeks since the onset of feeding with cow's milk and the cessation of breast-feeding until the time of blood-sampling. As shown in the Table there were significant inverse correlations; i.e. the earlier the introduction of cow's milk the lower the value of IgE at the age of 12 months and the later the cessation of breast-feeding the higher the value of IgE at the same age. This was particularly obvious as regards babies with heredity for allergy ($r=0.43$; $P<0.01$).

The effect of a hypoallergenic diet compared to a normal diet on serum IgE at the age of 12 months in babies who were weaned at that age is shown in Table 4. Babies with heredity for allergy subjected to the hypoallergenic diet had significantly higher

Table 2. Serum IgE levels (u/ml) in infants at different ages in relation to feeding with breast and/or cow's milk

Type of feeding	Age groups							
	3 months			6 months			12 months	
	<i>n</i>	g.m.	± 1 s.d.	<i>n</i>	g.m.	± 1 s.d.	<i>n</i>	g.m. ± 1 s.d.
Breast milk	37	1.5	0.4-5.3	8	2.9	0.7-12.4	—	
Breast and cow's milk	8	2.1	0.7-6.2	17	7.4	2.1-24.6	4	5.9 0.8-44.7
Cow's milk	23	1.9	0.8-4.1	31	3.5	1.1-11.0	61	4.4 0.9-170

Abbreviations as in Table 1.

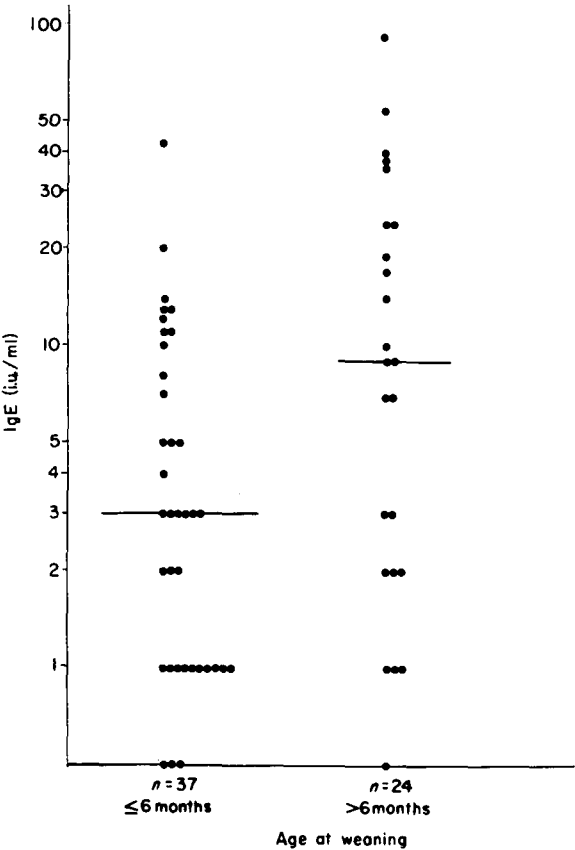


Fig. 1. Serum IgE levels at the age of 12 months in sixty-one infants weaned before or after the age of 6 months. The horizontal bars indicate median values. Significantly different values between the two groups can be seen ($P < 0.05$).

Table 3. Coefficients of correlation between the time since onset of feeding with cow's milk (sixty-five infants) and the time since cessation of feeding with breast-milk (sixty-one infants) and serum IgE levels (u/ml) at the age of 12 months with regard to the presence or absence of heredity for allergy.

Heredity for allergy	Coefficients of correlation with regard to the time since			
	Onset of feeding with cow's milk		Cessation of feeding with breast milk	
Present	$r = -0.36$	$P < 0.05$	$r = -0.43$	$P < 0.01$
Absent	$r = -0.17$	n.s.	$r = -0.32$	$P = 0.06$
Total	$r = -0.29$	$P < 0.05$	$r = -0.36$	$P < 0.01$

Table 4. Serum IgE levels (u/ml) at the age of 12 months in relation to a hypoallergenic diet adhered to for 6 months and a normal diet in infants with or without heredity for allergy.

