

Atopic babies with wheezy bronchitis

Follow-up study relating prognosis to sequential IgE values,
type of early infant feeding, exposure to parental
smoking and incidence
of lower respiratory tract infections

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Clinical course and sequential IgE values were recorded in a 4-year prospective study of 80 atopic wheezing babies at ages from 6 months to 4-5 years. At final assessment, 68 % of the children had been symptom-free for at least 1 year whilst 32 % still suffered from wheezing attacks. Total IgE levels from the first visit until final assessment were > 2 SD above normal for age in 63 % of all children, but no significant correlation could be found between sequential IgE levels and the clinical picture or course of the disease. In all cases IgE levels rose steadily with increasing age, independently of whether wheezing disappeared or persisted. The most significant rise in IgE values occurred between 1 and 2 years of age, and IgE levels at 4 years could be predicted by the value at the age of 2 years ($r = 0.97$). In the group of children that lost their wheezing tendency there was: a), a significantly greater number of infants that were breast-fed during at least the first 3 months of life ($P < 0.01$), b), a lower incidence of exposure to parental smoking ($P < 0.01$), and c), a lesser incidence of lower respiratory tract infections ($P < 0.01$). Though there was no correlation between increase of IgE levels and type of feeding or exposure to cigarette smoke, statistical data confirms that bottle feeding and parental smoking lead to persistence of wheezing in atopic children.

Key words: allergy prevention; atopic infants; IgE levels; wheezy bronchitis.

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“Wheezy” or “spastic” bronchitis associated with upper respiratory tract viral infections is not uncommon in babies and usually disappears by the age of 2 years (14). In atopic patients, however, wheezing is often the first sign of a hyperactive respiratory tract, since 70 % of these children will continue having symptoms at the age of 4 years, and many will have a tendency to suffer from asthma throughout childhood and some until puberty (15). This group is of particular interest because of the challenge to find factors that could either predict or influence the natural history of their illness. For this reason we followed 80 atopic babies between the ages of 6 and 24 months with wheezy bronchitis from their first visit to our allergy clinic until they reached the age of 4-5 years. It was our aim to observe the course of their respiratory

symptoms under standard conditions of life and medical care. At final assessment we analysed the relationship between persistence of wheezing and type of early feeding, presence of parental smoking, incidence of lower respiratory tract infections, and production of IgE. The study was carried out at the Pediatric Allergy unit of the Kaplan Hospital. All babies in the district are born in this hospital's maternity unit where cow's milk is not offered to breast-fed newborns between meals. The decision regarding the type of early feeding is taken by the parents, although the pediatricians make a point of stressing the advantages of breast feeding. Once at home, virtually all babies come under the care of the local well-baby clinic nurses and pediatricians. Babies with allergic illnesses are referred to our hospital's pediatric

allergy clinic for evaluation, treatment and follow-up. They usually arrive for their first visit to our clinic with a detailed report from the local pediatrician and are further interviewed and then undergo a complete physical examination and skin testing.

PATIENTS AND METHODS

Eighty babies between 6 and 24 months of age who were seen in the clinic or hospital because of respiratory wheezing attacks were selected for this study if they fulfilled at least two of three of the following criteria: a), previous atopic disease diagnosed by the family pediatrician (atopic eczema, allergic rhinitis), b), atopic disease in first degree relatives (atopic eczema, allergic rhinitis, allergic asthma, hayfever), and c) positive skin tests to common allergens. The group consisted of 56 males and 24 females with a mean age of 13.3 months of whom 49 were totally breast-fed and 31 bottle-fed during the first 3 months of life. In 48 cases, either one or both parents smoked cigarettes in the home. Each patient was reexamined at 6-month intervals by the same allergist during the 4 years following the first visit. The degree and grade of their respiratory symptoms was assessed on a scale from 0 (no symptoms) to 3 (maximum severity), and any intercurrent illnesses were recorded. In all cases, stools were analysed at least twice for parasites. Skin tests were performed with common allergens using the modified prick-test (21). The following allergenic extracts (in 50 % glycerol) obtained from Hollister-Stier were used: cow's milk casein and albumin, egg yolk, banana, chocolate, and *Alternaria* in concentrations of 1:10 (w/v); whole cow's milk, egg white and whole egg, 1:20; and *Dermatophagoides farinae*, 1:50. Total blood IgE levels were measured by the Phadebas Prist technique on entry to the study and at ages 1, 2 and 4 years, and the results kept by the laboratory and given to the investigators only at final assessment. As control (normal) IgE reference values we used results obtained by us from 60 healthy, non-atopic babies aged between 6 months and 5 years living in the same geographical area (unpublished data).

