Airway reactivity in parents of infants and young children with recurrent wheeze: a case-control study

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Abstract

Increased airway reactivity has been found in family members of school age children and adults with asthma. As the relation between recurrent wheeze in infancy and bronchial reactivity is not yet clear, it was decided to test bronchial reactivity to methacholine in both parents of 50 preschool age children with recurrent wheeze and in 200 population based controls matched for sex, age, smoking habits, and atopy. Wheezy children fulfilled the following criteria: first attack of wheezing before the age of 2 years, at least four wheezing episodes triggered by a respiratory infection, negative skin prick tests, and no symptoms related to allergy. Four parents and five controls did not undergo the methacholine challenge because their forced expiratory volume in one second was <80% of the predicted value. Methacholine reactivity was not significantly different in parents and controls.

In summary, an increased bronchial responsiveness was not found in parents of infants and young children with recurrent wheeze triggered by infection.

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Recurrent bronchial obstruction during acute infectious respiratory illnesses is one of the most common chronic diseases of childhood. Several authors regard recurrent wheeze in infants and young children and asthma as the same disorder because of common clinical signs and possible similarities in the pathogenesis, but this issue is still controversial.[1] Airway hyperreactivity is considered to be an important manifestation of asthma. In several studies both in school age children and in adults the degree of bronchial reactivity to histamine or methacholine correlates with asthma symptoms.[2–4] It has been suggested that genetic factors are responsible for airway hyperreactivity in asthmatic subjects. Townley *et al* found a bimodal distribution of bronchial responses to methacholine in normal (non-atopic, non-asthmatic) individuals from families with asthma and atopy in contrast to a unimodal distribution in normal individuals from normal families.[5] A similar bimodal distribution in bronchial reactivity to carbachol and methacholine was found in healthy parents of asthmatic school age children and adults by Longo *et al* in Italy[6] and Hopp *et al* in North America.[7] These studies suggest that an increased background of bronchial reactivity exists in families of asthmatics even though clinical disease is not evident.

We therefore decided to investigate if familial hyperreactivity also plays a part in recurrent wheeze triggered by infections in infants and young children by performing a methacholine challenge test in their parents and comparing the results with those obtained in control adults.

Subjects and methods

Natural fathers and mothers of 50 infants and young children with recurrent wheeze sequentially attending our outpatient clinic from June 1992 to March 1994 participated in a matched case-control study. Only two couples eligible for inclusion in the study could not participate because the mothers were pregnant at the time.

The patients (27 boys and 23 girls) had a mean age of 3·1 years (range: 1·5–6 years) at the time of the test, and fulfilled the following criteria: first attack of wheezing before the age of 2 years; at least four wheezing attacks associated with evidence of an acute respiratory infection (rhinitis+fever); no history of eczema, urticaria, hay fever, or symptoms of inhalation allergy; and negative skin prick tests to egg and milk and to 11 aeroallergens common in our geographic area. The allergens used were *Dermatophagoides pteronyssinus*, mixed antigens of grass, four weed pollens, birch, *Alternaria* spp, *Cladosporium* spp, and cat and dog danders (Lofarma, Milano, Italy). Weals of 3 mm diameter or greater were considered positive in the absence of a reaction of the control solution. Saline was used as a negative control and histamine (0·1%) as a positive control. Preterm children or those with cystic fibrosis or any other chronic bronchopulmonary illness were not included.

For each parent two controls were randomly selected from a larger sample participating in a cross sectional regional survey on bronchial reactivity. The controls were matched for sex, age, smoking habits (non-smokers, ex-smokers, smokers: 0–10, 11–20, 21+ cigarettes/day) and atopic status (skin prick test positive or negative). The same aeroallergens were used as with paediatric patients. Non-smokers were defined as subjects who had not smoked more than 100 cigarettes in their lives. Ex-smokers had smoked

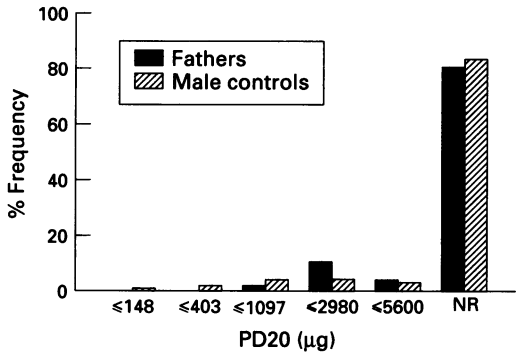

Figure 1 Distribution of bronchial reactivity in fathers and male controls expressed as PD20 (% of each group); NR=non-responders to 5600 μg of methacholine.

daily but had given it up. Subjects were classified as smokers if they were smoking daily at the time of the study. Among the parents, 54% were non-smokers. In the group of smokers, 41% smoked one to 10 cigarettes/day, 50% 11–20, and 9% more than 20. Twenty five per cent of the parents were atopic.

