

Role of atopy in the natural history of wheeze and bronchial hyper-responsiveness in childhood

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The role of atopy in the development of asthma has become increasingly recognised. We have been prospectively following a birth cohort of children of atopic parents to document the development of atopic disease. Our aim in this study was to document the natural history of BHR and wheeze at 10 years of age and to relate this to atopy. We reviewed 47 of our original cohort of 79 infants at 10 years of age and documented their clinical history of atopic disease and performed allergen skin prick tests and BHR to histamine. Thirty-three (70%) children wheezed at some time during their 10 years of life, with 13 commencing in infancy. Twenty-two children (47%) had current wheeze at 10 years of age. Wheeze in infancy was a poor predictor (RR 1.23, CI₉₅ 0.66–2.23) of current wheeze while wheeze commencing after infancy was a good predictor (RR 2.89, CI₉₅ 1.45–5.2). In contrast both atopy in infancy (RR 2.94, CI₉₅ 1.92–4.53) and current atopy (RR 3.58, CI₉₅ 1.43–9.03) were strong predictors of current wheeze. Analysis of BHR confirmed the importance of atopy in predicting its occurrence and severity. Sensitisation to *D. pteronyssinus* appeared to be the strongest predictor of both current wheeze and BHR. These observations confirm the importance of atopy in predicting outcome in children with asthma and suggest that wheezing in infancy and wheezing in later childhood may have different pathogenetic mechanisms.

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The role of atopy in the development of asthma has become increasingly recognised. A number of studies of asthmatic children have demonstrated an association between the severity of asthma symptoms and bronchial hyper-responsiveness (BHR) and the degree of atopy (1–5). Prospective studies of birth cohorts of children at risk for the development of atopic disease have also demonstrated the importance of atopy in predicting the subsequent development of asthma (6, 7).

We have been following a birth cohort of infants of atopic parents to document the development of atopy and atopic disease (8–11). At 5 years we demonstrated that atopy to inhalant allergens was associated with wheeze at 5 years of age but not during infancy (10). At 7 years we demonstrated that atopy in infancy predicted the severity of BHR at 7 years of age (11).

We have recently completed a further follow up of our birth cohort of infants of atopic parents at 10

years of age. The aim of this study was to confirm our previous observations of the association between atopy and both wheeze and BHR and to document the natural history of BHR & wheeze in this cohort.

Patient and methods

Patients

We originally followed 79 infants, born to parents with a history of atopic disease, every 4 months up to 20 months of age (8, 9) and 57 and 52 were reviewed at 5 (10) and 7 (11) years respectively. We have now reviewed 47 of these children at 10 years of age to document their clinical history of atopic disease (atopic dermatitis, allergic rhinitis and wheeze) and perform allergen skin prick tests and BHR to histamine. As stated previously (10) these children were representative of the initial 79 infants in terms of a family history of atopic disease and atopic disease during infancy.

Wheeze

For descriptive purposes, wheeze, which had been documented at each visit has been categorised according to the following definitions:

<i>Current wheeze (CW)</i> –	wheezing between 7 and 10 years.
<i>Infancy wheeze (IW)</i> –	wheezing in the first 20 months of life.
<i>Post infancy wheeze (PIW)</i> –	onset of wheeze after 20 months of age.

Atopy

Allergen skin tests were performed on the volar aspect of the forearm using the skin prick method (12). Histamine 1 mg/ml was used as a positive control and saline was used as a negative control. Reactions were read after 10 minutes and wheal size was recorded with pen tracing and micropore tape. The following allergens were used:

Infancy whole cow's milk (Hollister Stier Laboratories, Spokane, Washington) egg albumen (Commonwealth Serum Laboratories, Melbourne, Australia) wheat (Commonwealth Scientific and Industrial Research Organisation, Sydney, Australia) and *Dermatophagoides pteronyssinus* (Bencard, Middlesex, England).

5, 7 and 10 years whole cow's milk, egg albumen (Hollister Stier Laboratories) peanut (roast extract) (Commonwealth Scientific and Industrial Research Organisation) rye grass, cat fur (Hollister Stier Laboratories) and *Dermatophagoides pteronyssinus* (Dome, Miles Laboratories, Slough, England).

