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Natural history of asthma in childhood—a birth cohort study

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Abstract

A cohort of 67 babies at risk of developing atopic disorders was followed up prospectively for 11 years. Clinical assessment and skin prick allergen sensitivity testing were performed annually over the first five years. At 11 years the cohort was restudied, symptoms were assessed by questionnaire, and bronchial reactivity (BHR) to histamine was measured. On the basis of skin testing, 35 children were atopic and 32 remained non-atopic. The expression of atopy increased with age. The lifetime prevalence of eczema, wheeze, and hay fever were 46%, 63%, and 56% respectively. The yearly period prevalence of hay fever increased with age, that of eczema declined, while that for wheeze showed a bimodal distribution with a peak before the age of 2 years and a gradual increase thereafter. Of the 21 children who wheezed before their second birthday, most never wheezed again and did not show BHR at 11 years. Of the 21 children whose first wheezing was after 2 years of age, 17 were still wheezing at 11 years and 12 showed BHR. Of the children who wheezed before 2 years of age, 10 were or became atopic, compared with 20 of the 23 children who wheezed at 11 years. These findings suggest that childhood asthma is a heterogenous condition with atopy being strongly associated with the persistence of wheeze.

Asthma affects at least 10% of school age children, yet despite this high prevalence there is much that remains unclear about the natural history of the disorder. Longitudinal studies of asthma in childhood are few and prospective information about preschool children is lacking from the British Cohort Study of 1958[1] and the long term follow up of wheezy children in Melbourne.[2] Although these workers have drawn attention to the differences between the preschool children who wheezed with viral infections and children with 'classical asthma', they concluded that children with recurrent wheeze and cough belonged to a single population with a common underlying defect.[3] This conclusion has recently been challenged on methodological and theoretical grounds.[4]

Recurrent wheezing in childhood has a strong association with atopy and this genetic abnormality is one of the strongest risk factors predicting whether a child develops asthma.[5 6] In an attempt to learn more of these variables we have conducted a prospective study from birth to 11 years in a cohort of children at risk of developing atopy. The study represents the continuation of the longitudinal investigation of recurrent wheezing in preschool children.[7–9]

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Subjects and methods

SUBJECTS

One hundred babies were selected for the study before birth on the grounds that one parent gave a history of hay fever or asthma. This selection was designed to provide a cohort of children of whom, on the assumption of an autosomal dominant inheritance, half would be expected to develop evidence of atopy, those without atopy acting as controls. In this study a stringent definition of atopy was taken as the presence of one or more positive skin prick tests (≥4 mm weal diameter) to common allergens. The study had the approval of the health district ethical committee. After full explanation, written consent was obtained from the pregnant mothers. All the babies were born in the maternity department of Poole General Hospital during 1977 and 1978. The cohort of 100 babies was initially studied for five years and later restudied when aged 11 years when all except one were prepubertal. As most of the families continued to live in the area served by the hospital there remained 92, 73, and 67 children in the cohort at 1, 5,[7] and 11 years respectively. The results presented in this report are on those 67 remaining children.

METHODS

All children were examined annually for their first five years and again when aged 11. The presence of eczema and wheeze was confirmed in all cases by a research nurse, a specialist, or a general practitioner during the first five years. A diagnosis of eczema was made when the skin of the face or of the flexures showed roughening, redness, or pruritus that persisted for four weeks or more. Hay fever was regarded as present if nasal discharge occurred in at least two spring or summer seasons. At the age of 11 years the diagnoses of hay fever and wheeze were based on a questionnaire administered to the patients inquiring into symptoms over the previous year and six years, while that for eczema was clinically confirmed.