These values are similar to those reported by Kjellman in 1976 (16). During the 4-year study all patients received our routine management for allergic children which included instructions for the avoidance of allergens and preparation of an allergen-free room. Patients with positive skin tests to foods were instructed to eliminate the offending food from their diet. Conventional bronchodilator drugs were used where necessary, and in 44 cases nebulised disodium cromoglycate (DSCG) was used prophylactically. This treatment was advised for those children who had frequent, troublesome wheezy bronchitis despite regular bronchodilator therapy, either at the first clinic visit or during the follow-up period. Information on compliance with recommended preventive measures and medical treatment was obtained from parents and from written reports from the local health-care staff.

RESULTS

At final assessment between 4 and 5 years of age, 68 % of the 80 children had been symptom-free for at least 1 (the last) year, whereas 32 % had persistent wheezing attacks (Table 1). In the symptom-free group (vs the persistent wheezing group), 70 % were males (69 %), 72 % were breast-fed (38 %), 52 % were subjected to parental smoking (77 %) and 74 % reported less than two lower respiratory tract infections

Table 1
Final assesement of clinical outcome after 4 years in 80 wheezing babies

	Recovered (n = 54)**%	Continued wheezing (n = 26) %	P
Male	70	69	NS
Breast feeding	72	38	< 0.01*
Parental smoking	52	77	< 0.01*
Positive skin tests	33	53	NS
IgE > mean + 2 SD	65	57	NS

* Significant at 1 % level; SD = Standard deviation; NS = Non-significant; ** Free of wheezing attacks for at least 1 year.

including pneumonia, bronchitis, bronchiolitis or croup (34 %); 33 % had positive skin tests (53 %), 31 % required conventional anti-spasmodic medications (47 %) and 69 % received, in addition, nebulished DSCG preventative therapy (53 %). In 63 % IgE levels were greater than 2 SD above the mean for the healthy, age-matched control population (57 %). Chi-square analysis for ascertaining the association between patient characteristics and clinical outcome of wheezing showed a significantly better prognosis in breast-fed infants as well as in those whose parents did not smoke. There was a negative correlation between lower respiratory tract infections and recovery rate, i.e. in the children that recovered the majority (74 %) had less than two infections during the trial period, whereas in the persistent wheezing group only 35 % had less than two infections (Table 2). Amongst all the children, 27 of 48 (56 %) who were exposed to passive smoking had more than two lower respiratory tract infections, whilst only four of 32 (12 %) of non-smoking parents had an increased number of infections.

To assess whether exposure to smoking, tendency to lower respiratory tract infections, and clinical outcome were correlated, we used two different models (12) of statistical analysis (Table 2). The first was a model of independence,

where the hypothesis is that each one of the three factors acts independently and has no effect upon the other two. The values expected from this model were significantly different from those observed in our study population and this was interpreted as meaning that there is a mutual interaction between the factors (Table 2). We therefore tried another statistical model where the hypothesis is that each one of the three factors interacts with one of the remaining two. This is a log-linear model where the three factors interact pairwise but do not interact simultaneously. The values expected from this model match the ones observed in the study and therefore we chose to use the second model because it best fits our data. It shows that the chance of recovery from wheezing attacks is 1.6 times less in the smoke-exposed infants, and that the odds for complete recovery in those with a tendency for repeated lower respiratory tract infections compared to those with less than two such infections is 0.226 to 1. At final assessment no significant correlations were found between sex, positivity of skin tests, or elevated IgE levels and early recovery from wheezing (Table 1). The results of nebulished DSCG as preventative treatment in small children with recurrent wheezing attacks have been reported previously and showed that DSCG was effective

Table 2
Lower respiratory tract infections and parental smoking during 4-year study of wheezing atopic infants

