Comparison of atopic cough with cough variant asthma: is atopic cough a precursor of asthma?

M Fujimura, H Ogawa, Y Nishizawa, K Nishi

Background: We have described a group of patients who present with isolated chronic bronchodilator resistant non-productive cough with an atopic constitution, eosinophilic tracheobronchitis, and airway cough receptor hypersensitivity without bronchial hyperresponsiveness, which we have termed “atopic cough”. Although cough variant asthma (in which the cough responds to bronchodilators) is recognised as a precursor of typical asthma, it is not known whether atopic cough is also a precursor of asthma.

Methods: Eighty two patients with atopic cough were retrospectively examined for onset of typical asthma and compared with 55 patients with cough variant asthma (20 untreated patients and 35 treated with long term inhaled beclomethasone dipropionate [BDP], 218–467 µg/day). The median follow up period for patients with atopic cough and cough variant asthma was 4.8 (1–11.5) years and 3.7 (1–12.4) years, respectively.

Results: Onset of typical asthma occurred in only one of the patients with atopic cough. In patients with cough variant asthma, typical asthma developed in two of 35 patients taking BDP and six of 20 untreated patients (difference 24.3%, 95% CI 2.8 to 45.8, p<0.02).

Conclusions: These findings suggest that cough variant asthma is a precursor of typical asthma but that atopic cough is not. Treatment with inhaled steroids may prevent the transformation of cough variant asthma into typical asthma.
### Table 1 Pulmonary function, capsaicin cough threshold (C5), methacholine bronchial responsiveness (PC20), and bronchial reversibility in patients with atopic cough and cough variant asthma

<table>
<thead>
<tr>
<th></th>
<th>Sex (N/F)</th>
<th>Age (years)</th>
<th>FVC (% pred)</th>
<th>FEV1 (% pred)</th>
<th>FEV1/FVC ratio (%)</th>
<th>C5 (µM)</th>
<th>PC20 (mg/ml)</th>
<th>Bronchial reversibility (% increase)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atopic cough</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>6/18</td>
<td>48.7 (12.0)</td>
<td>106.0 (14.8)</td>
<td>100.6 (14.4)</td>
<td>78.7 (7.6)</td>
<td>0.70</td>
<td>43.3</td>
<td>4.2 (2.2)***</td>
</tr>
<tr>
<td>Probable</td>
<td>13/45</td>
<td>42.6 (15.2)</td>
<td>106.6 (12.2)</td>
<td>100.7 (16.3)</td>
<td>81.8 (6.4)</td>
<td>1.73</td>
<td>15.3 (1.34)***</td>
<td>3.4 (4.3)****</td>
</tr>
<tr>
<td>Total</td>
<td>19/63</td>
<td>44.3 (14.4)</td>
<td>106.4 (12.9)</td>
<td>106.6 (15.6)</td>
<td>80.8 (6.9)</td>
<td>1.22</td>
<td>22.1</td>
<td>3.7 (3.7)****</td>
</tr>
<tr>
<td><strong>Cough variant asthma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With BDP</td>
<td>10/25</td>
<td>44.1 (14.9)</td>
<td>105.7 (17.5)</td>
<td>95.7 (15.2)</td>
<td>79.2 (7.7)</td>
<td>8.60</td>
<td>4.46</td>
<td>9.3 (6.0)</td>
</tr>
<tr>
<td>Without BDP</td>
<td>6/14</td>
<td>51.4 (13.9)</td>
<td>106.6 (12.3)</td>
<td>101.3 (13.3)</td>
<td>77.2 (7.6)</td>
<td>12.0</td>
<td>2.94</td>
<td>7.1 (5.1)</td>
</tr>
<tr>
<td>Total</td>
<td>16/39</td>
<td>46.7 (14.8)</td>
<td>106.0 (15.7)</td>
<td>97.8 (14.7)</td>
<td>78.5 (7.6)</td>
<td>9.73</td>
<td>3.83</td>
<td>8.6 (5.8)</td>
</tr>
</tbody>
</table>

FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity; C5=provocative concentration of capsaicin eliciting five or more coughs; PC20=provocative concentration of methacholine causing a 20% or more fall in FEV1; bronchial reversibility=percentage increase from baseline in FEV1 after 300 µg salbutamol following 250 mg aminophylline.