7 and 10 years insect allergen extracts to German cockroach (*Blattella germanica*) house fly (*Musca Domestica*) and tropical warehouse moth (*Ephestia cautella*), prepared as described previously (13) were used. These allergen extracts were added at age 7 to characterise the significance of insect allergen sensitisation in these children and their parents (14).

For the purposes of this study atopy was defined as any wheal reaction 3 mm or greater to one or more of the allergens used. In the case of a positive saline control, only wheal sizes at least 3 mm or greater than the control wheal were considered positive. Atopy was further categorised as follows:

<i>Current atopy (CA)</i> –	atopic at 10 years of age.
<i>Infant atopy (IA)</i> –	atopic during the first 20 months of life.

Bronchial responsiveness

Baseline spirometry was measured with a Vitalograph (Vitalograph Ltd, Buckingham, England) with measurements repeated until two curves with FEV₁ and forced vital capacity (FVC) within 100 ml were obtained with the highest value being recorded. If the FEV₁/FVC or the FEV₁ (percentage predicted) was $\leq 65\%$, the subject was not challenged with histamine, but was administered Salbutamol, 200 µg via a metered dose aerosol, and spirometry was repeated after 10 minutes. A positive bronchodilator response (Δ FEV₁) was defined as $\geq 15\%$ change in FEV₁ from baseline.

Bronchial provocation testing was performed according to the methods of Yan et al. (15), modified as previously described (11) using histamine in increasing increments from 0.03 µmol – 7.8 µmol. Dose-response curves were plotted for each challenge, demonstrating the percentage fall in FEV₁ from post saline value against the logarithms of the cumulative dose of histamine. The PD₂₀ or dose causing a 20% fall in FEV₁, was calculated for the challenge if the percentage fall in FEV₁ was $\geq 20\%$. In addition the dose response slope (DRS) was calculated for each patient as described previously (16). The values of DRS described in the results are the logarithmically transformed values of the percentage fall in FEV₁ at the last dose divided by the total dose administered with the addition of a constant of 3. DRS was also calculated for the provocation tests performed at age 7 for comparison with the 10 year results.

Statistical evaluation

For categorical data, relative risks and 95% confidence intervals were calculated (17). For continuous data, mean values were compared using student t-test and 2 tailed t-tables and a p value < 0.05 considered significant (18). Changes in DRS were expressed as fold differences calculated according to the method described by Peat et al. (19).

Results

Wheeze & atopy

Forty-seven children were reviewed at 10 years of age and 33 (70%) wheezed at some time during their 10 years of life. Thirteen children wheezed during infancy (IW), while the remaining 20 commenced wheezing after infancy (PIW). Twenty-two children had wheezed between 7 & 10 years (CW) and 15 (68%) of these had commenced wheezing after 20 months of age.

Allergen skin prick tests were performed at 10 years of age in 46 children while all 47 were tested

Table 1. Relative risk of current wheeze according to atopy & wheeze onset

Atopy RR (95% confidence)	Wheeze RR (95% confidence)
Infancy (n = 9) 2.94 (1.92–4.53)	Infancy (n = 13) 1.23 (0.66–2.23)
Current (n = 25) 3.58 (1.43–9.03)	Post infancy (n = 20) 2.89 (1.45–5.2)

at the previous visits. Atopy, as defined by a 3 mm or greater wheal to at least one allergen, was present in 25 (54%) children at 10 years (CA), and 9 (19%) children during infancy (IA).

The relative risks for the presence of current wheeze are illustrated in Table 1. Both infant atopy and current atopy were strong predictors of current wheeze. In fact all 9 atopic infants had a history of current wheeze at 10 years of age. In contrast, onset of wheezing in infancy was poorly predictive of current wheeze. Furthermore the age of the first episode of wheezing during infancy was not predictive of current wheeze. However, the onset of wheezing after 20 months of age was predictive of current wheeze.

