

Higher risk of infantile atopic dermatitis from maternal atopy than from paternal atopy

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Summary

The risk of infantile atopic dermatitis (AD) posed by maternal atopy and paternal atopy, respectively, were compared in the infants from a birth cohort in whom one of the parents had been designated atopic by skin prick testing. Nineteen with atopic mothers were compared with 20 with atopic fathers. AD, other atopic manifestations and potentially influential factors such as breast-feeding were documented prospectively during the first year in all infants. At 3, 6 and 12 month assessments skin prick sensitivity and total serum IgE concentration were determined. Nine of 19 infants with atopic mothers and two of 20 with atopic fathers had AD ($P=0.023$) giving a relative risk of 4.7 (95% confidence interval 2.5 to 9.0). Seven of 19 with atopic mothers and none with atopic fathers had AD with onset before 6 months ($P=0.007$). When all types of disease evidence (AD, recurrent wheeze and food reactions) were analysed together no significant difference was apparent between the groups. The two groups were found to be well matched with regard to breast-feeding, time of starting cow's milk, solids and egg, sex, month of birth, parental AD and smoking, race, household pets and neonatal IgE concentration. IgE concentrations at each age and the prevalence of skin prick positivity were similar between the groups. Maternal atopy poses a higher risk for infantile AD and paternal atopy. Whether this may be due to genetic or congenital factors or both is uncertain, but clearly the finding is of relevance in the prediction of allergy in childhood.

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Introduction

Sixty years ago Bray [1] concluded from a retrospective survey that mothers transmitted allergic disease twice as often as fathers. In another retrospective analysis, Happle and Schnyder [2] reported that asthmatic mothers had more children with asthma than asthmatic fathers, although the actual figures did not reach statistical significance.

Few prospective studies have confronted this issue specifically. Two reports on the predictive value of cord IgE concentrations noted higher concentrations in infants of atopic mothers [3,4]. In a third study maternal and

paternal allergy had the same bearing on atopic disease in the first 18 months [5]. Only one of these studies [3] had explored the influence of maternal atopy on disease as a primary aim and none had attempted to control for confounding variables such as breast-feeding.

We have been documenting atopy and atopic disease prospectively in a birth cohort of children with a genetic predisposition to atopy. Parental atopy had been determined at the outset and many factors which have been associated with allergic disease in childhood were explicitly recorded. Atopic dermatitis (AD) was the commonest and most reliably diagnosed atopic disease during infancy. The present study aim was to compare the risk of AD posed by maternal and paternal atopy, respectively, in all infants from the cohort in whom only one of the parents was atopic.

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Subjects and methods

Details of 92 of the 93 children in the cohort who were monitored from birth to one year have been given in a previous study which evaluated neonatal IgE screening [6]. The parents had been skin prick tested to mixed grass pollens, house dust mite (*D. pteronyssinus*), cat fur, cows' milk, hens' eggs (Bencard), mixed moulds (Dome/Hollister-Stier), and histamine 1 mg/ml and diluent control solutions (Bencard). A forearm weal at 15 min exceeding 3 mm in diameter or more caused by the diluent control was considered positive. Recruitment to the cohort had depended on confirming atopy by a positive skin test in at least one of the parents.

The 39 children in whom one of the parents was atopic and the other non-atopic were the subjects of the present study. Nineteen had atopic mothers and 20 atopic fathers. All atopic parents had given positive skin tests to at least one of the three common inhalant allergens: grass pollens, dust mite and cat fur, except one mother who had given a positive reaction to milk alone.

Infants were assessed at 3, 6 and 12 months when skin prick tests to the same allergens as had been used in parents were performed on the back. A weal 2 mm larger than that from the diluent control was regarded positive. Blood tests were also performed at every assessment and total serum IgE concentration subsequently measured by an enzyme-linked immunosorbent assay [7]. Additional examinations were made whenever the parents reported coughs or rashes in the children. Details of the infants' feeding, exposure to cigarette smoke, and other factors which may be associated with allergy in childhood were documented as well as evidence of atopic disease.