Bronchial responsiveness to inhaled histamine was assessed at the age of 11 years in 66 children using the deVilbiss method.[10] After a saline challenge, increasing doubling doses of histamine were administered, followed at one minute by measurements of forced expiratory volume in one second (FEV_1) using a Vitalograph spirometer. The histamine dose was progres-

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sively increased until the FEV_1 fell by 20% of the post-saline (baseline) value. Children were considered to have hyperresponsive airways if this occurred up to or before the maximal cumulative dose of 7·8 μmol of histamine. The majority of children were challenged four times during the course of the year 1988/9 and were considered to have BHR if positive reaction occurred on one or more of the four challenges. Testing of the children was deferred if they had a history of a respiratory tract infection in the preceding month. In this age group the test has been shown to be repeatable to within a doubling dose.[11 12]

The atopic states of the children were determined by skin prick testing to a panel of six allergens (*Dermatophagoides pteronyssinus*, mixed grass pollen, cat fur, dog dander, hens' eggs, cows' milk; Bencard UK Ltd), with a positive histamine and a negative control. This testing was undertaken by a standard technique at the ages of 1, 2, 3, 4, 5, and 11 years.[13] The same investigator performed these tests from the second year of follow up. A positive reaction was recorded if the mean diameter of the skin weal at 15 minutes was ≥ 4 mm more than a negative control; and the children were defined as atopic if they responded to one or more allergen at any age. At the final assessment the majority of parents were also skin tested to the same panel of allergens.

STATISTICS

Relative risks were calculated as the ratio of prevalence of a trait among exposed individuals to the prevalence of a trait among non-exposed individuals.[14] A relative risk of <1 suggests the exposure or trait may be protective, while >1 suggests an association, the higher the number the greater its strength. The significance was calculated by the χ^2 test and 95% confidence intervals were expressed. Smaller contingency tables were analysed by Fisher's exact test.

Results

On the basis of skin testing the total cohort of 67 children (31 boys) could be divided into 35 atopic and 32 non-atopic. The parents who had been selected on clinical grounds were subsequently shown to be atopic, with 10 false positives and 21 false negatives among the 115 parents who were skin tested.

The lifetime prevalence of eczema, wheeze, and hay fever was 46%, 63%, and 56% respectively. The number of children expressing atopy increased progressively with age: zero at 1 year two (3%) at 2 years, six (9%) at 3 years, 11 (16%) at 4 years, 14 (21%) at 5 years, and 35 (52%) by the age of 11 years. The yearly period prevalence of eczema declined, tending only to persist in the atopic children, that of hay fever increased occurring again mainly in atopic children, while that of wheeze showed a bimodal distribution with an early peak before 2 years and a gradual rise thereafter (table 1). Ten of the 21 children who wheezed before their second birthday were or became atopic, while 20 of the 23 children who wheezed at 11 were atopic ($p<0·01$). The majority of wheezy children did not present a major clinical problem, with only three having required hospital admission because of wheeze. Of the children who wheezed at 11 years (13 boys and 10 girls) eight were on regular medication (six inhaled β_2 agonists, three sodium cromoglycate, and four inhaled steroids). Sixteen (70%) of these children were sensitised to house dust mites, 12 (52%) to cats, and 10 (43%) to pollen. In contrast, of the 21 children who wheezed under 2 years of age (nine boys and 12 girls) only six (28%) became sensitised to house dust mites, five (23%) to cats, and six (28%) to pollen by the age of 11 years.

Bronchial hyper-responsiveness (BHR) to histamine was seen in 23 of the children at 11 years, of whom 21 were atopic, 17 had wheezed in the previous year, and three of the remaining six had previously had a recorded episode of wheeze. The degree of BHR was related to the child's atopic status; the two non-atopic children required greater than 1·8 μmol of histamine to respond, compared with the 16 of the atopic children who responded to less than this dose ($p<0·001$). The relative risk of a child wheezing before his or her second birthday, wheezing at 11, or showing BHR at 11 was calculated (table 2). There was no association between atopy and wheezing in infancy, but it was strongly associated with wheeze at 11 years of age.