METHACHOLINE PROTOCOL

At the time of the study no subject was receiving treatment for asthma or medications known to affect bronchial responsiveness to methacholine and all were free from respiratory tract infections in the preceding two weeks. Three expiratory manoeuvres were performed on a water sealed spirometer (Biomedin, Padova, Italy). Subjects whose forced expiratory volume in one second (FEV_1), from the best of three curves, was less than 80% of the predicted value[8] underwent a bronchodilation test with salbutamol. The others underwent the challenge with lyophile methacholine (phosphate buffer) (Lofarma, Milano, Italy). A 1% concentration of methacholine was prepared by dilution in distilled water. A metered nebulised dosimeter (Mefar, Brescia, Italy) delivered methacholine from a DeVilbiss ampoule (DeVilbiss Corp, Somerset, PA) by means of an air compressor (driving pressure, 1·5 kg/cm^2). The inhalation time was set at 0·8 seconds, every inhalation delivering 100 μg of methacholine. A phosphate buffer was inhaled and three forced expiratory curves were obtained. If the FEV_1 after phosphate did not change more than 5% from the baseline value, methacholine, starting at a dose of 100 μg and increasing cumulatively (200, 400, 800, 1600, 3200, 4800, 5600 μg) was delivered with increasing numbers of inhalations. Each inhalation was performed with a slow submaximal inspiratory manoeuvre, beginning at functional residual capacity. One minute after each dose three forced expiratory curves were recorded. The test was continued until there was a drop of >20% in FEV_1 (PD20) as compared with phosphate buffer or until the highest cumulative dose of 5600 μg of methacholine had been inhaled. The whole test was performed in 20 minutes.

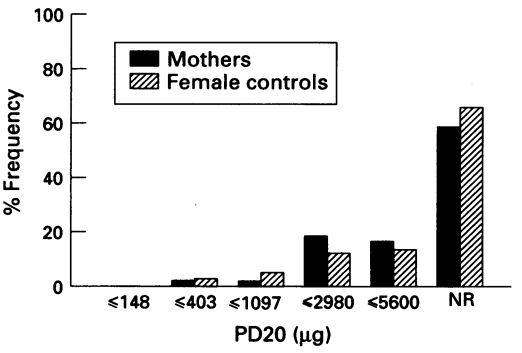

Figure 2 Distribution of bronchial reactivity in mothers and female controls expressed as PD20 (% of each group); NR=non-responders to 5600 μg of methacholine.

STATISTICAL ANALYSIS

As bronchial reactivity is affected by gender, its distribution in parents and controls was compared separately for males and females with a distribution free procedure (Kolmogorov-Smirnov test). All negative tests (non-responders to the cumulative dose of 5600 μg) were assigned a value of 5601. The statistical package SPSS/PC+ was used.[9]

The potential confounding effect of baseline lung function (FEV_1) on bronchial reactivity was assessed by logistic regression analysis, recoding bronchial reactivity as a dichotomous variable.[10] Subjects with a threshold of 1900 μg or less were defined as hyperreactive. This cut off value was chosen because it corresponds to the fifth centile in the general population in this area.[11]

Results

Four parents and five controls did not undergo the methacholine challenge because their FEV_1 was less than 80% of the predicted value. None of the parents responded to salbutamol (<20% change of FEV_1 from baseline) whereas 4/5 controls did.

The distribution of bronchial reactivity in parents and controls is shown in figs 1 and 2. PD20 values were grouped after log transformation, and then antilogged for graphic presentation. No differences were found between cases and controls in either males or females ($p>0·7$ and $p>0·9$ respectively by Kolmogorov-Smirnov test).

No confounding effect of baseline airways calibre was observed. Even when bronchial reactivity was adjusted for baseline airway calibre (expressed as % of predicted FEV_1) there was no significant difference between parents and controls. The odds ratio for a positive methacholine response for cases versus controls before taking into account FEV_1 was 0·89 for males and 0·82 for females, and after adjusting for FEV_1 it was 0·93 for males (95% confidence interval: 0·35 to 2·5; $p=0·89$) and 0·75 for females (95% confidence interval: 0·33 to 1·69; $p=0·48$).

Discussion

This study showed that increased airway hyperreactivity is no more frequent in the

parents of infants and young children with recurrent wheeze triggered by infections than in controls.