AD was diagnosed according to the modification of the Hanifin and Rajka criteria [8] for use in infancy [9] and graded on the scale of Matthew *et al.* [10]. Upon making a diagnosis of AD, the age of onset was obtained by asking parents for how long the rash had been present. Had the parents failed to notice any rash the age of onset was recorded as the time when first noted by the examiner. Wheezing on two or more occasions and a history of recurrent immediate-type food reactions were also regarded as possible evidence of atopic disease. The same person (R.G.G.R.) made all the assessments and had been unaware of the aim of the present study at the time.

The Ethical Committee of King's College Hospital had approved the study and in all cases, informed parental consent had been obtained prior to cohort entry.

Statistical analysis

All associations between pairs of variables were investigated by Fisher's exact test. A stratified analysis of maternal atopy to look for an effect of confounding

Table 1. Infant feeding factors which may influence development of atopic dermatitis: numbers of infants with each factor in the groups with atopic mothers and fathers

Factor	Atopic mother (n=19)	Atopic father (n=20)
Breast-feeding		
Never	1	0
≤3 months	7	9
>3 months	11	11
Cow's milk formula		
In first week	9	8
Regularly in first 3 months	10	12
Delayed >6 months	3	2
Soya formula		
Regularly in first year	3	2
Solids introduced		
≤3 months	8	10
>3 months	11	10
Number of solids at 3 months		
None	11	10
≤2	6	6
>2	2	4
Egg introduced		
≤3 months	1	1
3-6 months	3	8

variables such as a logistic regression model was not attempted due to the small sample size. The relative risk of AD with maternal atopy was calculated with a 95% confidence interval. The Mann-Whitney test was used to compare total serum IgE concentrations between groups.

Results

AD was diagnosed in 11 of the 39 infants (28.2%) during the first year of life. The age of onset was below 6 months in seven and above 6 months in four.

AD was present in nine of 19 (47.4%) infants with atopic mothers contrasting with two of 20 (10%) infants with atopic fathers ($P=0.023$). The relative risk of AD among infants with atopic mothers compared to atopic fathers was 4.7 with 95% confidence interval 2.5 to 9.0.

The difference in prevalence between children with atopic mothers and fathers was emphasized if only AD with onset before 6 months was considered. Seven of 19 (36.8%) infants with atopic mothers and none with atopic fathers had AD with earlier onset ($P=0.007$).

Five infants had recurrent wheezing and 11 had food reactions. If these manifestations were considered

Table 2. Other factors which may influence development of infantile atopic dermatitis: numbers of infants with each factor in the groups with atopic mothers and fathers

Factor	Atopic mother (<i>n</i> = 19)	Atopic father (<i>n</i> = 20)
Male gender	8	7
Month of birth		
Jan-Mar	4	5
Apr-Jun	4	8
Jul-Sep	3	2
Oct-Dec	8	5
Parental atopic dermatitis (history)		
Either parent	14	16
Mother	9	11
Father	9	8
Parental smoking		
Neither parent	10	13
Smoking mother	5	6
Both parents Caucasian	15	16
Pets in house	7	7
IgE on Day 7		
≥ 0.7 IU/ml	2	0
Undetectable	18	14

together with AD, 19 children would have had some evidence of atopic disease. Nearly twice as many would have had atopic mothers (12/19) as atopic fathers (7/20) but the difference was not statistically significant.

In order to check for possible confounding effects the infants with atopic mothers and atopic fathers were compared with regard to a wide range of factors which might have influenced allergic manifestation. They were found to be very well matched (Tables 1 and 2). The group with atopic fathers had a tendency to start eating eggs earlier than the group with atopic mothers, who tended to be born between October and December. However, no statistically significant differences between the groups were observed in these or any of the other factors listed.