Bronchial responsiveness

A total of 44 children underwent histamine challenge at both 7 & 10 years, while the remaining 3 children refused retesting at 10 years of age. Twelve children had evidence of BHR at 7 years, including 1 child with a positive bronchodilator response ($\Delta FEV_1 = 33\%$) and 11 with a PD_{20} varying from 0.03 μmol – 4.0 μmol . At 10 years of age 6 retained evidence of BHR, 3 failed to fall 20% on challenge while the remaining 3 refused retesting. An additional 2 had evidence of BHR at 10 years of age. Thus 8 of 44 children demonstrated BHR at 10 years including 1 with a positive bronchodilator response ($\Delta FEV_1 = 56\%$) and 7 with a PD_{20} varying between 0.38–2.54 μmol . Seven of the 8 (88%) with BHR at 10 years had current wheeze. All 8 with BHR at 10 years demonstrated current atopy while 4 (50%) were atopic during infancy.

Dose response slope (DRS) was calculated for the 43 children who underwent histamine challenge at both 7 & 10 years. Figure 1 illustrates the relationship between DRS and wheeze. Those with current wheeze (n = 18) were significantly more sensitive to histamine at 10 years of age when compared to those with past wheeze (PW) (n = 10) or those who had never wheezed (NW) (n = 15) [$\log_{10}$ mean $\pm$ SD DRS 0.83 ± 0.40 vs 0.54 ± 0.12 vs 0.57 ± 0.26 ; $P < 0.05$]. DRS decreased with age in both NW (fold difference [95%] = 0.83 [$0.65, 1.07$]) and PW (0.65 [$0.50, 0.95$]) but increased for CW (1.48 [$0.87, 2.51$]). Figure 2 illustrates the relationship between DRS and atopic status. Both current atopy (n = 22) and atopy in infancy (n = 7) were associated with a

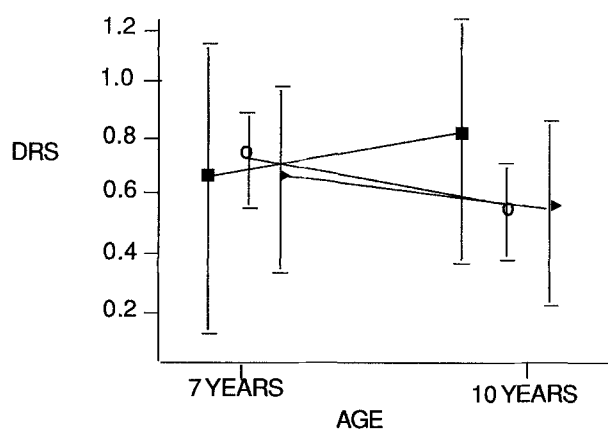


Fig. 1. This figure illustrates the natural history of BHR according to wheeze status, between 7 and 10 years of age as evidenced by the change in dose response slope (DRS). Those with current wheeze (■) had a significantly higher DRS ($P < 0.05$) when compared with those with past wheeze (○) and those who had never wheezed (▴).

higher mean DRS at 10 years when compared to non-atopic children (n = 13). [$\log_{10}$ mean $\pm$ SD DRS 0.80 ± 0.39 vs 0.84 ± 0.49 vs 0.57 ± 0.11]. The DRS was significantly higher for those with current atopy when compared to the non-atopic children ($P < 0.05$) but the difference between the atopic infants and the non-atopic children did not reach statistical significance ($0.05 < P < 0.10$). DRS decreased with age in the non-atopic children (fold difference [95%] = 0.91 [$0.71, 1.17$]) and increased in those with both current atopy (1.29 [$0.81, 2.04$]) and atopy in infancy (1.05 [$0.46, 2.40$]) but these changes were small and unlikely to be clinically significant.

