

Family patterns of asthma, atopy and airway hyperresponsiveness: an epidemiological study

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Summary

Background The patterns of inheritance of asthma have largely been explored using data of symptom history collected by questionnaires which are subject to bias and which may therefore distort the measured relationship.

Objective The purpose of this study was to examine family patterns of allergic disease using objective measurements of atopy and of airway hyperresponsiveness (AHR).

Methods A large random sample of children aged 8–11 years was studied and 3 months later, their parents were also invited for study. Of the sample of 1655 children, both parents of 661 children were studied. In all subjects, respiratory illness history was measured by questionnaire, atopy by skin tests and AHR by responsiveness to histamine.

Results The odds ratio for a child to have AHR if either parent had the same condition was approximately 2.0, which was the same as the odds ratio for wheeze or diagnosed asthma in the presence of the same condition in either parent. The odds ratio for atopy was smaller (approximately 1.4, NS) but the risk of a nonatopic child having AHR if the parent had AHR was 3.0 ($P = 0.01$). The correlation between weal size in the child and parent was poor and the severity of AHR in the child was only modestly correlated with the severity of AHR in the parent ($R = 0.51$, $P = 0.04$).

Conclusion The use of objective measurements did not strengthen the association between atopic or asthmatic conditions in the parent and child, but did suggest that atopy and AHR are inherited independently.

Keywords: airway hyperresponsiveness, asthma, atopy, genotype, phenotype

Clinical and Experimental Allergy, Vol. 30, pp. 393–399. Submitted 1 October 1998; revised 20 May 1999; accepted 31 May 1999.

Introduction

Although environmental factors play a large part in the expression of asthma, we also need to have more precise knowledge about the inherited nature of this disease. It is important to quantify the genetic factors not only because we need to differentiate the separate etiological aspects of asthma but also because there is a growing consensus that such factors make a major contribution to determining the inheritance of phenotype [1]. However, asthma does not

seem to follow the characteristics of a single gene disorder and the evidence suggests that a number of genes or interactions between genes and the environment are involved [2,3]. Although new techniques of gene mapping are proving useful in investigating the asthma phenotype, it remains important to quantify associations at an epidemiological level in order that children who are most at risk for expressing various phenotypes can be readily identified using noninvasive methods.

To date, family associations have usually been examined using questionnaire definitions [3–5] and the patterns of inheritance of atopy and airway hyperresponsiveness (AHR) in relation to the same conditions in the parents have not been widely explored. Studies of families and of

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twins have suggested that there is a genetic component in the regulation of AHR [4,6] and that the pattern of inheritance is autosomal-dominant [7]. However, it is still not clear whether atopy and AHR are inherited together or independently [8,9].

In this paper, we have used the data collected from two population samples of children and their parents [10] to examine the risk of children having atopy, asthma or AHR in the presence of the same condition in either parent. We have also examined whether severity of atopy or AHR in the child is related to severity of either of these conditions in the parent and whether there is any evidence that atopy and AHR are inherited independently.

Methods

Population samples

The studies were conducted in Lismore, a town situated in a hot, humid, subtropical region near the coast in northern New South Wales, and in Wagga Wagga, which is a dry, inland, rural town in southern New South Wales [10]. A random sample of children age 8–11 years was studied in both regions using all public and Roman Catholic primary schools as a sampling frame. All children in school years 3, 4 and 5 (aged approximately 8–11 years) at each selected school were invited to participate in the study and only those for whom informed parental consent was obtained were studied.

The parents of these children were then invited for study 3 months after the children's study. Initial contact by a letter to the home address asked all adults in the household to complete a questionnaire and then to attend a location in the town centre for lung function and allergy tests. Follow-up telephone calls were made to arrange appointments.

Questionnaires

A parent self-administered questionnaire was obtained for each child and a self-administered questionnaire was completed by each adult. The children's questionnaire had been developed in previous studies and the questions used in analyses have a high degree of repeatability [11]. Questions asked whether the child's natural parents had ever had asthma, nasal allergies, hay fever or eczema, whether the child had ever had wheeze, exercise wheeze or night cough, had ever used any medications for asthma or had asthma diagnosed by a doctor. The question of recent wheeze was 'Has your child ever wheezed? (Wheezing is a whistling noise that comes from the chest)' and, 'If yes, was this in the last 12 months?'