Heredity for allergy	Type of diet				
	Hypoallergenic			Normal	
	<i>n</i>	g.m.	± 1 s.d.	<i>n</i>	g.m. ± 1 s.d.
Present	9	10.8	2.3-49.0*	26	3.5 1.1-11.0
Absent	5	3.5	1.0-12.4	21	4.0 1.0-15.9
Total	14	6.3	1.4-28.2	47	3.6 1.0-12.9

* Statistically significant difference compared to infants with heredity for allergy and a regular diet ($P < 0.05$).

Abbreviations as in Table 1.

IgE than babies with similar heredity on a normal diet ($P < 0.05$). For infants without heredity for allergy there were not significant differences as regards these types of diet.

Cow's milk-specific IgE antibodies were present in nine of fifty-seven infants at the age of 12 months. The presence of such antibodies appeared to be influenced by the time that had passed since cessation of breast-feeding, since they were present in six of twenty-five infants (24%) with a period of less than 6 months since weaning and in three of thirty-two infants (9%) in infants with a period of more than 6 months since weaning. However, the differences were not statistically significant.

The duration of mixed feeding with breast milk and cow's milk also seemed to influence the occurrence of cow's milk-specific IgE antibodies. Thus infants with these antibodies had a duration of mixed feeding of 2.6 ± 2.2 months and infants without them 1.5 ± 1.5 months ($P = 0.06$). Total IgE was significantly higher in babies who had cow's milk specific IgE antibodies than in babies lacking them (12.3 ± 3.7 and 3.2 ± 3.4 u/ml, respectively ($P < 0.001$)). Cow's milk specific IgE antibodies were not signifi-

cantly more common in infants with heredity for allergy than in infants lacking this heredity.

Discussion

The association between atopic allergy and serum IgE in children is well established (Johansson, 1967; Berg & Johansson, 1969; Havne *et al.*, 1976). Intolerance in infants to foods such as cow's milk is often associated with elevated IgE levels (Dannaeus *et al.*, 1977) and these elevated levels can decrease during a period of strict elimination diet (Crouch, 1977; Juto, Engberg & Winberg, 1978). There are, however, few studies in which the development of serum IgE in healthy infants has been studied in relation to the type of feeding. Matthew *et al.* (1977) in a study of infants of allergic parents found a lower serum IgE level at the age of 6 weeks in infants who received an allergen-avoidance diet than in those on a normal infant diet. Saarinen *et al.* (1979) very recently reported that feeding with home-prepared cow's milk formula compared to exclusive breast-feeding was associated with significantly higher serum IgE levels at the ages of 1, 2 and 4 months. These authors have also reported that cow's milk-specific IgE antibodies were only detected in exclusively breast-fed infants (Björkstén & Saarinen, 1978). Stevenson *et al.* (1972) found that breast-fed babies developed positive skin reactions to anti-IgE later than babies with cow's milk feeding.

Data obtained in the present longitudinal study support previous findings that the type of feeding influences serum IgE during infancy. However, our data do not agree in all respects with those in previous reports, since the cow's milk-fed babies in our study did not show significantly higher IgE levels than breast-fed babies during early infancy. In the present study the highest IgE levels at the age of 6 months were recorded in the group with both breast- and cow's milk-feeding. When the IgE levels at the age of 12 months were related to the time passed since the onset of cow's milk feeding and the cessation of breast-feeding the rather surprising result was that babies with the longest duration of breast-feeding had significantly higher IgE-levels. This was particularly obvious in babies with heredity for allergy subjected to an allergen-avoidance regimen. A possible explanation for these results would be that in the early phase of antigenic stimulation, particularly with low doses of antigen, the IgE response to the antigen is facilitated. If the antigen stimulation is then continued with increasing amounts of antigen the IgE response is inhibited. This explanation is supported by data received from experiments with mice, which have shown that the IgE response in certain so called high-responder strains is facilitated by low doses of antigens and inhibited by large doses (Tada, 1975; Jarret, 1977; Katz 1978).

