Outcome for children of parents with atopic asthma and transient childhood wheezy bronchitis

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Abstract

***Background* – Childhood asthma and wheeze only in the presence of respiratory infection (wheezy bronchitis) appear to have different prognoses and may differ in their aetiology and heritability. In particular, slight reductions in lung function may be associated with episodes of wheezing associated with intercurrent viral infection.**

***Methods* – Outcomes for wheezing symptoms and lung function were studied in 133 offspring of three distinct groups of 69 middle aged probands with childhood histories of (1) atopic asthma (n = 18), (2) wheeze associated with upper respiratory tract infection (wheezy bronchitis, n = 24), and (3) no symptoms (n = 27). Probands were selected from a previously studied cohort in which outcomes of wheezy bronchitis and asthma had been shown to differ.**

***Results* – Children of probands with wheezy bronchitis had a lower prevalence of current wheezing symptoms. Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) in boys of probands with a history of wheezy bronchitis were significantly reduced compared with either of the other two groups ($p<0.0001$). In a multivariate analysis, grouping based on parent proband had a significant effect on lung function, independent of factors such as symptoms, atopy or smoking history.**

***Conclusions* – The different symptomatic and lung function outcome in children of probands with wheezy bronchitis and asthma provides further evidence that wheezy bronchitis and asthma differ in their natural history and heritability, and suggests that there may be familial factors specific to each wheezing syndrome.**

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The definition of asthma, particularly in children, remains controversial.[1] The significance of early childhood wheezing illness associated only with clinical evidence of upper respiratory tract infection, previously described as "wheezy bronchitis", and its relationship to atopic asthma is unclear,[2] although there is increasing support for the view that childhood wheezing illness is a heterogeneous group of syndromes.[3] Wheezing in infancy and early childhood appears to be associated with impaired airway function rather than atopy,[4 5] in contrast to later childhood where atopy is a major determinant of wheezing illness.[6 7]

Although previous twin and family studies have provided convincing evidence of familial aggregation in asthma,[8–12] few previous studies have investigated the familial associations of different wheezing syndromes in childhood. Sibbald[13] suggested that the families of wheezy bronchitic children did not differ significantly from those of asthmatic children, implying a common underlying genetic defect. In contrast, Konig and Godfrey showed higher levels of skin test positivity and exercise-induced airway lability, but no increase in prevalence of atopic disease amongst first degree relatives of children with wheezy bronchitis compared with controls.[14] A large case-control study showed no difference in prevalence of bronchial hyperreactivity in parents of non-atopic children with recurrent wheezing associated with upper respiratory tract infection and adult controls matched for age, sex, atopy, and smoking status.[15] In a community study parental history of asthma or bronchiolitis, particularly before the age of three, was associated with wheezing illness in their children aged under one year, further supporting the possibility that there may be a familial component to early childhood respiratory illness separate from atopy and asthma.[16]

We have previously shown that children diagnosed as having wheezy bronchitis rather than asthma have a significantly better outcome in early middle age, independent of the effects of atopy,[17 18] which suggests that asthma and wheezy bronchitis are different syndromes. We therefore examined families of three distinct groups of well characterised adult probands with (1) childhood onset atopic asthma, (2) transient childhood wheezy bronchitis with no symptoms in adulthood, and (3) non-atopic subjects with no symptoms in either childhood or adulthood.[17] We tested the hypothesis that different patterns of symptomatology and lung function occur in the offspring of probands with these apparently different syndromes.

Methods

SUBJECTS

Probands were selected from individuals originally studied as children in the 1960s.[19] At that time 121 individuals with a clinical dia-

gnosis of asthma (defined as "recurrent dyspnoea of an obstructive type without other demonstrable cause") and 167 individuals with a clinical diagnosis of wheezy bronchitis (defined as "wheeze occurring only in the presence of infection") were identified in a larger random community sample of 2511 schoolchildren aged 10–14 years. Twenty five years later all accessible individuals within these groups together with a comparison group of 167 individuals selected from the non-wheezing group within the original study population were restudied.[17]

Probands were selected on the basis of both their original classification and outcome 25 years later in order to identify those in whom natural histories were clearly different. Three groups were identified: 20 individuals with childhood onset asthma, continuing symptoms in early middle age and atopy (group 1); 30 with childhood wheezy bronchitis and no symptoms in early middle age (group 2); and 29 non-atopic probands without symptoms in either childhood or adulthood (group 3). This approach was adopted in order to study families based on probands who were divided into discrete groups based on natural history. Although restricting the numbers available for study, this approach concentrates on outcomes in the families of the "core phenotype" in a situation where classification is difficult and often ambiguous.