Outcome (n = 80)	Lower respira- tory tract infections	Parental smoking	Statistical analysis			
			a) Model of independence		b) Log linear model without 3rd order interactions	
			Expected values	Standardized residuals	Expected values	Standardized residuals
Recovered (n = 54)	a) ≥ 2	+ 11	12.55	0.44	11.76	-0.22
	n = 14	- 3	8.37	-1.86	2.23	0.51
	b) < 2	+ 17	19.85	-0.64	16.24	0.19
	n = 40	- 23	13.23	2.69*	23.77	-0.16
Persistent wheezing (n = 26)	a) ≥ 2	+ 16	6.05	4.05*	15.24	0.19
	n = 17	- 1	4.03	-1.51	1.76	-0.57
	b) > 2	+ 4	9.56	-1.8	4.76	-0.35
	n = 9	- 5	6.37	-0.54	4.25	0.37
Chi-square			30.1*		1.03	
P value			< 0.0001		= 0.31	

* Statistically significant; n = number of cases.

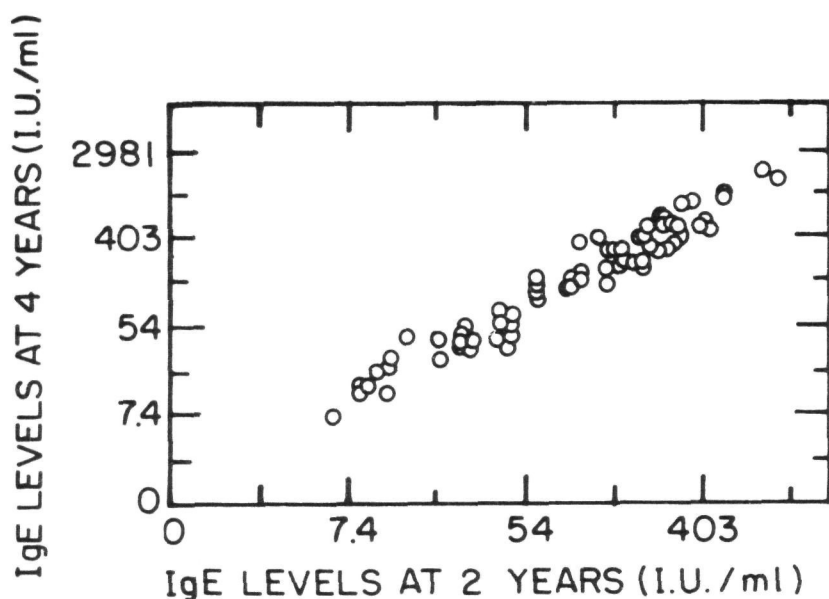


Fig. 1. Correlation between IgE levels at ages 2 and 4 years showing clear linear relationship ($r = 0.97$). Regression line: IgE at 4 years = $1.447 + 1.023 \times \text{IgE at 2 years}$.

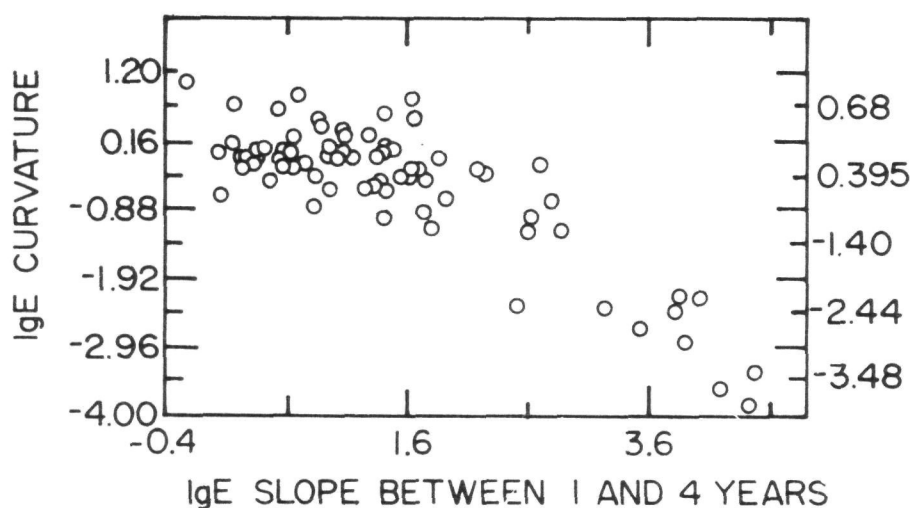


Fig. 2. Slope and curvature of IgE levels in individual cases.
Slope = $\text{IgE 4} - \text{IgE 1}$.
Curvature = $\text{IgE 4} - 2 \text{ IgE 2} + \text{IgE 1}$.
For explanation, see text.