Babies with heredity for allergy might represent a population of individuals with a genetic constitution comparable to the high-responder mice population. This would explain the higher IgE response in babies with heredity for allergy and prolonged breast-feeding. Mixed feeding may diminish the quantity of absorbable intact immunogenic proteins in the gut, since secretory IgA in breast milk may agglutinate the species' foreign proteins and make them more available to proteolytic digestion with subsequent loss of immunogenic properties (Walker & Bloch, 1974; McClelland & McDonald, 1976). Thus feeding with breast milk in combination with other food items, paradoxically, would stimulate to synthesis of IgE antibodies during late infancy in infants belonging to the high responder population. Early onset of cow's milk-feeding would on the other hand, particularly in the low-responder population, lead to lower IgE levels. This would thus implicate that early onset of cow's milk-feeding

activates antigen non-specific suppression of IgE synthesis provided these suppressor mechanisms are intact.

Several clinical studies have shown that early cessation of breast-feeding is associated with increased risk of developing atopic disease (Grulee & Stanford, 1936; Koivikko, 1974; Blair, 1977; Chandra, 1979; Saarinen *et al.*, 1979). There are also studies which have demonstrated that elevated IgE levels during infancy are good predictors of atopic allergy (Orgel *et al.*, 1975; Kjellman, 1976). Our findings may seem to conflict with these reports. Indeed, even in our study early weaning onto cow's milk resulted in higher symptom scores suggesting atopy rather than did late weaning (Juto, 1980). However, the IgE levels were not significant when correlated to symptom scores. This latter finding would indicate that serum IgE is not so well correlated to atopy in this particular age group. Apparently, other factors, e.g. heredity for allergy, type of feeding and the duration of a particular type of feeding influence serum IgE levels. High or only moderately elevated levels at the age of 1 year in a baby who had been weaned early might be an indication of diminished capacity to suppress the IgE antibody synthesis in spite of massive and prolonged antigenic stimulation. Thus such an individual would be at risk of developing atopic disease. On the other hand an elevated level in another baby at the same age a short time after weaning may be less predictive, since this individual would be in the stimulatory phase of IgE synthesis. A second, later IgE determination would in that case give a lower value indicating a suppressive capacity of the IgE synthesis.

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References

- BERG, T. & JOHANSSON, S.G.O. (1969) IgE concentrations in children with atopic diseases. A clinical study. *International Archives of Allergy and Applied Immunology*, **36**, 219.
- BJÖRKSTÉN, F. & SAARINEN, U.M. (1978) IgE antibodies to cow's milk in infants fed breast milk and formulae. *Lancet*, **ii**, 624.
- BLAIR, H. (1977) Natural history of childhood asthma. 20-year follow-up. *Archives of Disease in Childhood*, **52**, 613.
- CHANDRA, R.K. (1979) Prospective studies of the effect of breast feeding on incidence of infection and allergy. *Acta Paediatrica Scandinavica*, **68**, 691.
- CROUCH, T.H. (1977) Serum IgE levels and cow's milk and egg antigens. *Lancet*, **ii**, 979.
- CHURCH, J., KLEBAN, D. & BELLANTI, J. (1976) Serum Immunoglobulin E concentration and radioallergosorbent tests in children with atopic dermatitis. *Pediatric Research*, **10**, 97.
- DANNAEUS, A., JOHANSSON, S.G.O., FOUCARD, T. & ÖHMAN, S. (1977) Clinical and immunological aspects of food allergy in childhood. 1. Estimation of IgG, IgA and IgE antibodies to food antigens in children with food allergy and atopic dermatitis. *Acta Paediatrica Scandinavica*, **66**, 31.
- GERRARD, J.W., HORNE, S., VICERS, P., MACKENZIE, J.W.A., GOLUBOFF, N., GARSON, J.L. & MANIGAS, C.S. (1974) Serum IgE levels in parents and children. *The Journal of Pediatrics*, **85**, 660.
- GLASER, J. & JOHNSTONE, D. (1953) Prophylaxis of allergic disease in the newborn. *The Journal of the American Medical Association*, **153**, 620.
- GRULEE, S. & SANFORD, H. (1936) The influence of breast and artificial feeding on infantile eczema. *The Journal of Pediatrics*,