The adult questionnaire was a shortened version of the IUAT questionnaire [12] which included questions of recent

and past respiratory symptoms, family history of allergic disease, diagnosed asthma, medication use and hospital and doctor attendances. In parents, the question used to classify subjects as having recent wheeze was 'Have you ever had wheezing or whistling in your chest?' and if yes, 'Have you had this wheezing in your chest in the last 12 months?'

In the children's studies, a survey of all non-responders was carried out on the same day as the testing of responders. A member of the research team visited each class and asked non-responder children if they had used any medication for asthma in the last month. The same question of recent medication use was asked of responders. The response rate for the children's studies were 77% in Lismore and 83% in Wagga Wagga and the rate of recent medication use was similar in the responders and the non-responders (10.4 vs 11.2% in Lismore and 12.0 vs 11.1% in Wagga Wagga). We estimated that the response rate in the adults was approximately 60% in Lismore and 62% in Wagga Wagga. Information of recent asthma medication use was also collected from a random telephone survey of 158 adult nonattenders. In the study sample, 18.8% had recent wheeze and 6.6% had recently used an asthma medication compared with 13.2% and 5.1%, respectively, in the nonattenders. Although these rates were not significantly different, they suggest that adults with asthma were slightly more likely to attend.

Ethical approval to conduct the study was received from the Ethics Review Committee at Royal Prince Alfred Hospital and permission to study children at their schools was obtained from the New South Wales Department of Education and from the Catholic Education Office. A respiratory physician attended all studies and reviewed the test results. An information sheet was given to each child to take home to parents. Parents were encouraged to contact the research team if they required additional information of the test outcomes but to consult with their general practitioner if they required follow-up treatment or further medical advice.

Atopy

Atopy to common allergens was measured by skin prick test reactions to the forearm. The eight allergens tested were house dust; house dust mites (*Dermatophagoides pteronyssinus* and *D. farinae*); cat dander; ryegrass; plantain; *Alternaria tenuis* and cockroach. Histamine and glycerol were used as positive and negative controls. Subjects with a negative histamine or a positive glycerol test were retested and the few subjects in whom the result remained were excluded from analyses. After 15 min, weal size was recorded as the long axis and its perpendicular; mean weal size was used in analyses. Atopy was treated as a continuously distributed variable and, in addition, was categorized

as positive or negative. A skin prick reaction was regarded as positive if the weal size was 3 mm or greater for children and 4 mm or greater for adults. Subjects were considered to be atopic if they had a positive reaction to any of the allergens in the testing panel.

Airway responsiveness

A histamine bronchial challenge test was administered to all subjects using the rapid method [13]. Lung function was recorded by Mijnhardt VRS 2000, Mijnhardt BV, Bunnik, Holland dry rolling seal spirometers connected to IBM-PC computers running Scientific and Medical software for immediate data acquisition. Forced expiratory manoeuvres were repeated until two readings of forced expiratory volume in 1 s (FEV₁) and forced vital capacity within 100 mL were obtained of which the largest value was used in analyses. Subjects who had taken a beta agonist within 6 h of presenting were asked to withhold medication before returning for later testing. Histamine diphosphate was administered by use of De Vilbiss no. 45 (De Vilbiss Medizinische, Lauden, Germany) hand-held nebulizers in doses ranging from 0.03 to 3.9 µmol histamine. The test was stopped if the FEV₁ fell by 20% or more or if all histamine dose steps to 3.9 µmol had been administered. Salbutamol aerosol was given to aid recovery when necessary.

For subjects who had a fall in FEV₁ of 20% or greater, the dose of histamine that caused a 20% fall (PD₂₀FEV₁) was calculated. Subjects with a PD₂₀FEV₁ were classified as having airway hyperresponsiveness and the remainder were classified as having normal responsiveness. All subjects who had both recent wheeze and AHR were classified as having 'current asthma'.