The problem of whether bronchial hyperreactivity is involved in recurrent wheeze in infants is still controversial and the published studies have yielded discrepant results. Voter *et al*[12] and Godden *et al*[13] demonstrated that in adolescents and in adults who had had wheeze triggered by infections early in life, bronchial reactivity was not significantly higher than in subjects without respiratory symptoms in childhood.

On the other hand three studies investigated the families of infants and young children with wheeze and concluded that bronchial reactivity was involved in its pathogenesis. Konig and Godfrey demonstrated a higher response to exercise test in 48 relatives of 16 patients with wheezy bronchitis than in 24 relatives of 10 controls.[14] That study differed from ours in the inclusion criteria for patients and controls, the lack of standardisation of the number of relatives tested for each patient and, above all, the lack of attempt to control for atopic status. Subjects with positive skin tests, in fact, were much more frequent in cases than in controls and this could have biased the results. Moreover, the bronchial challenge test used was different. Konig and Godfrey chose an indirect test, such as exercise, that may be assessing something different from a direct one such as methacholine. It is known, for example, that indirect bronchial challenge shows a closer relationship with clinical symptoms than does direct challenge. Gurwitz *et al* reported a high incidence (33%) of positive methacholine reactivity in 66 first degree relatives of 24 children with a previous history of one or more episodes of bronchiolitis who were already known to be positive to methacholine.[15] This was a highly selected population and furthermore only historical controls were available.

In a recent study performed in Italy Pifferi *et al* showed a significant increase in either FEV_1 or forced expiratory flow rate at 25% to 75% or in both after salbutamol administration, but not after placebo inhalation, in 24% of 66 parents of infants with bronchiolitis.[16] No significant change in these parameters was found in 66 parents of children without bronchiolitis. Also in this study no attempt was made to carefully control for the atopic status of the parents. In our study both cases and controls were carefully chosen.[17] The cases were all the infants and children who fulfilled the inclusion criteria seen over a defined period of time. All couples participated except two who could not because the mother was pregnant at the time. We restricted the inclusion criteria in order to enrol subjects who had a low probability of having atopic asthma,[18 19] although an atopic background could not be excluded with certainty at this age. This had two purposes: to render the group of patients more homogeneous[10] and to reduce the confounding due to atopy. In any case, according to the previously reported findings of bronchial lability in the families of school age children and adults with asthma,[5–7] the inclusion of a few subjects who continued to have wheezing also in response to allergens would have increased the probability of finding a high airway hyperreactivity in the parents of our patients. We did not attempt to make an aetiological diagnosis of the respiratory infections that triggered the wheezing attacks, but there is a general consensus that viral infections play a large part in exacerbations of wheezing in infants and young children.[20] Recurrent wheeze in infancy was originally called wheezy bronchitis because it manifests in association with a suspected or proved viral infection.

As for the controls, they were randomly taken from a population based study. Confounding variables known to modify bronchial reactivity were carefully considered by selecting controls matched for age, smoking habits, and atopic status in the design phase,[21–24] and by controlling for differences in FEV_1 in the analysis stage.

The negative result of the study is unlikely to be due to a small sample size: the study had a 95% power of detecting an odds ratio smaller than 3 in females or smaller than 3·5 in males.[25] Our results do not even suggest a trend toward an increased bronchial reactivity in parents compared with controls, as the odds ratios in both males and females were <1. The bronchial challenge procedure adopted by us is well standardised. The dose of methacholine was sufficiently high to recognise adequately 'responders' and 'non-responders' beyond the range that is usually seen in asthmatics. This is especially important when the target population is not asthmatic.

The results of our study further confirm the hypothesis that recurrent wheeze in infants and young children could in most cases have a different pathogenesis from wheeze occurring later in life.

The availability of devices to test lung function in infants has recently allowed Martinez *et al* to demonstrate that lower levels of lung function compatible with intrinsically abnormally small airways or abnormally compliant airways are present before the first wheezing illness in subjects who wheeze very early in life,[26] suggesting that the functional diameter of the airways may predispose infants to develop signs of bronchial obstruction during viral infections when the airways could be further narrowed by oedema and mucus secretions. As for bronchial reactivity this functional (anatomical) abnormality might be genetically determined as it is suggested by a further study done by the same group in which an association was found between a parental history of asthma or bronchiolitis early in childhood and wheezing in the first year of life in their children.[27]

In conclusion, unlike studies on adults and on older children with asthma, our study does not demonstrate a higher airway reactivity in parents of infants and young children with recurrent wheeze triggered by airway infection, suggesting that other mechanisms such as the anatomical characteristics of the airways may predispose infants to develop signs of bronchial

obstruction during viral respiratory infections early in life.

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