A family study of the genetic basis of asthma and wheezy bronchitis

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SUMMARY The family histories relating to asthma and wheezy bronchitis were examined in 77 asthmatic, 78 wheezy bronchitic, and 87 control children, aged between 1 and 12 years. The percentage of children with at least one asthmatic relative was significantly greater in the asthmatic and wheezy bronchitic probands than in the controls; and asthma was more prevalent in the relatives of both groups of wheezy probands than in the relatives of controls. Similarly, the percentage of children with at least one wheezy bronchitic relative tended to be greater in asthmatic and wheezy bronchitic probands than in the controls; and wheezy bronchitis tended to be more prevalent in the relatives of both groups of wheezy probands than in the relatives of controls. However these differences did not reach significance. The strong similarities between asthmatic and wheezy bronchitic children in their family histories of asthma and wheezy bronchitis suggest that these two forms of wheezy illness share a common genetic defect.

Childhood wheezy bronchitis is characterised by recurrent episodes of wheeze which occur only in association with a respiratory infection. It can be distinguished from asthma in which episodes of wheeze may be provoked by allergens, exercise, or emotion, and by infection.

The clinical differences between these two forms of wheezy illness are not well defined, resulting in confusion about the relationship of wheezy bronchitis to asthma. Although many children with wheezy bronchitis grow out of this tendency, some develop frank asthma later. Moreover wheezy bronchitis is known to precede asthma in many childhood asthmatics. Therefore it is possible that asthma and wheezy bronchitis have a common defect, as suggested by Williams and McNicol.

Other findings suggest that the aetiologies of the disorders may differ. Despite the viewpoint expressed by Williams and McNicol, their data showed that the incidence of hay fever, skin test sensitivity, and nasal eosinophilia was lower in children with wheezy bronchitis than in those with asthma. Taussig and Lebowitz confirmed these observations and they showed also that wheezy bronchitic children have fewer abnormalities in pulmonary function than asthmatic children. Therefore, it is possible that aetiologies of asthma and wheezy bronchitis differ, the former depending on factors which are not essential for the development of wheezy bronchitis.

Since it is well established that asthma has a hereditary basis, the relationship between asthma and wheezy bronchitis may be clarified by family studies designed to assess the degree of genetic similarity between them. If the disorders have a common genetic basis, we would expect family histories to be similar in asthmatic and wheezy bronchitic children. On the other hand, if they do not have a common hereditary defect, family histories would differ. In this paper, we report the findings of a family study in which comparison was made of the hereditary similarities and differences between asthma and wheezy bronchitis.

Methods

The study group comprised 242 children, aged between 1 and 12, and their families attending a general practice in Roehampton, south-west London. The data had been collected for a survey on asthma and wheezy bronchitis carried out between 1967 and 1976.
The first child from each family to be recruited in the survey was designated the proband for the purposes of the present study. Probands were classified into the following groups according to history of respiratory illness.

Wheezy bronchitis: one or more episodes of wheezing which occurred only in association with symptoms suggesting respiratory infection. On auscultation there would be a high pitched wheeze over most parts of the lungs in addition to medium crepitations or rhonchi.

Asthma: recurrent episodes of wheezing which occurred in response to allergens, exercise, or emotion, as well as with symptoms suggesting respiratory infection. On auscultation there would be a high pitched wheeze over most parts of the lungs.

Control: no history of wheeze. Although most children had experienced at least one episode of respiratory infection, wheeze had never been detected on auscultation.

The groups were each subdivided into atopic and nonatopic groups according to the proband’s reactions to skin prick tests of house dust, pollens, house dust mite, animal danders, and moulds. The criterion for a positive reaction was a weal of at least 2 mm in diameter in the absence of any equivalent reaction to the control solution. A patient with at least one positive reaction was designated atopic, while a patient with no positive reactions was designated nonatopic.

The age, sex, and history of hay fever and eczema were recorded for each proband. The history of asthma and wheezy bronchitis in each of the proband’s first-degree relatives (that is, parents and siblings) was obtained by interviewing at least one member of his family and by scrutinising medical records.

A relative was said to have a history of wheezy bronchitis if, at any time during his life, he had had at least one episode of wheezing which occurred only in association with symptoms suggesting respiratory infection. On the other hand, if the relative had had wheezy episodes which occurred in response to allergens, exercise, or emotion as well as with symptoms suggesting respiratory infection, then he was said to have a history of asthma.

Results

Table 1 summarises the clinical characteristics of the probands in each of the asthma, wheezy bronchitis, and control groups. There were no significant differences between groups in the proportion of males or the mean age of the probands. The prevalences of atopy, hay fever, and eczema were all significantly higher in asthmatic than in wheezy bronchitic or control children. The proportion of children with a positive family history of asthma was greater in both the asthma and wheezy bronchitis groups than in the control group, but the proportion with a positive family history of wheezy bronchitis did not differ significantly among groups.

The prevalences of asthma and wheezy bronchitis in the first-degree relatives of probands are summarized in Table 2. The overall prevalence of asthma was higher in the relatives of both asthmatic and wheezy bronchitic probands than in the relatives of controls ($\chi^2=16.02; P<0.01$). A similar trend was observed in the prevalence of wheezy bronchitis, but the differences did not reach significance ($\chi^2=1.94, P>0.10$).

