The long term outcome of patients with unexplained chronic cough

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KEYWORDS
Unexplained chronic cough; Fixed airflow obstruction; COPD

Summary
Introduction: Up to 40% of patients seen in a cough clinic have unexplained chronic cough. The long term outcome of these patients is uncertain.
Objective: To determine the long-term outcome in patients diagnosed with unexplained chronic cough.
Methods: We have performed a longitudinal study of symptoms, airway inflammation and spirometry in a cohort of patients with unexplained chronic cough diagnosed over 7 years ago. Cough was assessed using a 100 mm visual analogue scale (VAS). At the first and final visit cough reflex sensitivity was assessed as the concentration of inhaled capsaicin at which the volunteer coughed 2 (C2) and 5 times (C5).
Results: We identified 42 patients (32 females) with unexplained chronic cough who had been assessed at least 7 years previously and agreed to a further assessment. The mean (SD) duration of cough was 11.5 (4.5) years at the time of their final assessment. Nine patients (21%) had organ specific autoimmune disease and twenty (48%) had a peripheral blood lymphopaenia. Six (14%) patients had complete resolution of symptoms and 11 (26%) had a significant >10 mm improvement in their cough VAS during follow up. Longitudinal spirometry data was available in 30 patients. The median rate of FEV₁ decline was 44 ml/year and four (13%) patients developed a post-bronchodilator forced expiratory volume in 1 s (FEV₁)/forced vital capacity of less than 0.7. FEV₁ decline was similar in patients with persistent cough and those whose cough improved. No other independent predictors of FEV₁ decline were identified. There were no independent predictors of improvement in cough.
Conclusions: Cough persists over time in the majority of patients with unexplained chronic cough. Patients have an increased rate of decline in FEV₁ and a significant minority develop fixed airflow obstruction.
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Introduction

Cough is an important symptom, responsible for considerable impairment of quality of life and accounting for a large proportion of both primary and secondary care referrals. Chronic cough, defined as a cough lasting longer than 8 weeks, can be ascribed to a specific cause in 60–80% of patients. The remainder have unexplained chronic cough and suffer impairment of quality of life, equivalent in some domains to that seen in severe asthma and COPD. Unexplained chronic cough is a challenge for the respiratory physician as there are no satisfactory treatments and almost nothing is known about the long-term prognosis. More definitive information on the natural history of unexplained chronic cough is needed both to guide the management of patients in clinic and to direct further research.

We conducted a longitudinal observational study to investigate the natural history of unexplained chronic cough diagnosed at our institution over 7 years ago.

Methods

We identified all patients attending a specialist cough clinic and diagnosed with unexplained chronic cough at Glenfield Hospital between January 1998 and December 2001. Unexplained chronic cough was defined as a cough lasting greater than 8 weeks, with normal spirometry [forced expiratory volume in 1 s (FEV1) >80% of predicted and FEV1/forced vital capacity (FVC) ratio of >70%], a provocative concentration of methacholine required to cause a 20% fall in FEV1 (PC20) of >8 mg/ml, a normal induced sputum eosinophil count (<3%) and a normal high resolution computed tomography (HRCT) scan of the thorax. Subjects had failed treatment trials with asthma treatment, a proton pump inhibitor and a nasal steroid spray as per British Thoracic Society guidelines.4 The study was approved by Leicestershire, Northamptonshire and Rutland Ethics committee and all patients provided written informed consent before inclusion.

Study measurements

Spirometry was performed with a Vitalograph spirometer (Vitalograph, Buckinghamshire, UK) as the best of at least 3 successive readings within 100 ml. A capsaicin cough challenge was then performed. Subjects inhaled a single vital capacity breath of 10 µL of 0.9% saline solution followed by doubling concentrations of capsaicin from 0.49 mL/L over 1 min. Coughs were counted for 30 s following each inhalation. The counting of coughs was aided by a sound recording device. The investigation was stopped when 500 µL/L solution was inhaled or when the subject coughed 5 times or more. The concentration of capsaicin required to make the subject cough 2 (C2) and 5 (C5) times was calculated by the linear interpolation of the log-dose response curve. Sputum was induced using nebulised hypertonic saline and processed for cell differential count using the sputum selection protocol as described before. At the first visit patients had a full blood count and a full assessment for the presence of organ-specific autoantibodies was done as patients were participants in an earlier case-control study. The following autoantibodies were measured: antinuclear (in house indirect immunofluorescence); rheumatoid factor (nephelometry, Dade Behring BNII protein analyser; UK); islet cell (in house indirect immunofluorescence); adrenal (indirect immunofluorescence; Biodiagnostics Limited, Worcestershire, UK); parietal (in house indirect immunofluorescence); endomysial (indirect immunofluorescence, Binding Site Limited, Birmingham, UK); and thyroid peroxidase (fluorescent enzyme linked immunosorbent assay system, Pharmacia Diagnostics, Milton Keynes, UK).