Data are expressed as mean (SD) except for C5 and PC20 which are expressed as geometric mean (SE) values.

* p<0.001, ** p<0.0001 v all patients with cough variant asthma.

### Table 2 Cough sensitivity, bronchial responsiveness, bronchial reversibility, and findings indicative of atopic constitution in study subjects

|                                             | Atopic cough | | Cough variant asthma | | | | |
|---------------------------------------------|-------------|---|---------------------|---|---|----------------|---|---|
|                                              | Definite    | Probable | With BDP | Without BDP |
| Heightened cough sensitivity (C5 <3.9 µM)    | 24/0        | 0       | 33/16    | 9         | 12/19    | 4        | 2/15    | 3        |
| Bronchial hyperresponsiveness (PC20 <10 mg/ml) | 0/24      | 0       | 15/33    | 10        | 35/0     | 0        | 20/0     | 0        |
| Increased bronchial reversibility (>10%)     | 0/24       | 0       | 1/50     | 7         | 13/15    | 7        | 3/11     | 6        |
| Peripheral blood eosinophilia (>6% and/or >400/µl) | 8/16       | 0       | 27/31    | 0         | 13/22    | 0        | 8/12     | 0        |
| Sputum eosinophilia (>2.5%)                  | 7/4        | 13 (9)* | 16/10    | 32 (17)*  | 9/13     | 13 (10)* | 6/4      | 10 (8)*  |
| Increased total IgE (>200 IU/ml)             | 9/15       | 0       | 24/34    | 0         | 15/20    | 0        | 3/14     | 0        |
| Positive specific IgE                        | 10/14      | 0       | 27/31    | 0         | 21/14    | 0        | 11/9     | 0        |
| Positive skin test                           | 3/3        | 18      | 6/12     | 40        | 1/2      | 32       | 1/0      | 19       |
| Positive past history and/or complication of allergic disease | 19/5       | 0       | 46/12    | 0         | 24/11    | 0        | 14/6     | 0        |
| Positive for one or more of (4)–(9)          | 24/0       | 0       | 58/0     | 0         | 33/2     | 0        | 17/3     | 0        |

*Number of patients in whom sputum induction was performed but the specimen was inappropriate is shown in parentheses.

### Discussion

- **Inhalation of 300 µg salbutamol sulphate following intravenous administration of 250 mg aminophylline.**
- **Bronchial responsiveness within normal limits (provocative concentration of methacholine causing a 20% fall in FEV1 (PC20) ≥10 mg/ml).**
- **Increased cough receptor sensitivity (capsaicin concentration eliciting 5 or more coughs (C5) ≤3.9 µM).**
- **Cough resistant to bronchodilator therapy (oral clenbuterol 40 µg/day plus inhaled procaterol or salbutamol at bedtime and on demand for ≥1 week).**
- **No abnormal findings indicative of cough aetiology on chest radiograph.**
- **Normal FEV1 (≥80% of predicted value), FVC (≥80% of predicted value), and FEV1/FVC ratio (≥70%).**

When all criteria were satisfied, a definite diagnosis of atopic cough was made. If one or more criteria were not satisfied or examined, a diagnosis of probable atopic cough was made when all of the following were present:

1. **Non-productive cough lasting more than 8 weeks without wheezing or dyspnoea.**
2. **Cough resistant to bronchodilator therapy.**
3. **Presence of one or more findings indicative of atopic constitution as a global feature described above and/or induced sputum eosinophilia (2.5% or more).**
4. **Complete relief of cough after treatment with histamine H1 antagonists and/or corticosteroids for 1 month.**

Using these diagnostic criteria, patients with atopic cough were divided into two groups: definite atopic cough and probable atopic cough groups.