Sixty nine probands and their families (18 group 1, 24 group 2, and 27 group 3) agreed to participate (87.3%). Of the remaining 10 probands seven refused to participate, one had died, and two had moved outwith the study area. One proband had divorced and remarried, and both his current and previous spouse and children of both marriages were seen. One spouse had died (of a non-respiratory cause), one spouse refused to participate, and six spouses could not be contacted following divorce or separation. Of the 143 children from these families, 133 (93%) agreed to participate.

STUDY DESIGN

After initial contact individuals were seen at home by a research nurse and a semi-structured questionnaire based on the ATS DLD78A questionnaire[20] was administered. Subjects were thereafter invited to attend for skin prick testing for common aeroallergens and spirometric tests. Children were interviewed together with their parents to obtain information about events in infancy and early childhood. Spirometric tests were carried out using a wedge spirometer (Vitalograph, Buckingham, UK) with the subject standing. Nose clips were not used. In those individuals who declined to attend a Compact portable spirometer (Vitalograph, Buckingham, UK) was used to record spirometric data at home. Children's lung function was expressed as % predicted adjusted for height using the values of Rosenthal *et al*.[21] These data were not normally distributed and were log transformed to normalise the distribution.

Skin prick testing was carried out by the method of Hendrick *et al*[22] using house dust mite (*D pteronyssimus*), cat and mixed grasses (Dome Hollister Steir, Spokane, Washington, USA). Skin prick tests were regarded as positive if the maximum weal diameter was at least 2 mm greater than the negative control for any of the allergens tested. Methacholine bronchial hyperreactivity was measured using the method of Yan *et al*.[23]

STATISTICAL ANALYSIS

Data were analysed on a personal computer using the package STATA (Stata Corporation, Texas, USA). Chi squared tests were used to study associations between categorical variables as appropriate. Multivariate regression analysis was used to investigate effects on lung function. In this analysis allowance was made for the correlation structure of the data within families using Huber corrections for clustered sampling within families.[24] Separate models were developed for both FEV_1 and FVC in boys and girls.

Table 1 Characteristics of children grouped by parent proband

Symptom	*Group 1 (n=35)*	*Group 2 (n=48)*	*Group 3 (n=50)*
Mean (SD) age	12.7 (4.9)	14.1 (4.6)	14.7 (4.3)
Age under 15 years	20	26	28
Sex (M/F)	20/15	23/25	29/21
Current wheezing (within the last 12 months)	13 (36%)	7 (14%)**	13 (26%)
Ever wheeze	17 (49%)	13 (27%)	18 (36%)
Maternal smoking in pregnancy	9 (26%)	10 (21%)	15 (30%)
Parental smoking (mean pack years smoked by both parents)	21	10	15
Positive skin prick test (n=117)	16/30 (53%)	19/42 (45%)	28/45 (62%)
$PD_{20}FEV_1$ <16 μmol methacholine (n=115)	13/29 (45%)	14/42 (33%)	18/44 (41%)

$PD_{20}FEV_1$ = dose of methacholine required to provoke a fall of 20% or more in forced expiratory volume in one second.
** $p<0.02$, $\chi^2=8.74$, 2 df.

Results

Questionnaire data were available on all 133 children in the nuclear families studied. Complete data including bronchial challenge testing, atopic status, and lung function were available for 114 children (85%). Sixteen children declined skin prick testing while spirometric tests were not performed on four children aged under five years and were refused by 10 further children. Bronchial challenge testing was not performed on children under five years and was refused by 14 further children. There were no significant differences in age or sex ratio between the groups studied. The prevalence of current and ever wheezing symptoms in all 133 children is shown in table 1. Significantly fewer children of wheezy bronchitic probands (group 2) than of asthmatic probands had wheezed in the last 12 months. Parental smoking, as assessed by total pack years smoked by both parents, was lowest in group 2 but did not differ significantly between the groups.