Dose-response ratio (DRR) was calculated for all subjects as the percent fall in FEV₁ at the last dose, divided by total dose administered [14]. Because many subjects had an FEV₁ which remained stable or improved slightly during bronchial challenge, and thus gave a zero or negative DRR value, a constant of 3 was added to all DRR values to obtain a positive value for logarithmic conversion [15] so that they are indicated by units %fall FEV₁ µmol + 3.

The few subjects (less than 1%) who presented with an FEV₁ less than 60% of predicted did not undergo histamine challenge but were given a bronchodilator challenge. After measurement of baseline lung function, 200 µg of salbutamol was administered and lung function measured again after 10 min. Subjects with an increase in FEV₁ of 15% or more were considered to have a positive bronchodilator response.

Statistical analyses

Data for the children and their parents were linked using Clinical Reporting System (CRS) software, and were

analysed using the statistical package SAS (SAS Institute Inc., Cary, NC, USA). Geometric mean values were reported for DRR and PD₂₀FEV₁ values which were converted to base 10 logarithms prior to analyses. For all analyses, *P*-values less than 0.05 were regarded as statistically significant and values greater than this as non-significant (NS). Prevalence figures and mean values are presented with their 95% confidence intervals (CI). Chi square tests were used to determine the significance of differences in prevalence between samples. The chi-square statistic was used to determine the association between atopy in the child and atopy in either parent. Where the expected value of any cell was less than five, the *P*-value reported was for a Fisher's exact test statistic. Spearman's rank correlation coefficient was used to assess the relation between skin weal size in the child and the parent and Pearson's correlation coefficient was used to assess the relation between PD₂₀FEV₁ or DRR in the child and the parent. Logistic regression was used to calculate odds ratios for conditions in the child standardized for the condition in both parents.

Results

In the total study sample of 1655 children, there were 352 children with one parent tested and 661 children with both parents tested. Only the data for the 661 children for whom both parents were tested are reported. The demographic characteristics of the study samples have been described [10]. Table 1 shows the prevalence of asthma and of atopy in these 661 children compared with the total sample of 1655 children. The prevalence of recent wheeze, current asthma and AHR were not significantly different between the study and total samples of children but the prevalence of atopy was approximately 5% higher in the study sample (*P* < 0.05).

Table 2 shows the proportion of children who had current asthma, AHR or atopy in relation to the same condition in their parents. A higher percentage of children with atopy had a parent who was atopic but very few children with current asthma or AHR had a parent with either of these conditions.

The odds ratios for a child to have respiratory symptoms, asthma or atopy, as measured by subjective and objective methods, in the presence of the same condition in either parent are shown in Fig. 1. All conditions in a parent except current asthma were significant risk factors for the same condition in the child, with an approximate doubling of risk. The risk of a child having diagnosed asthma was 2.4 (95% CI 1.7–3.4), for recent wheeze was 1.7 (95% CI 1.2–2.4) and for current asthma was 1.5 (95% CI 0.7–3.4) in the presence of the same condition in the parent. The finding that current asthma in the parent was not a significant risk factor for the same condition in the child is likely to be a

Table 1. Prevalence (%) of recent wheeze, current asthma, AHR and atopy in children in the study sample compared with the total sample

	Children in study sample	Children in total sample
Total number	661	1655
Recent wheeze	24.2 (20.9, 27.5)	25.3 (23.2, 27.4)
Current asthma	10.6 (8.2, 12.9)	10.3 (8.8, 11.8)
AHR	19.2 (16.2, 22.2)	18.7 (16.8, 20.6)
Atopy	41.7 (37.9, 45.5)	36.6 (34.3, 38.9)

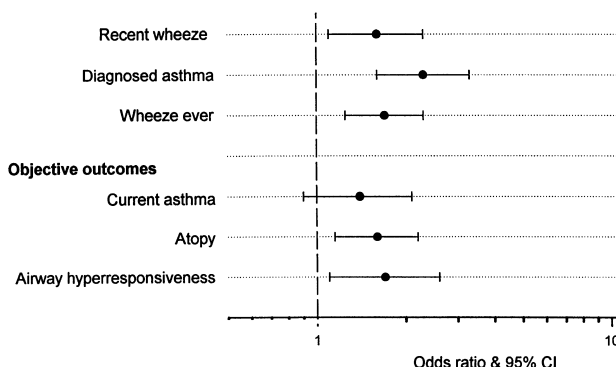
Type II error resulting from the small number of parents with this condition.