The natural history of wheeze was dependent on the age at the first wheeze (figure). Of the 21 children whose first wheezing episode was under 2 years of age, 16 (76%) were wheeze free, and 13 (61%) did not show BHR, at 11 years; that is, there was only a 1 in 4 chance of wheezing at age 11. Four of the five infants whose wheeze persisted were atopic and showed BHR. Among this subgroup were the three children who had required hospital admission, were on regular inhaled steroids, showed BHR to <0·98 μmol of histamine, and were considered the 'worst' asthmatics of the cohort. The one non-atopic child did not show BHR and was on no medication. These five children could be distinguished clinically during infancy by the greater frequency of their wheezing episodes: they had three or more each year while most of the other children had only

Table 1 Yearly prevalence of children with wheeze, eczema, and hay fever from the total cohort of 67

	Age (years)					
	Birth–1	1–2	2–3	3–4	4–5	10–11
Wheeze						
Total	11	15	7	10	16	23
Atopic†	6*	7**	6	7	11	20
Eczema						
Total	15	23	8	7	6	1
Atopic	8	12	4	5	5	1
Hay fever						
Total	‡	3	2	10	11	27
Atopic	—	2	2	9	9	22

†Atopy was defined as those children who had a skin weal ≥ 4 mm to an allergen during childhood.
*p=0·05, **p<0·01 for the comparison with the number of atopic children to non-atopic children wheezing at 11 by Fisher's exact test.
‡Excluded by definition.

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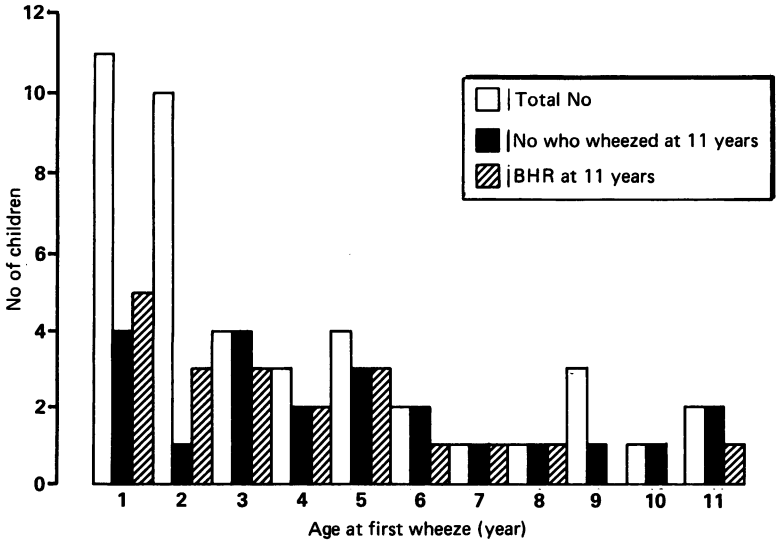
Table 2 Relative risk (95% confidence intervals) of children having atopy, wheeze at 0–2 years, wheeze at 11 years, bronchial hyperreactivity (BHR) at 11 years

	Atopy	*Wheeze 0–2 years*	*Wheeze at 11 years*	*BHR at 11 years*	*Wheeze + BHR at 11 years*
Wheeze 0–2 years (n=21)	0·9 (0·5 to 1·5)	— —	0·6 (0·3 to 1·3)	0·9 (0·4 to 2·0)	0·9 (0·4 to 2·2)
Atopy (n=35)	— —	0·8 (0·4 to 1·6)	6·1*** (2·5 to 14·4)	10·0*** (3·8 to 25·5)	14·6*** (3·9 to 54)
		Positive skin test at 11 years			
House dust mite (n=25)	— —	0·7 (0·3 to 1·5)	4·2*** (2·0 to 8·6)	4·4*** (2·2 to 8·8)	5·3*** (2·3 to 12·6)
Cat dander (n=20)	— —	0·6 (0·2 to 1·3)	3·4*** (1·8 to 6·5)	4·4*** (2·3 to 8·3)	4·5*** (2·1 to 9·9)
Mixed pollen (n=18)	— —	1·4 (0·6 to 2·9)	2·1* (1·0 to 4·0)	3·9*** (2·0 to 7·3)	6·0*** (2·4 to 15·1)
		Skin reaction in infancy			
Egg (n=14)	1·7* (1·1 to 2·8)	1·0 (0·5 to 2·3)	2·0* (1·0 to 4·0)	2·3* (1·2 to 4·6)	2·9** (1·3 to 6·3)

*p<0·05, **p<0·01, ***p<0·001. All other values were not significant p>0·05.