for the prevention of attacks in babies over 1 year of age, whereas below 1 year it proved ineffective (10). Stools were negative for parasites in all cases.

Total IgE levels (mean + 1 SD) were $70 + 79$ IU/ml at 1 year of age, $163 + 168$ IU/ml at 2 years and $284 + 331$ IU/ml at 4 years. Total IgE levels were above the mean + 2SD in 50 of the 80 patients (63%), and in 26 of the 32 who had positive skin tests (81%). Statistical analysis was done using log values for IgE. In all cases, IgE levels increased with age. This increase was analysed for each individual separately. The scattergram (Fig. 1) shows a clear linear relationship between log IgE levels at ages 2 and 4 years. The IgE level at age 4 years (IgE 4) can be predicted from the IgE level at

age 2 (IgE 2) with an accuracy of 97% ($r = 0.97$) by using the regression line: $\text{IgE 4} = 1.447 + 1.023 \times \text{IgE 2}$. In Fig. 2, individual points showing the slope and curvature in IgE levels are displayed. Slope is measured by $\text{IgE 4} - \text{IgE 1}$ and curvature by $\text{IgE 4} - 2 \text{ IgE 2} + \text{IgE 1}$. It appears that in one third of cases there was a sharp rise of IgE levels between ages 1 and 2 years as expressed by a large slope associated with a negative curvature. On further analyses of this group, it was found that those IgE values which rose sharply between 1 and 2 years reached the highest values of the entire study group at the time of final assessment. In the remaining two thirds of cases the rise in IgE levels was steady from 1 to 4 years. The degree of rise in IgE levels with age was not signifi-

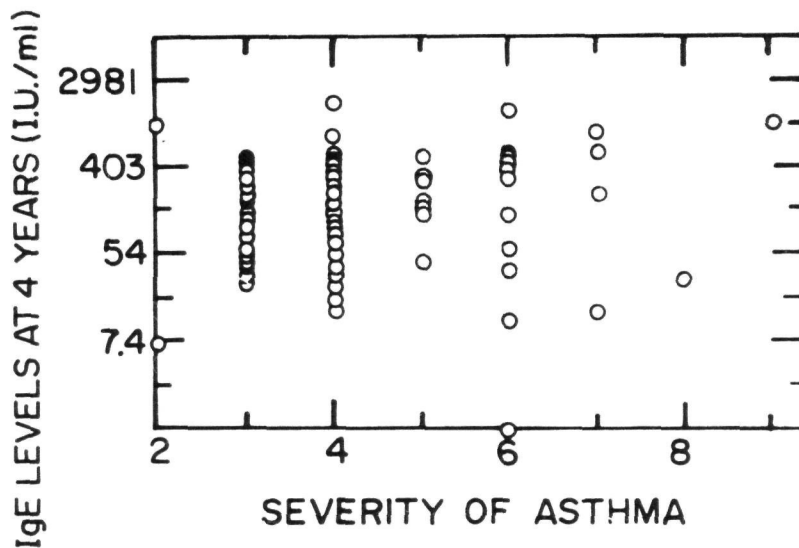


Fig. 3. Correlation between rise in IgE level and severity of asthma expressed as the sum of three annual clinical scores, where 0 = no clinical signs or symptoms of asthma and 3 = maximal severity (see text).

cantly influenced by feeding or parental smoking, although there was a trend of a greater rise in IgE levels in bottle-fed babies (Table 3). There was no correlation between the dynamics of IgE development and severity of asthma which was measured by the sum total of clinical scores (from 0-3) obtained at ages 1, 2 and 4 (Fig. 3).