The risk of a child having atopy was significantly higher if both parents were atopic. The proportion of children with atopy was significantly higher if both parents were atopic (57%) compared with if only the mother was atopic (41%), only the father was atopic (40%) or neither parent was atopic (33%) ($P < 0.01$). Figure 2 shows the odds ratio for a child to have atopy or AHR in the presence of a parental history of each condition. The risk of the child having atopy if only the mother was atopic was 1.4 (95% CI 0.9–2.1) which was very similar to the risk if only the father was atopic which was 1.4 (95% CI 0.8–2.0). Neither estimate was statistically significant. However, the risk of the child having atopy if both parents were atopic was significant with an odds ratio of 2.8 (95% CI 1.7–4.3; $P < 0.01$).

The risk for a child to have AHR in the presence of AHR in both parents could not be estimated with precision because there were only five families in which both parents had AHR. However, the risk of a child having AHR if either

Table 2. Number of children, shown with percent in brackets, with current asthma, atopy and AHR and categorized according to parental status of the same condition

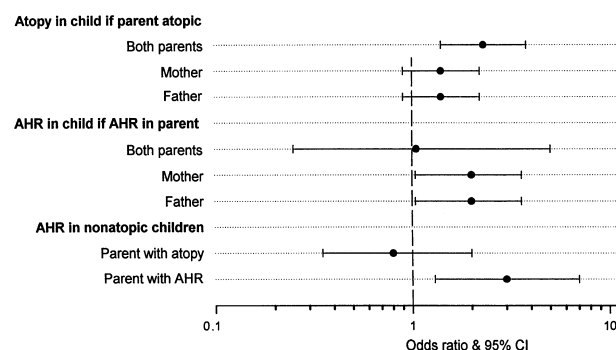
	Mother (–)	Mother (+)	Father (–)	Father (+)
<i>Current asthma</i>				
Child (–)	566 (85.5)	25 (4.0)	569 (86.0)	22 (3.3)
Child (+)	67 (10.0)	3 (0.5)	65 (10.0)	5 (0.7)
<i>AHR</i>				
Child (–)	500 (76.0)	34 (5.0)	502 (76.0)	32 (5.0)
Child (+)	113 (17.0)	14 (2.0)	114 (17.0)	13 (2.0)
<i>Atopy</i>				
Child (–)	245 (37.1)	140 (21.2)	221 (33.5)	164 (24.8)
Child (+)	141 (21.3)	135 (20.4)	127 (19.2)	149 (22.5)

Subjective outcomes**Fig. 1.** Odds ratio for children to have subjective and objective markers of asthma and atopy in the presence of the same condition in either parent

parent had AHR was both significant and similar with an odds ratio of approximately 2.0. The correlation between DRR in the child and in the father was small with $R = 0.14$, $P < 0.001$ and between DRR in the child and in mother was $R = 0.10$, $P = 0.002$.

Because atopy occurred in over 40% of parents and may have masked the risk associated with a parental history of AHR, only the nonatopic children were considered in assessing if atopy and AHR were inherited independently. The risk of AHR in the nonatopic child if the parent was atopic was not significant (OR = 0.8, 95% CI 0.3, 2.0) (Fig. 2). However, if the parent had AHR, the risk of a nonatopic child having AHR was three times greater (OR = 3.0, 95% CI 1.1, 8.3) suggesting that the risk of a child having AHR if the parent had AHR was independent of whether the child was atopic.

We also examined whether the severity of atopy in the child was related to the severity of the atopy in the parent. Only 2.0% of the variation in the largest weal size in the

**Fig. 2.** Odds ratios for children to have atopy or AHR in the presence of the atopy or AHR in the mother, the father or in both parents

child was explained by the largest weal size in the parent ($R = 0.124$, $P = 0.001$). The relationship was poor because 25% of atopic children had parents who were nonatopic and 55% of atopic parents had nonatopic children. The severity of AHR in the child as measured by PD₂₀ was modestly correlated with the severity of AHR in the parent. Approximately 26% of the variation in PD₂₀ in the child was explained by the PD₂₀ value in the parent ($R = 0.51$, $P = 0.04$).