### Cough variant asthma

The diagnosis of cough variant asthma was made according to the following criteria proposed by the Japanese Cough Research Society:

1. **Isolated chronic non-productive cough lasting more than 8 weeks.**
2. **Absence of a history of wheeze or dyspnoea, and no adventitious lung sounds on physical examination.**
3. **Absence of postnasal drip to account for the cough.**
4. **FEV1, FVC, and FEV1/FVC ratio within normal limits.**
5. **Presence of bronchial hyperresponsiveness (PC20 <10 mg/ml).**
6. **Relief of cough with bronchodilator therapy.**
7. **No abnormal findings indicative of cough aetiology on chest radiograph.**

All patients with cough variant asthma had been successfully treated with bronchodilators and/or steroids.
specific bronchial responsiveness. Spirometric tests were performed and evaluated according to ATS criteria. (Chestac 11, Chest Co Ltd, Tokyo, Japan). Spirometric tests were performed and evaluated according to ATS criteria. Cough sensitivity: capsaicin cough threshold (C5) was measured as an index of non-specific bronchial responsiveness. Methacholine bronchial responsiveness (PC20) before and after treatment was determined from spirometric tests performed before and 30 minutes after inhalation of 250 mg aminophylline.

Eleven patients diagnosed with definite atopic cough, 19 with probable atopic cough, 26 with cough variant asthma treated with BDP, and 11 with cough variant asthma not treated with BDP had been seen regularly as outpatients; the onset of typical asthma was confirmed in 20 of the 35 patients in the BDP+ group and in six of the 20 patients in the BDP– group (difference 13.3%, 95% CI –13.0 to 39.6, p=0.002; table 3). In patients with atopic cough the onset of typical asthma was confirmed in only one patient in the probable group and in none of the patients with definite atopic cough. The onset of typical asthma was thus significantly less prevalent in patients with atopic cough than in those with cough variant asthma (both BDP+ and BDP– groups) (difference 13.3%, 95% CI –13.0 to 39.6, p=0.002; table 3). The onset of typical asthma in patients with definite atopic cough and with probable atopic cough was significantly less prevalent than in the BDP– group (difference 30.0%, 95% CI 9.9 to 50.1, p=0.0030 and 28.2%, 95% CI 7.8 to 48.6, p<0.0001, respectively), but did not differ from that in the BDP+ cough variant asthma group.

The same analysis was performed on patients who were regularly seen at our outpatient clinics. The onset of typical asthma was not seen in any of the 11 patients with definite atopic cough.
The rate of recurrence of isolated non-productive cough did not differ significantly between patients with definite atopic cough (12/24), probable atopic cough (30/58), BDP+ cough variant asthma (20/35), and BDP– cough variant asthma (7/20).

Methacholine challenge was carried out before treatment in 47 of the 55 patients with cough variant asthma (fig 1). The geometric mean (GSEM) PC20 value was 0.69 (1.20) mg/ml in patients with cough variant asthma who developed typical asthma, which was significantly lower than that in patients with cough variant asthma who did not develop typical asthma (5.18 (1.28) mg/ml; p=0.0015).

**DISCUSSION**

This study was neither randomised nor controlled, particularly with regard to the assessment of bronchodilator therapy efficacy, which was a key criterion for the diagnosis of cough variant asthma. In our experience this assessment is not difficult. When sleep and daytime quality of life are improved with treatment, efficacy can be judged as “good”, leading to the diagnosis of cough variant asthma. Indeed, bronchial responsiveness,2–6 bronchial reversibility,2–7 and cough sensitivity2–5 were all significantly lower between patients with atopic cough and those with cough variant asthma diagnosed in this assessment in our previous studies, as well as in the present study (probable atopic cough vs cough variant asthma in table 1).

Cough variant asthma was first described by Glauser.18 The only presenting symptom is isolated chronic cough responsive to bronchodilator treatment. Recognition of cough variant asthma is clinically important because bronchodilator treatment is only effective in cough variant asthma. Bronchodilators usually exert no antitussive effect in other causes of isolated chronic cough.16

Atopic cough is a new clinical entity that we have proposed as a cause of isolated chronic non-productive cough.2–5 16 17 Although the character of the cough is similar in both atopic cough and cough variant asthma (except for the response to bronchodilator therapy), they differ with regard to pathophysiological features. BAL eosinophilia is present in cough variant asthma, whereas bronchial tissue and induced sputum eosinophilia are common in both.11 12 The defining physiological feature is increased cough sensitivity without BHR in atopic cough, and BHR without cough hypersensitivity in cough variant asthma.11 Although other researchers have reported that cough sensitivity was heightened and recovered to a normal level following successful treatment of cough variant asthma,29 it should be recognised that cough sensitivity is entirely independent of bronchial responsiveness46 or bronchomotor tone,27 and that it is within normal limits in typical asthma.14 We therefore suggest that increased cough sensitivity is not a primary feature of cough variant asthma.