It might be noted in passing that neither were any statistically significant differences found in the prevalence of AD related to the presence of potential risk factors for the disease apart from that already mentioned for maternal atopy (Table 3). The small numbers are recognized.

Seven children gave positive skin tests in the first year. Three had no disease manifestations. All the remaining four had AD. Positive skin prick tests occurred in 3/19 infants with atopic mothers and 4/20 with atopic fathers.

Table 3. Prevalence of atopic dermatitis (AD) in the presence and absence of potential risk factors

Risk factor	Percentage (proportion) with AD/risk factor		Fisher's exact probability
	Present	Absent	
Maternal atopy	47.4 (9/19)	10.0 (2/20)	0.023
Breast-feeding			
≤ 3 months	29.4 (5/17)	27.3 (6/22)	n.s.
Regular cow's milk in first 3 months	18.2 (4/22)	41.2 (7/17)	n.s.
Solids started			
≤ 3 months	22.2 (4/18)	33.3 (7/21)	n.s.
Egg started			
≤ 3 months	15.4 (2/13)	34.6 (9/26)	n.s.
Male gender	20.0 (3/15)	33.3 (8/24)	n.s.
Born Jul-Dec*	33.3 (6/18)	23.8 (5/21)	n.s.
Parental AD (history)	26.7 (8/30)	33.3 (3/9)	n.s.
Parental smoking	37.5 (6/16)	21.7 (5/23)	n.s.
Maternal smoking	36.4 (4/11)	25.0 (7/28)	n.s.
Household pet	35.7 (5/14)	24.0 (6/25)	n.s.
Neonatal IgE			
≥ 0.7 IU/ml	00.0 (0/2)	29.7 (11/37)	n.s.

* Arbitrary period without necessarily any potential risk

Table 4. Atopic characteristics of infant groups with atopic mothers and atopic fathers

Characteristic	Atopic mother (<i>n</i> = 19)	Atopic father (<i>n</i> = 20)	Probability
No. infants with positive skin test	3	5	n.s.
Median (range)	3 1.8 (0.9-3.6)	1.4 (0.0-6.7)	n.s.
Total IgE			
concentration	6 3.4 (1.1-12.2)	2.9 (0.6-5.8)	n.s.
(IU/ml) at	12 4.4 (0.0-24.0)	3.6 (1.0-12.5)	n.s.

There were no statistically significant differences in total serum IgE concentration between these two groups (Table 4) or between children with and without AD at any age during the first year, although the modest numbers should be emphasized again.

Discussion

The risk of having AD in infancy if the mother was atopic was over four times that if the father was atopic. The 95% confidence interval for this relative risk was very wide because of the small sample size but the lower limit was still over twice the risk.

Few of the factors listed in Tables 1 and 2 may be regarded to influence AD or allergic disease unequivocally. Although most paediatricians and allergists would consider prolonged breast-feeding an allergy-preventative measure it has been subjected to many studies over the past 50 years which have yielded conflicting results [11]. On balance, early feeding with cow's milk or solids is thought to increase slightly the risk of atopic disease [12]. The discrepancy in AD prevalence between the infants with atopic mothers and with atopic fathers could not be attributed to these or any of the other factors. It might indeed be optimistic to expect to see a clear-cut influence of a single factor on the development of AD in a study of the present size (Table 3). That one is seen with maternal atopy suggests that it may outweigh any of the other variables in terms of the risk of AD in the infants.

It was recognized that in performing multiple significance tests comparing variables, strictly, the significance level of the test should be adjusted. However, as no significant differences were observed other than for the main variable of interest for which there was a hypothesis, this became academic. Caution should be exercised in interpreting this lack of significance. Real differences may exist but be too small to be detected by a study of the present size. In spite of these reservations, matching of the groups with atopic mothers and fathers (Tables 1 and 2) could probably not be improved if the study had been a controlled clinical trial to determine the influence of maternal atopy. The close matching allowed conclusions to be drawn from simple bivariate analysis regardless of whether other variables were affecting the manifestation of AD.