Discussion

The results from this study of family patterns of asthma and allergy suggest that atopy and AHR are inherited independently. In addition, we validated the magnitude of the risks obtained from previous studies which have used questionnaires [16,17] and found that the use of objective classifications did not strengthen the association between a history of asthmatic conditions in the child and the parent. The risks of a child having wheeze, AHR or atopy in the presence of the same condition in either parent were all roughly equal with an odds ratio of approximately 2. It was surprising that there was only a small difference in the magnitude of the risk to the child if conditions were measured by subjective classification of symptoms or by objective classification of atopy or AHR. We expected that subjective measures may have overestimated the risk because parents who have respiratory symptoms themselves would be more likely to recognize and report the same conditions in their child. It was also surprising that we did not find that the severity of atopy or AHR in the child was even moderately related to severity of either condition in the parent.

In this study, we achieved a high response rate for children but a lower response rate for parents and those with current symptoms were more likely to participate [10]. However, the prevalence of atopy, wheeze and AHR was similar to other studies of children and of adults [11,18–20]. Although estimates of the prevalence of symptoms in parents lack precision as a result of non-response bias, estimates of adjusted odds ratios are more robust in that the bias is unlikely to have been systematic so that the odds ratios calculated are more likely to have been underestimated than overestimated. Because of the relatively small numbers of parents with AHR, the odds ratios for estimating the association between AHR in the parent and their child had, in some cases, very wide confidence intervals and were therefore imprecise although there was a trend towards more AHR in the offspring of AHR-positive parents. These non-significant associations may in fact be the result of type II error but, to resolve this issue, family studies with a very large sample size would be required. In this study, we improved reliability by obtaining information directly from the parents who completed their own questionnaires

at the time of testing rather than collecting information indirectly using replies on the child's questionnaire as in previous studies [17,21].

The use of the epidemiological definition of current asthma as the presence of both AHR and recent wheeze identifies the group with most severe condition [22] but the small number of children and parents with current asthma in common led to an imprecise estimate of heritability of this condition. This is clearly not a useful definition when examining patterns of inheritance because the individual components of recent wheeze and AHR are likely to be under separate genetic control, and because the definition does not take account of parents who carry the gene which predispose to wheeze but have not experienced symptoms since childhood. In addition, the prevalence of asthma in Australian children has increased in recent years [23] and this may have reduced perceived familial associations because the parent may carry the gene for asthma but it may not have been expressed because of different environmental conditions during their childhood. In studies of inheritance patterns, it would seem preferable to use unifactorial definitions and, ideally, to take account of both a past and present history of symptoms.

The magnitude of risk of a maternal or paternal history of asthma in this study was similar to that reported in another Australian study of 1494 adults age 32 years who were first tested as children aged 7 years [16]. These researchers found that the risk of a child having asthma, defined as an attack of asthma in the previous 12 months, was identical at 1.7 (CI 1.2–2.5) if the mother or father had asthma. These estimates are lower than reported in a European study in which asthma was defined as one or more episodes of wheezing which could not be explained by another disease. In that study, the risk of a child having asthma if one parent had asthma was 4.3 (95% CI 3.7–5.0) but doubled to 9.6 (95% CI 6.7–13.9) if both parents had asthma [24]. In another study in which asthma was defined as a doctor diagnosis or multiple episodes of wheezy bronchitis, the risk for a child to have asthma was 1.5 (95% CI 0.7–2.7) if their mother had asthma and 4.4 (95% CI 2.5–7.8) if their father had asthma, suggesting a stronger paternal influence [25].

We did not find that the risk of a child having any condition was more strongly related to the gender of one parent than the other. Other studies have suggested that maternal atopy poses a higher risk than paternal atopy [26–28] with reports that children with an atopic mother have a threefold risk of atopy compared with children with an atopic father [29]. It has also been suggested that allergic diseases generally run true to type in families so that the risk of a child having asthma is greater if the parent has had asthma as opposed to rhinitis or atopic dermatitis [17].