Nearly 30% of patients with cough variant asthma eventually develop typical asthma.30 In this study the onset of typical asthma was seen in two of 35 patients taking long term BDP and in six of 20 patients not receiving treatment with BDP. The rate in patients without BDP is consistent with previously reported rates.3 11 17 It is noteworthy that the rate of onset of typical asthma was significantly lower in patients treated with BDP, which suggests the usefulness of long term inhaled steroids as an intervention against cough variant asthma. It is believed that both early diagnosis and intervention are important in controlling asthma.11 As cough variant asthma is thought to be a precursor of typical asthma, early intervention for cough variant asthma may be as important as in mild asthma. To address this, longitudinal studies evaluating the effect of inhaled steroids on the long term decline of pulmonary function are needed, as are studies delineating the effect on both symptoms and transformation to typical asthma.

The onset of typical asthma was seen in only one of 58 patients with probable atopic cough and in none of 24 patients with definite atopic cough. The patient with probable atopic cough, who developed wheezing following an upper respiratory infection 11.5 years after her first visit, had BHR (PC20 2.5 mg/ml) but not bronchial reversibility (–3.5% increase in FEV1, by bronchodilators) or increased diurnal variation in peak expiratory flow rate (3.6%). This patient refused a capsaicin cough provocation test. Bronchodilator treatment proved ineffective against her cough, which was successfully treated with the histamine H1 antagonist azelastine. Thus, despite BHR, we diagnosed her as having probable atopic cough, although others might label this case as cough variant asthma. With the exception of this case, the onset of typical asthma was not seen in any patients with atopic cough. These findings, in addition to the pathophysiological differences between atopic cough and cough variant asthma, support the hypothesis that atopic cough represents a distinct clinical entity. The absence of transformation to typical asthma from definite atopic cough can be explained by BHR within normal limits2–5 16 27 and eosinophilic inflammation limited to the large airways.2–6 27 Although BHR was increased in 15 of 48 patients with probable atopic cough who underwent methacholine challenge, typical asthma occurred in only one patient. This low prevalence of typical asthma may be explained by the low level of BHR (median PC20 2.5 mg/ml, range 1.25–5.0) and the absence of eosinophilic inflammation of peripheral airways.2–6

A diagnosis of cough variant asthma has been made based on the efficacy of steroids by some investigators,13–15 but steroids are effective not only in cough variant asthma but also in atopic cough. It is therefore likely that the use of steroid efficacy as a criterion to diagnose cough variant asthma may incidentally misclassify patients who actually have atopic cough. This may account for the increased cough sensitivity in patients with cough variant asthma studied by McGarvey and colleagues.20

Eosinophilic bronchitis without asthma (EB), as originally described by Gibson et al.20 seems to resemble atopic cough. The diagnostic criteria used by Gibson (personal communication) were sputum or induced sputum eosinophilia (>2.5%) and lack of physiological or symptomatic features of asthma with the exception of cough. Gibson et al20 have reported a similar degree of BAL eosinophilia and granulocyte-macrophage colony stimulating factor and interleukin 5 gene expression in patients with EB as in those with asthma, which suggests that EB and atopic cough are not similar.20 On the other hand, Brightling et al30 found that cough sensitivity to capsaicin was heightened in patients with EB diagnosed by induced sputum eosinophilia and normal bronchial responsiveness, suggesting that EB and atopic cough resemble each other. Further investigation is required to elucidate the relationship between atopic cough and EB.10 13 20

In conclusion, this study has shown that the onset of typical asthma occurred significantly less frequently in patients with atopic cough than in those with cough variant asthma. In addition, long term inhaled steroids significantly decreased the development of typical asthma in patients with cough variant asthma. If mild asthma benefits from early intervention with long term inhaled steroids, it will be also useful for cough variant asthma. As atopic cough differs from cough variant asthma with regard to both outcome and pathophysiological features, we strongly recommend that atopic cough is recognised as a new clinical entity characterised by isolated chronic non-productive cough.
REFERENCES
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