Parents were also asked about recall of their own wheezing symptoms. The accuracy of the proband's recall of their own childhood symptoms was tested using the questionnaire as a guide to the accuracy of recall of childhood symptoms in middle age in their spouses who

Table 2 Geometric mean (95% CI) percentage predicted lung function in children

Parent proband (group)	*Atopic asthmatic (group 1)*	*Wheezy bronchitic (group 2)*	*Control (group 3)*
Boys			
FEV_1 (%)	121 (111 to 132)	98 (94 to 102)*	109 (103 to 115)
FVC (%)	114 (105 to 124)	94 (90 to 98)*	105 (100 to 110)
Girls			
FEV_1 (%)	109 (100 to 115)	105 (98 to 112)	105 (100 to 110)
FVC (%)	112 (105 to 119)	102 (95 to 109)	108 (102 to 114)

FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity.
* $p<0.0001$ (one way ANOVA, df = 54).

Table 3 Predictors of forced expiratory volume in one second (FEV_1) in boys

Variable	*Coefficient*	*95% CI*	*p value*
Age (per year)	0.101	0.028 to 0.173	0.007
Height (cm)	0.042	0.030 to 0.053	<0.001
Group 1	0.400	0.126 to 0.675	0.005
Group 2	−1.029	−0.665 to −1.393	<0.001
Current wheeze	−0.485	−0.255 to −0.715	<0.001
Positive atopy	−0.564	−0.377 to −0.752	<0.001
Atopic (group 2)	0.803	0.447 to 1.159	<0.001
Age <15 (group 2)	−0.459	−0.109 to −0.808	0.011

did not take part in the 1964 study. The overall accuracy of recall was found to be 69%. However, it was striking that, although probands in groups 1 (childhood onset asthma) and 3 (asymptomatic) correctly recalled their childhood symptoms in over 90% of cases, the accuracy of recall in group 2 (transient wheezy bronchitis) was less than 50%. Recall of wheezing symptoms at any time by parent probands was 91% for group 1, 23% for group 2, and 16% for group 3. Recall of wheeze ever for spouses was 23%, 27% and 22%, respectively.

Skin prick test results were available for 117 children. The prevalence of at least one positive skin prick test did not differ between the three groups. There was no difference between the groups in the prevalence of a dose of <16 μmol methacholine required to provoke a fall in FEV_1 of 20% ($PD_{20}FEV_1$) amongst the 115 children who were tested (table 1).

The geometric mean values for FEV_1 and FVC % predicted together with 95% confidence intervals for boys and girls are shown in table 2. Values for FEV_1 and FVC were significantly lower for boys in group 2 than in either of the other two groups (FEV_1: one way analysis of variance, $p<0.0001$, df = 59; FVC: one way analysis of variance, $p<0.0001$, df = 59). These differences were due largely to poorer lung function amongst children aged 14 or less in group 2. There were no significant differences in FEV_1 or FVC between the groups studied amongst the girls or when all data from all children were combined. The intraclass correlation coefficient for boys calculated using analysis of variance[25] was 0.683 for FEV_1 and 0.591 for FVC, suggesting significant familial aggregation of lung function in boys. In girls the corresponding intraclass correlation coefficient for FEV_1 was 0.097 and for FVC was 0.036.

Mutivariate regression analysis was used to investigate potential predictors of lung function including correction for intrafamily correlations. Separate models were developed for both FEV_1 and FVC in boys and girls. The initial model in both sexes included age, height, current wheezing, atopic status, parental smoking, and parental lung function expressed as % predicted. In girls only age and height were significant predictors of FEV_1 and FVC whereas in boys all of the variables in the initial model apart from parental smoking had significant effects. Interaction terms were included for current wheezing and atopy (not significant), atopy and family type (significant only for boys in group 2), and age under 15 and family type (significant only for boys in group 2). After inclusion of these interaction terms parental lung function was no longer significant in boys and was excluded from the final model. The final models for FEV_1 and FVC in boys were similar. The resulting model for FEV_1 in boys fitted the data satisfactorily ($r^2 = 0.89$, residual standard deviation 0.34) and is shown in table 3. As expected, age and height were highly significant predictors of FEV_1 while atopy and current wheezing had significant negative effects. Effects due to family grouping were significant, group 1 having a favourable effect on FEV_1 in boys whilst group 2 had a significant negative effect. No significant effect of parental smoking history, including maternal smoking in pregnancy, was observed. There were significant interactions between grouping, age, and atopy in group 2 only. Atopic children in group 2 fared significantly better than the remainder of the group, suggesting that the negative effect on lung function in this group was not due to atopy. Similarly, there was a significant negative effect of age under 15 in group 2, confirming the impression that the negative effect on lung function in boys in this group was principally prepubertal. A similar pattern was observed for FVC in boys while in girls only age and height were significant predictors of FEV_1 and FVC.