In our study, the proportion of atopic children and adults was approximately equal and the risk of a child having

atopy was higher when both parents had atopy, compared with one parent or neither parent having atopy. Other researchers have reported similar findings [27,30,31]. Ownby showed that the risk of a child having an allergic disease increased from 20% in the general population to 50% if the child had one allergic parent to 66% if both parents were allergic [32]. Cookson and Hopkin found a pronounced familial clustering of atopy in that 90% of atopic children had at least one atopic parent, that 66% of children were atopic if one parent was atopic and the other parent was unaffected, and 75% of children were atopic if both parents were atopic [30]. Hopkin also suggested a single gene control of atopy [33], but the many children without atopy who have both parents who are atopic suggests that environmental factors are also important [34,35].

Studies of twins are better able to provide evidence of the genetic contribution to asthma. Investigations of monozygotic (MZ) and dizygotic (DZ) twins find a significant correlation in the liability to asthma with the correlation being higher in MZ than in DZ twins ($r=0.65$ and $r=0.25$, respectively) and in male MZ twins compared with female MZ twins ($r=0.75$ and $r=0.60$, respectively) [36]. A significant difference in correlation between MZ and DZ twins was also confirmed in a separate analysis [37]. A study of the concordance of asthma in a population of 13 888 adult MZ and DZ twin pairs found that only 7.2% of the MZ and 3.5% of the DZ twin pairs were concordant for asthma [38]. In this study, the correlation in liability to asthma was 0.43 for MZ and 0.25 for DZ twins and the heritability of asthma was estimated at 35.6%. Another study found that the concordance for allergic disease was 50% of MZ and 35% of DZ twins [39]. The large proportion of MZ twins discordant for asthma, despite a shared prenatal and family environment, suggest that concordance rates could also be due to the sharing of a common environment [4]. However, a recent study found very limited evidence for the genetic control of IgE responses in a large population sample of twins [40].

The genetic contribution of atopy to asthma has been examined in several studies which show that total serum IgE levels and skin test scores are heritable traits. Correlation coefficients for MZ twins are significantly higher than for DZ twins [3] and clinical data from 32 MZ and 71 DZ twin pairs showed that rates of concordance for atopy to at least one allergen was 51.7% for MZ and 36.8% for DZ twins, and for atopy to the same allergen was 24.1% for MZ and 14.0% for DZ twins [39]. Although the concordance rate in MZ twins was higher, the differences were not statistically significant. In a study of twins reared together and apart, the concordance rates for asthma and positive skin prick tests were greater in MZ twins than DZ twins no matter where they were reared [41]. These data from twins suggests a

substantial genetic component in the variation of total IgE levels and a lesser contribution of common environments and are at variance with the low concordance in the severity of atopy or AHR between the parents and children in our study.

Although it has also been suggested that atopy and AHR are under separate genetic control [7], no studies have examined whether atopy and AHR are inherited independently. Because odds ratios are multiplicative when conditions coexist, our results suggest that the risk of a nonatopic child having AHR was four times greater if either parent had AHR than if either parent had atopy, and suggests that the risk of a nonatopic child having AHR if either parent had AHR was independent of whether either parent had atopy. It has also been reported that atopic asthma is more common than nonatopic asthma among the relatives of asthmatics, irrespective of atopic status [8]. However, among the relatives of control children, neither the prevalence of asthma nor the atopic status of asthmatic relatives was influenced by atopic status which also suggests that asthma and atopy are inherited independently.

The inherited patterns of asthma from an epidemiological perspective seem to be consistent whatever the methods chosen. Unless exceptionally large numbers of families are studied, epidemiological studies will not be able to advance much further in quantifying the inherited component of this disease and future studies will need to rely on genetic technology to more accurately describe the genetic contribution to carefully characterized phenotypes of asthma. This should lead to a better understanding of the factors that influence respiratory health and to a better clarity in the factors that influence the expression of asthma.

Acknowledgements

We thank the National Health and Medical Research Council, Allen and Hanburys, the Asthma Foundation of NSW and the Community Health and Anti-Tuberculosis Association for providing funding for these studies. We also thank all of the subjects who took part and the research personnel who collected the data over the years and who made the study a success.

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