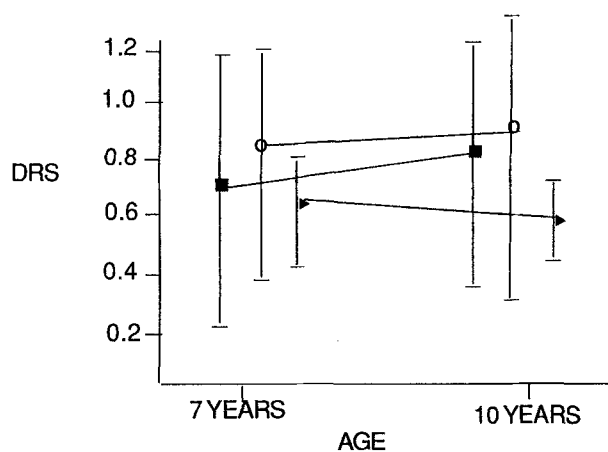


Fig. 2. This figure illustrates the natural history of BHR according to atopic status, between 7 and 10 years of age, as evidenced by the change in dose response slope (DRS). Those with current atopy (■) had a significantly higher DRS ($P < 0.05$) when compared to non-atopic children (▴). Those who were atopic in infancy (○) also had a higher DRS ($0.05 < P < 0.10$) when compared to non atopic children.

Table 2. Relative risk of current wheeze & BHR for specific allergen sensitisation at 10 yrs of age

Allergen	Current wheeze (n = 21) RR (95% confidence)	BHR (n = 8) RR (95% confidence)
D. pteronyssinus (n = 17)	3.41 (1.73-6.75)	13.53 (1.84-100.5)
Rye grass (n = 15)	2.27 (1.26-4.10)	2.14 (0.57- 7.32)
Insect (n = 7)	2.23 (1.38-3.60)	3.8 (1.22-11.94)
Alternaria (n = 7)	1.74 (0.90-3.22)	1.76 (0.45- 6.96)
Cat Fur (n = 5)	1.36 (0.61-3.06)	3.33 (0.99-11.14)

Specific Allergen Sensitisation

To determine the association between specific allergen sensitisation at 10 years of age and current wheeze and BHR, the relative risks were calculated for *Dermatophagoides pteronyssinus*, rye grass, insect, alternaria and cat fur sensitisation. (Table 2). Sensitisation to *D. pteronyssinus* was most strongly associated with current wheeze (RR = 3.41) and BHR (RR = 13.53). All 5 infants who demonstrated sensitisation to *D. pteronyssinus* during the first 20 months of life had current wheeze at 10 yrs and 3 of the 4 who underwent histamine provocation had evidence of BHR. Sensitisation to rye grass or one of the insect allergens was also associated with an increased risk for current wheeze but only insect allergen sensitisation was significantly associated with BHR. Sensitisation to cat fur or alternaria was not significantly associated with current wheeze or BHR.

Discussion

Our results indicate the importance of atopy in predicting persistence and severity of wheezing in childhood, confirming our previous findings (10, 11) and those of other prospective studies (5-7). The presence of atopy in infancy was associated with a 3 fold increased risk of current wheeze at 10 years of age – in fact all 9 atopic infants had a history of wheezing between 7 & 10 years of age. The presence of atopy at 10 years was also strongly predictive of current wheeze, (RR = 3.6). Both atopy in infancy and current atopy were associated with higher dose response slope at 10 years of age when compared to non-atopic subjects, reflecting increased bronchial responsiveness and presumably asthma severity. This latter observation is consistent with our findings at 7 years, indicating that atopy in infancy was predictive of the severity of bronchial hyper-responsiveness in later childhood (11).

The poor predictive value of wheezing in infancy demonstrated in this study confirms our findings at the 5 year follow-up (10) and the recent findings of Sporik et al. (7). While the presence of wheezing in infancy (up to 20 months of age) was not associated

with an increased risk of current wheeze (RR = 1.23), the onset of wheeze after infancy was associated with a 3 fold increase in current wheeze. While our definition of infancy was arbitrarily based on our period of initial follow up, the fact that the age of the first episode of wheezing in infancy did not relate to the cessation or persistence of wheezing at 10 yrs of age support our conclusions. These findings are consistent with those of Sporik et al. (7) who demonstrated that wheezing in the first 2 years of life was poorly predictive of wheeze & BHR at 11 years of age while onset of wheeze after 2 years was associated with persistent wheezing and BHR at 11 years of age. This suggests that wheezing in infancy and early childhood may relate more to airway size than BHR, while persistent wheezing in later childhood relates more to BHR, with atopy being significantly associated with this BHR. This speculation is supported by the recent studies indicating that wheezy infants have smaller airways than non-wheezy infants (20, 21) but do not demonstrate increased bronchial responsiveness (21).