Subjects completed a 100 mm cough Visual Analogue Score (VAS) set at the bottom end by no cough and the top end the worst cough ever. Patients were asked to mark a cross at a point indicative of the severity of their cough over the past 24 h. A change of >15 mm was regarded as significant.

Study design

Subjects had spirometry, cough VAS, sputum differential cell count and a capsaicin cough challenge test at baseline when they first presented to clinic. These tests were repeated 7–10 years from diagnosis.

Analysis

C2 and C5 were log transformed prior to analysis to assume a normal distribution. Correlations between variables were analysed using Spearman’s rank correlation coefficient for non-parametric data. Statistical analysis was performed using SPSS 18. The rate of FEV1 decline was calculated as the total decline in FEV1 (calculated from a baseline FEV1 measurement and repeat FEV1 measurement 7–10 years later) divided by the number of years between the measurements.

Results

We identified 45 patients who were diagnosed with unexplained chronic cough out of a total of 286 patients with cough seen between January 1998 and December 2001. Of these patients 3 declined to take part in the study. Of the remaining 42 patients (32 female), 12 declined to have repeat airways assessment but agreed to complete a cough VAS.

Patient characteristics are given in Table 1. The mean (SD) duration of cough was 11.5 (4.5) years at the time of their final assessment. Nine patients (21%) had organ specific autoimmune disease (3 with hypothyroidism, 1 with ulcerative colitis, 1 with coeliac disease, 1 with type 1 diabetes mellitus, 1 with vitiligo, 1 with pernicious anaemia and 1 patient with hypothyroidism, vitiligo and pernicious anaemia) and twenty (48%) had a peripheral blood lymphopaenia. Six (14%) patients had complete resolution of symptoms; 10 (23%) patients showed no change in their symptoms (change in VAS of <15 mm); 11 patients (25%) had a significant (>15 mm) improvement in their cough.
with a mean (95% CI) decrease in VAS of 31 mm (20, 42 mm); and 14 patients (33%) had significant >10 mm worsening of their symptoms (Fig. 1) with a mean (95% CI) increase in the VAS score 35 mm (20, 50 mm). Repeat C2 and C5 were available in 10 patients. There was no significant difference in the change in these measures and no evidence that the change differed in patients whose cough improved or not (Table 1, Fig. 2).

Longitudinal spirometry data was available in 30 patients. The median (IQR) rate of FEV₁ decline was 45 (25, 84) ml/year (Fig. 3). Four (13%) patients had an FEV₁ rate of decline of greater than 100 ml per year, seventeen (57%) patients had an FEV₁ decline of 30–100 ml per year, four (13%) patients had and FEV₁ change ranging from 1 to 29 ml per year and 4 patients had an improvement in FEV₁ of up to 30 ml per year. Four (13%) patients developed a post-bronchodilator FEV₁/FVC of less than 0.7. FEV₁ decline was similar in patients with persistent cough and those whose cough improved. No other independent predictors of FEV₁ decline were identified. There were no independent predictors of improvement in cough.

**Discussion**

This is the first longitudinal study of outcome in patients with unexplained chronic cough. Our patient group was similar to those described previously with a predominance