Age at the first wheeze (year) and the subsequent presence of wheeze and bronchial hyper-responsiveness (BHR) at 11 years of age.

one or two episodes. In contrast to the 21 children whose first wheezing episode was after their second birthday, only four (19%) were wheeze free at 11 years of age (p<0·001) and nine (43%) did not show BHR (not significant); that is, the chance of wheezing at 11 was 4 in 5.

Discussion

This prospective study of children born of atopic parents, and therefore at risk of atopic disease, has shown the number of children expressing their atopic status and the prevalence of atopic disease increases with age. It is estimated that in the UK 50% of couples have an atopic member so a large proportion of children would have a similar atopic pedigree as those in this small cohort study. The definition of atopy used was an objective one using allergen skin prick testing to demonstrate immediate hypersensitivity. A skin weal size of 4 mm greater than the negative control was arbitrarily chosen as there were clear examples of children losing all skin reactivity to allergens when a less stringent threshold was used. The validity of this definition was supported by both the strong association of positive skin tests in the children and allergic disease and the close correlation between allergic symptoms and subsequent skin testing in their parents.

Under 2 years of age we have identified a peak of children who had their first wheezing episode. Many of these very young children wheezed only once. On a nine year follow up the natural history of wheeze in these children differed from those who started to wheeze after their second birthday. This is in keeping with a study from a general practice which found that the earlier a child wheezed, the better the prognosis. It was also found that the parental recall of wheezing in infancy was increased if later respiratory problems occurred.[15] This bias resulted in an overestimation of the number which progress to persistent wheezing in later childhood and may explain the differences between the findings in prospective and retrospective studies.

It seems likely that respiratory viral infections have an important part to play in the production of wheeze in young children. Positive viral isolates have been made in several studies,[16 17] although in earlier reports of the present cohort there was little success at culturing virus during episodes of wheeze.[9] It is possible that the effects of infection on the smaller calibre airways of infants is sufficient to produce clinical wheeze; indeed, a prospective study has shown that infants with reduced lung volumes are more prone to wheeze.[18] In the older children it is those who were atopic and, as a consequence, capable of developing immediate hypersensitivity, who had persistent wheeze and hyperreactive airways. There was no evidence to support the theory that viral infections in infancy influenced the subsequent development of atopy. It has been suggested that all wheezy children belong to a homogenous group with a similar genetic background.[3] However, evidence from this longitudinal study of children with a similar genetic background suggests that there are at least two groups of wheezy children, one group who progress to develop 'asthma' in later childhood and another who do not develop atopy and do not wheeze again.

We understand atopy to be an inherited

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trait,[19 20] which is expressed after prolonged allergen exposure.[21] Our findings confirm cross sectional studies showing that atopy is strongly associated with childhood asthma.[5 6] An important finding in this study based on the general population was that the prevalence of wheeze had not declined by 11 years, which is in contrast to findings of previous studies.[22 23] Contrary to popular opinion,[24] this study has not confirmed that infantile eczema, based on our clinical definition, was a useful predictor of atopy as many non-atopic children were affected. This supports the observation that it is frequently confused with seborrhoeic dermatitis.[25] Our most useful early predictor of atopy was a reaction (weal size greater than 2 mm) to egg on skin testing (sensitivity 78%, specificity 54%).

This longitudinal study of children at risk of atopy has shown that it is those children who develop immediate hypersensitivity who are more likely to have persistent symptoms of wheeze and that the risk of a child whose first episode of wheeze is before 2 years of age continuing to wheeze at 11 is low. We interpret these findings to suggest that heterogenous mechanisms operate in the causation of wheeze at different ages.

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