Objective measurement of bronchial responsiveness in this population supports the clinical findings highlighted above. Bronchial hyper-responsiveness was present in 8 children at 10 years of age, all of whom were atopic at 10 years of age with 4 being atopic in infancy. Seven of the 8 had current wheeze but only 2 had been wheezy during infancy. The 3 children who refused histamine challenge at 10 years of age may have further strengthened this association as it seems likely they would have had evidence of BHR at 10 years of age. All 3 had evidence of BHR at 7 years of age, were atopic at 7 & 10 years and had current wheeze. If true, of the 11 children who had (or were likely to have) evidence of BHR at 11 years, all were atopic at 10 years and 6 (55%) were atopic in infancy. In contrast while 10 (91%) had current wheeze only 3 (27%) had wheeze during infancy. We have previously demonstrated the limitations of measurement of bronchial responsiveness using an arbitrary cut off to define BHR (11). We confirmed the considerable overlap between symptoms of asthma and the presence of BHR as reported previously (22-24). However we demonstrated that more severe degrees of BHR were associated with early manifestations of atopy (11). Rather than repeat this analysis with its inherent problems, we chose to calculate the dose response slope on all patients who underwent bronchial provocation at both 7 and 10 years of age.

Analysis of the dose response slope allowed us to include a measure of bronchial responsiveness for all patients, apart from the one with airway obstruction who had a positive bronchodilator response. Not unexpectedly those with current wheeze had a significantly higher DRS at 10 years of age when com-

pared to those with a past history of wheeze and those who had never wheezed. Previous cross sectional studies have also demonstrated that a higher DRS was associated with current symptoms of asthma (15, 25). DRS tended to decrease with age in those who had never wheezed or those with a past history of wheezing. This is similar to findings in a study of DRS in a non-asthmatic population (25). In contrast children with current wheeze tended to have an increase in DRS over time, (1.5 fold increase between 7 & 10 years of age). A similar finding was reported in cross sectional study of an asthmatic population (25). The mechanism for this normal decrease in airway responsiveness with increasing age is unclear, although Le Soeuf (26) has suggested it may simply reflect failure to adequately size correct test dosages, rather than representing a genuine physiological event. However, the fact that this decrease in responsiveness is also seen with exercise provocation (25, 27), would argue against this explanation. Whatever the cause it is clear that in those children with persisting wheezing in later childhood, this decrease in histamine responsiveness does not occur. The presence of atopy, both current and during infancy was also associated with a higher DRS at 10 years when compared to non-atopic subjects although the difference was only statistically significant for those with current atopy, possibly because of the small number ($n = 7$) of infants with atopy. These findings support previous observations of a strong association between bronchial hyper-responsiveness and atopy (3–5,7). We observed a trend for decreasing DRS in the non-atopic group compared to an increasing DRS in the atopic groups, however these differences were small.

We have confirmed the importance of sensitisation to *D. pteronyssinus* as a predictor of current wheeze and BHR which has been demonstrated in a number of previous Australasian studies (28–30). Furthermore the presence of sensitisation to *D. pteronyssinus* during infancy appeared to be even more strongly associated with current wheeze and BHR at 10 years of age. The high rate of sensitisation to *D. pteronyssinus* and its strong association with current wheeze and BHR presumably reflects the high levels of house dust mite and Der P1 allergen encountered in Sydney homes (31). Although sensitisation to rye grass was associated with current wheeze, it was not associated with BHR, suggesting that pollen allergens are less important in the Sydney environment. This poorer association between pollen allergen sensitisation and BHR has previously been demonstrated in other coastal Australasian cities (28–30). The significance of the relative risks demonstrated for the other allergens in our study needs to be interpreted with caution because of the small numbers demonstrating sensitisation and the wide confi-

dence intervals. Larger population studies are needed to document the relative importance of these other allergens to the development of asthma.

We conclude that there are 2 groups of wheezy children. One group commence wheezing in infancy and cease wheezing by early-mid childhood. This group probably wheeze due to smaller airway size and are non atopic. The other group, whose onset of wheeze is later, are characterised by persisting evidence of BHR and atopy, and have persisting wheeze into later childhood. These observations confirm the importance of atopy in predicting outcome in children with asthma.

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