Subject selection was based purely on the presence of uniparental atopy and there was no reason for atopy in one or other parent to bias towards a particular risk factor for AD. Nevertheless some differences might be expected between the present group of infants with parents who were sufficiently motivated to participate in a cohort study and a random group of infants with uniparental atopy. For example, although no attempt to influence feeding practice had been made, the proportion who were breast-fed was relatively high. Even if this had the effect of making the prevalence of infantile AD in the study group less representative of other infants with uniparental atopy, it would not invalidate the present observations.

When evidence of all types of atopic disease were analysed together the difference in risks from maternal and paternal atopy were no longer significant. However, wheezing in infancy and a history of food reactions provide less reliable evidence of atopic disease than the criteria for AD used here. Wheezing in the first year is not the best predictor of subsequent asthma [13]. Food allergy could not be confirmed by formal food challenge tests due to parental reluctance.

The present study offers several advantages over some of the previous investigations. Firstly, the prospective design allowed a consistent record of outcome, i.e. AD, by the same examiner using the same criteria which would have been impossible in a retrospective survey. Secondly, parental atopy was based on skin prick testing and not a history of parental atopic disease. The incertitude of the latter as a measure of parental atopy was illustrated by the present cohort. Potential recruits had been identified on the basis of a history of atopic disease in *both* parents. Yet in 39 of the 93 subjects followed to one year, atopy was not confirmed by skin test in one of the parents. Put another way, about 20% of parents who gave a history of atopic disease were not skin prick test positive to common allergens. Thirdly, potential confounding variables were recorded as assiduously as outcome. They cannot be accounted for adequately in retrospective analysis.

Carter [14] first suggested that in diseases which have a preponderance for a particular sex, the less affected sex is more likely to transmit the disease to subsequent generations if inheritance is polygenic. The hypothesis contends that the more rarely affected sex has a higher threshold for disease manifestation requiring relatively more predisposing genes. This sex would therefore impart more genetic material to offspring. Happle and Schnyder [2] proposed that such a phenomenon may operate with atopic disease.

The prevalence of atopic disease tends to be higher in males than females. AD is reported to be twice as common in boys than girls early in life [15]. However, a formal test of Carter's hypothesis would have involved assessing the risk of infantile AD in infants whose parents had the same infantile disease. This analysis was not possible here but the present findings would be consistent with atopic mothers carrying relatively more genes predisposing to disease than atopic fathers.

There was no evidence that atopy (positive skin prick tests and elevated total serum IgE) was commoner in the infants of atopic mothers than those with atopic fathers. Atopic status had only been determined during the first year of life, however, and longer follow-up could reveal many more atopic children. Nevertheless family pedigree studies in Oxford do suggest inheritance of atopy of 'IgE responsiveness' by a single autosomal dominant gene

rather than a polygenic mechanism [16]. A similar result might therefore be expected even after longer follow-up.

There may be non-genetic explanations for the present findings. In view of the close immunological contact between mother and child an atopic mother may be more likely to bring deleterious (or beneficial) immune factors to bear than an atopic father. Certainly immune responses in rat offspring can be influenced by maternal responses. Jarrett and Hall [17] demonstrated that production of IgE to egg albumin in suckling rats could be suppressed by maternal IgG to egg albumin. Possible factors need not be confined to IgG antibody. Little is known about whether factors regulating IgE production and inflammation cross the placenta. Should such congenital factors be operating they are likely to have a greater influence in earlier infancy. Although the numbers are small, the present study does suggest that maternal atopy has a greater bearing on AD manifested in the first 6 months than thereafter.

A family history of atopy or more specifically, parental atopy are arguably the strongest single risk factors for atopic disease in children. In the present study evidence is given that atopic mothers pose a higher risk for infantile AD than atopic fathers. This may have importance for the prediction of atopic disease in childhood.

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