Discussion

Although asthma is widely recognised to have a significant hereditary component,[10] few family studies have accounted for the heterogeneity of childhood wheezing illness. Previous studies have relied on the clinical description of affected children ascertained through community surveys or hospital attendance and have suggested strong similarities between relatives of children with wheezy bronchitis and asthma.[13,14] More recent studies have not demonstrated familial aggregation of bronchial hyperreactivity in families of children with recurrent wheezing illness associated with infection[15] and have suggested that there may be familial aggregation of early childhood wheezing illness.[16] A larger study in older children has also shown that parental histories of either "asthma" or "bronchitis" have significant independent effects on symptomatic outcome and FEF_{25-75} in children independent of the effects of smoking.[26] These studies suggest that there may be significant differences in the heritability of asthma and recurrent wheeze only in the presence of infection. The present study uses well characterised middle aged probands in whom childhood diagnostic labels of "asthma" or recurrent wheeze only in the pres-

ence of infection ("wheezy bronchitis") have been shown to have prognostic significance to early middle age independent of the effects of atopy and smoking.[17 18] Although there are large and important intermediate groups with wheezing illness outwith the classification used in the present study, the three well characterised groups examined allowed us to compare and contrast outcomes of their children across the spectrum of childhood wheezing illnesses.

The significantly lower prevalence of current wheeze in the offspring of wheezy bronchitic probands compared with atopic asthmatic probands is striking as is the relatively high prevalence of current wheezing symptoms among the children of the non-atopic asymptomatic probands. These differences were not associated with the prevalence of atopy or bronchial hyperreactivity nor with significant differences in exposure to parental smoking. Grouping based on parent proband appeared to have significant effects on the symptomatic outcome of offspring. The lack of apparent influence of the spouse may be explained by the similarity in spouse phenotype across the groups, and the highly selected nature of the probands studied who represent discrete and clearly defined groups along the clinical spectrum of wheezing illness. The high prevalence of wheezing in the children of non-atopic asymptomatic probands may reflect the well documented increase in asthma prevalence in this population over the last 30 years.[27 28]

The other notable finding in this study is the apparent difference in lung function in boys between groups. Boys in group 2 had poorer lung function than expected while those of atopic asthmatic probands (group 1) had better than expected lung function, effects which appeared to be due principally to grouping rather than potential confounding factors such as atopy, wheezing, or parental smoking. It appears unlikely that either respiratory illness or smoking was responsible for the observed differences in lung function between the groups studied. Atopy in particular did not account for the poorer lung function within group 2 as, although there was a significant interaction with atopy in this group, atopic individuals fared better than the remainder of the group. The finding of increased forced expired lung volumes in boys of asthmatic probands contrasts with the effects in children of wheezy bronchitic probands, again implying heterogeneity between asthma and wheezy bronchitis. While the effect of parental history of atopic asthma on lung function was most marked in those children without a history of wheeze, the reason for this finding is unclear. Although increased FVC and total lung capacity (TLC) have been reported in childhood asthma, these effects have been ascribed to changes in lung growth and development secondary to the disease[29] rather than to familial effects and would not explain the effects seen in asymptomatic children in the present study. The overall values, expressed as % predicted, were higher than expected. This was also seen when the parents were originally studied,[17 19] suggesting that the children were drawn from a population in which lung function values were consistently higher than predicted.

The effects on lung function observed in group 2 were significant in boys under the age of 15. Although data on age at puberty in these children were not available, this does suggest that the effects on lung function associated with a parental history of wheezy bronchitis are mainly prepubertal. In boys peak height velocity is achieved at approximately age 14 and none of the children studied had illnesses likely to cause significant pubertal delay. Transient early wheezing illnesses in the preschool years are more common in boys[30] and are associated with continuing impairment of lung function in later childhood.[31] Our finding of poorer lung function in boys whose parents had a history of childhood wheezy bronchitis would be consistent with increased susceptibility to early childhood wheezing illness associated with heritable effects on lung function.

Although the numbers studied were small, the present study provides further evidence that asthma and wheezy bronchitis differ significantly in their heritability and that gender specific effects are prominent in childhood.

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