### Table 1 Characterisation of probands

<table>
<thead>
<tr>
<th>Proband</th>
<th>No. (%)</th>
<th>Males</th>
<th>Hay fever</th>
<th>Eczema</th>
<th>Family history</th>
<th>Mean age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>Asthma</td>
<td>Wheezy bronchitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopic</td>
<td>64 (83)**</td>
<td>42 (66)</td>
<td>25 (39)*</td>
<td>33 (52)*</td>
<td>25 (39)**</td>
<td>17 (26)</td>
</tr>
<tr>
<td>Nonatopic</td>
<td>13 (17)</td>
<td>9 (69)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4 (31)</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Total</td>
<td>77</td>
<td>51 (66)</td>
<td>25 (32)**</td>
<td>33 (43)**</td>
<td>29 (38)**</td>
<td>22 (28)</td>
</tr>
<tr>
<td>Wheezy bronchitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopic</td>
<td>36 (46)</td>
<td>26 (72)</td>
<td>4 (11)</td>
<td>5 (14)</td>
<td>13 (36)*</td>
<td>8 (22)</td>
</tr>
<tr>
<td>Nonatopic</td>
<td>42 (54)</td>
<td>25 (59)</td>
<td>0 (0)</td>
<td>5 (12)</td>
<td>12 (29)</td>
<td>13 (31)</td>
</tr>
<tr>
<td>Total</td>
<td>78</td>
<td>51 (65)</td>
<td>4 (5)</td>
<td>10 (13)</td>
<td>25 (32)**</td>
<td>21 (27)</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopic</td>
<td>38 (44)</td>
<td>25 (66)</td>
<td>5 (13)</td>
<td>8 (21)</td>
<td>4 (10)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Nonatopic</td>
<td>49 (56)</td>
<td>24 (49)</td>
<td>0 (0)</td>
<td>8 (16)</td>
<td>5 (10)</td>
<td>13 (26)</td>
</tr>
<tr>
<td>Total</td>
<td>87</td>
<td>49 (56)</td>
<td>5 (6)</td>
<td>16 (18)</td>
<td>9 (10)</td>
<td>17 (19)</td>
</tr>
</tbody>
</table>

Excess as compared with control value: *P<0.05, **P<0.01.
In all groups, there was no significant difference between the relatives of atopic and nonatopic probands in the prevalences either of asthma or wheezy bronchitis. However, in the asthma and wheezy bronchitis groups, the prevalence of asthma tended to be higher in relatives of atopic probands; whereas the prevalence of wheezy bronchitis tended to be higher in relatives of nonatopic probands (Table 2).

**Discussion**

There was a strong similarity in the family history of asthma between asthmatic and wheezy bronchitic probands. The percentage of children with at least one asthmatic relative was significantly greater in the asthmatic and wheezy bronchitic probands than in the controls; and the prevalence of asthma was significantly higher in the relatives of both groups of wheezy probands than in the relatives of controls. This clustering of asthma in the families of wheezy children supports the hypothesis that at least some of the genetic factors underlying asthma may also be present in wheezy bronchitis.

The family history of wheezy bronchitis was similar to that of asthma. The percentage of children with at least one wheezy bronchitic relative tended to be greater in asthmatic and wheezy bronchitic probands than in controls; and the prevalence of wheezy bronchitis tended to be higher in the relatives of both groups of wheezy probands than in the relatives of controls. Although these differences did not reach significance, the tendency of wheezy bronchitis to cluster in the families of wheezy children lends support to the idea that wheezy bronchitis and asthma share a common genetic defect.

The composition of our control group may have contributed to the absence of a significant difference between wheezy and control probands in their family histories of wheezy bronchitis. Control children were not normal in that 62 (71%) had at least one episode of bronchitis. The prevalence of atopy (44%) and the sex-ratio (1.29) were higher in these probands than is generally found in children of this age, suggesting the control children may have had some genetic factors in common with the asthmatic and wheezy bronchitic children.

As wheezy bronchitis often precedes asthma in children, some of the probands with wheezy bronchitis may have had incipient asthma. Their presence would be expected to enhance the similarity in the family histories of asthma and wheezy bronchitis between asthmatic and wheezy bronchitic probands. However, the pronounced differences between the two groups of probands in their histories of atopy and allergic disease (Table 1) suggest there were not many children with incipient asthma among those with wheezy bronchitis. Therefore, it is unlikely that the family histories of asthma and wheezy bronchitis were altered appreciably by this bias.

The prevalences of atopy, hay fever, and eczema were lower in wheezy bronchitic than asthmatic probands. Although these differences may have arisen, in part, from the slightly lower age of the wheezy bronchitic compared with the asthmatic children, other investigations dealing with children of uniform age have also found that atopy and allergy were less prevalent in wheezy bronchitics.

These findings suggest that the reduced predisposition to asthma of many wheezy bronchitic children may result from their failure to inherit a predisposition to atopy or allergy. Our finding that the prevalence of wheezy bronchitis was higher in the relatives of nonatopic than atopic probands, whereas the reverse was true of asthma, lends support to this hypothesis.

In summary, the similarity between asthmatic and wheezy bronchitic children in their family histories of asthma and wheezy bronchitis suggests that these diseases share a common genetic defect. However the manifestation of asthma may be influenced by other factors, for instance atopy, which are not essential to the development of wheezy bronchitis.

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**References**

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