DISCUSSION

Predicting the long-term outlook for repeated attacks of wheezing bronchitis in atopic babies is a constant dilemma for pediatricians and pediatric allergists. Much effort has been invested by both specialities in an attempt to determine whether the outcome could be modulated by appropriate preventive measures or drugs. Our study group was under constant observation by parents and doctors, and according to

our interviews with parents and written reports from the family pediatricians and nurses, compliance with preventive measures and medication was very good. Our results show an overall recovery rate of 68% by the age of 4 years, which is higher than those given in some other reports (4). Overall improvement in groups of patients who are under constant medical care or in controlled clinical studies has been previously observed in several double-blind drug trials and is not considered a "placebo effect" but a direct result of the special attention and care which is given to all patients during a trial (11). It seems most likely that we observed this high recovery rate for the same reason.

The predictive value of IgE levels at birth and during infancy has been emphasized by several authors (1, 2, 5, 7, 17, 19, 20, 22, 23), and is confirmed by our results showing that 63% of the atopic babies in this study had

Table 3
Increase of IgE levels from 1-4 years related to type of feeding and smoking at home

Amount of increase of IgE levels from 1-4 years	Parental smoking at home		Early feeding	
	+	-	Bottle-fed	Breast-fed (at least 3 months)
0-50 U	15	13	10	18
51-100 U	8	4	8	4
101-200 U	11	4	9	6
> 200 U	18	11	15	10
Total	52	28	42	38
P (chi-square)	NS		NS	

NS = non-significant.

elevated IgE levels from an early age. We found no correlation between total IgE levels and severity and frequency of respiratory symptoms during the 4 years. Similar findings were reported by Foucard et al. (8) in a 12-year prospective follow-up study of wheezy children. The rise of both normal and high IgE levels with age is known. However, the high predictability (97%) of IgE levels at 4 years by applying the linear regression formula to the value at 2 years is an interesting finding and needs confirmation by others. The fact that the IgE levels which showed a rapid increase in one third of patients between the age of 1 and 2 years, reached the highest values of the entire group at final assessment, might be due to a greater exposure to environmental allergens between 1 and 2 years (13). These observations were made in an atopic group of patients and should be compared to the normal increase of IgE levels in healthy non-atopic babies followed individually over the years. This was not done in the present study, and data reported in the literature refer to normal population means without going into details about the dynamics of individual IgE development (16). It seems that within a selected group of babies, IgE levels have significance as to the presence of atopy, but the rise in IgE levels in atopic children during early childhood does not correlate with the clinical course of their wheezing.

Statistical analysis in this study using several statistical techniques showed a significant positive association (at the 1% level) between a better prognosis (earlier disappearance of wheezing attacks) and breast feeding as well as non-exposure to parental smoking. These children with the better prognosis also had fewer lower respiratory tract infections during the 4-year study. Although the group exposed to passive smoking has a poorer prognosis, this was not reflected in increased IgE levels. This is at variance with experimental work presented by Zetterstrom et al. (25), who found that cigarette smoke in rats induced increased IgE production, and data presented by Kjellman (18) on a more rapid early rise of IgE levels in children exposed to passive smoking. It is possible that exposure to cigarette smoke influenced

clinical outcome via local changes in the respiratory epithelium (24). Similarly, within the group of babies suffering from an increased incidence of lower respiratory tract infections, exposure to cigarette smoke was more common than in the group with less such infections.

In conclusion, this study confirms the discriminative value of IgE levels for the diagnosis of atopy, but does not show any prognostic value for the dynamics of IgE production in early childhood asthma. IgE values in atopic wheezing babies rise with age, following a predictable pattern. This rise is not influenced by feeding or parental smoking although there is a trend for higher IgE levels in bottle-fed babies. Clinically, this study emphasizes the importance of early preventive measures in babies who are at high risk for atopy, such as avoidance of allergens (like cow's milk) and irritants of the respiratory tract like cigarette smoke (9). The higher incidence of persistent wheezing in atopic bottle-fed infants, as seen in this study, has been demonstrated in many other studies (3, 22). Parental smoking has been found to correlate with infections of the lower respiratory tract (6) and in our group of atopic children it appears that passive exposure to cigarette smoke increases the risk for persistence of wheezing attacks.

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