- HAVNE, J., AMLIE, P.A., HVATUM, M., OSEID, S., VEGGAN, T. & AAS, K. (1973) IgE concentrations in allergic asthma in children. *Archives of Disease in Childhood*, **48**, 850.
- JARRET, E. (1977) Activation of IgE regulatory mechanisms by transmucosal absorption of antigen. *Lancet*, **ii**, 223.
- JOHANSSON, S.G.O. (1967) Raised levels of a new immunoglobulin class (IgND) in asthma. *Lancet*, **ii**, 951.
- JOHNSTONE, D. & DUTTON, A. (1966) Dietary prophylaxis of allergic disease in children. *The New England Journal of Medicine*, **274**, 715.
- JUTO, P., ENGBERG, S. & WINBERG, J. (1978) Treatment of infantile atopic dermatitis with a strict elimination diet. *Clinical Allergy*, **8**, 493.
- JUTO, P. & STRANNEGÅRD, Ö. (1979) T-lymphocytes and blood eosinophils in early infancy in relation to heredity for allergy and type of feeding. *The Journal of Allergy and Clinical Immunology*, **64**, 38.
- JUTO, P. (1980) Immune responses, type of feeding and atopic allergy in infants. *Umeå University Medical Dissertations*, **57**, 29.
- KATZ, D. (1978) Control of IgE production by suppressor substances. *The Journal of Allergy and Clinical Immunology*, **62**, 44.
- KJELLMAN, N.-I. M. (1976) Predictive value of high IgE levels in children. *Acta Paediatrica Scandinavica*, **65**, 465.
- KOIVIKKO, A. (1974) Childhood asthma in Finland. A survey of 559 Patients. *Acta Allergologica*, **29**, 30.
- MATTHEW, D.J., NORMAN, A.P., TAYLOR, B., TURNER, M.W. & SOOTHILL, J.F. (1977) Prevention of eczema. *Lancet*, **i**, 321.
- MCCLELLAND, D.B.L. & McDONALD, T. (1976) Antibodies to cow's milk proteins in human colostrum. *Lancet*, **ii**, 1251.
- ORGEL, G.A., HAMBURGER, R.N., BAZARAL, M., GORRIN, H., GROSHONG, T., LEONIR, M., MILLER, K.R. & WALLACE, W. (1975) Development of IgE and allergy in infancy. *The Journal of Allergy and Clinical Immunology*, **56**, 269.
- SAARINEN, U.M., KAJOSAARI, M., BACKMAN, A. & SIIMES, M.A. (1979) Prolonged breast-feeding as prophylaxis for atopic disease. *Lancet*, **ii**, 163.
- SAARINEN, U.M., BJÖRKSTEN, F., KNEKT, P. & SIIMES, M.A. (1979) Serum immunoglobulin E in healthy infants fed breast milk or cow's milk-based formulas. *Clinical Allergy*, **9**, 339.
- STEVENSON, D., ORGEL, A., HAMBURGER, R. & REID, R. (1972) Development of IgE in newborn human infants. *The Journal of Allergy and Clinical Immunology*, **48**, 61.
- TADA, T. (1975) Regulation of reaginic antibody formation in animals. *Progress in Allergy*, **19**, 122.
- WALKER, A., ISSELBACHER, K. & BLOCH, K. (1974) Immunological control of soluble protein absorption from the small intestine: a gut surface phenomenon. *The American Journal of Clinical Nutrition*, **27**, 1434.

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