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### Table 1 Demographic data and study measurements at diagnosis and re-assessment.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Re-assessment</th>
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<tbody>
<tr>
<td>Number (females)</td>
<td>42 (32)</td>
<td>11.5 (4.5)</td>
</tr>
<tr>
<td><em>Age at onset of cough</em></td>
<td>51 (10)</td>
<td>77 (5)</td>
</tr>
<tr>
<td><em>Duration of cough at final assessment (years)</em></td>
<td>105 (15)</td>
<td>93.8 (15)</td>
</tr>
<tr>
<td><em>Percentage predicted FEV₁</em></td>
<td>77 (5)</td>
<td>77 (11)</td>
</tr>
<tr>
<td>Sputum neutrophils (%)</td>
<td>49 (24)</td>
<td>61 (23)</td>
</tr>
<tr>
<td>Sputum eosinophils (%)</td>
<td>0.6 (0.7)</td>
<td>0.6 (0.7)</td>
</tr>
<tr>
<td>C2 (Mmol/L)</td>
<td>2.4 (0.6)</td>
<td>1.3 (0.9)</td>
</tr>
<tr>
<td>C5 (Mmol/L)</td>
<td>10.1 (0.9)</td>
<td>2.7 (0.8)</td>
</tr>
<tr>
<td><em>Cough visual analogue scale (mm)</em></td>
<td>47 (24)</td>
<td>44 (29)</td>
</tr>
<tr>
<td>Percentage of patients with organ specific autoimmune disease (%)</td>
<td>10 (23)</td>
<td>20 (48)</td>
</tr>
<tr>
<td>Number of patients with a peripheral blood lymphocyte count of &lt;1.5 (%)</td>
<td>10 (23)</td>
<td>20 (48)</td>
</tr>
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* Expressed as mean (standard deviation) or † as geometric mean (log standard deviation). FEV₁ = forced expiratory volume in one second. FEV₁/FVC = forced expiratory volume over one second divided by forced vital capacity. C2 = concentration of capsaicin required to induce 2 coughs, C5 = concentration of capsaicin required to induce 5 coughs.

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**Figure 1** Change in cough as measured by a cough VAS over a 7–10 year period.

**Figure 2** Capsaicin cough sensitivity over time.
of middle aged women and a high incidence of organ specific autoimmune disease and peripheral blood lymphopenia. Just over half of the patient in this series had either no change or worsening of cough after more than a decade, emphasising the potential long-term morbidity associated unexplained chronic cough. We were unable to identify predictors of persistence or improvement in cough. Unexpectedly, patients with chronic cough had a decline in FEV₁ well above what would be expected in a population of non-smoking patients of this age and a significant minority developed COPD. Decline in FEV₁ occurred independently of changes in cough severity.

Our findings should be regarded as preliminary and hypothesis generating rather than definitive as the population was small, not all participants consented to a full follow up assessment, and the findings may have been influenced by responder bias and regression to the mean. Further work in larger and better characterised populations is clearly necessary. However, the demonstration of a rapid decline in FEV₁ is consistent with earlier work by Birring et al. They described a small cohort of older female non-smokers with cough and unexplained fixed airflow obstruction in whom there was a high incidence of organ specific autoimmunity and peripheral blood lymphopenia. Collectively, these studies suggest that rather than being a benign condition, non-smokers with chronic cough may develop significant airflow obstruction linked to chronic cough and autoimmune disease.

The magnitude of the decline in FEV₁ is striking and also argues against a chance finding. The mean annual rate of decline of FEV₁ in non-smoking women and men of this age is 25 ml/year and 29 ml/year. In patients with COPD the rate of decline is 33 ml per year. This compares with a median FEV₁ decline of 44 ml per year in our population.

The over representation of autoimmune diseases in patients with chronic cough is suggestive of common aetiological factors. Polymorphisms of the gene encoding cytotoxic T-lymphocyte associated antigen 4 (CTLA4), an inhibitor of regulatory T cell activity, are associated with a number of autoimmune diseases including autoimmune thyroid disease and type 1 diabetes mellitus. Recently Zhu et al. have shown an association between several CTLA4 polymorphisms and the chronic bronchitis phenotype in patients with COPD. Further studies involving genotyping and perhaps involving direct small airway sampling are needed in this patient group to further explore the association with autoimmunity and to evaluate the pathological changes in the airways and the mechanism of decline in lung function. These studies may also help in identifying a potential therapeutic target.

Birring described a cohort of patients with unexplained chronic cough and a bronchoalveolar lavage (BAL) lymphocytosis. Potentially the lymphopenia seen in patients with cough might be linked to the homing of activated lymphocytes to the lung, as is the case in sarcoidosis. We have previously suggested that aberrant homing of activated lymphocytes from the primary site of autoimmunity or chronic infection related inflammation might lead to airway inflammation and damage. This might be expected to be most likely to occur when the chronic inflammatory conditions involve organs that are embryologically related to the lungs and it is notable that conditions such as inflammatory bowel disease, chronic hepatitis C infection, autoimmune thyroid disease, and Helicobacter pylori-induced gastritis have all been linked to airway disease. Alternatively, it is well recognised that many patients with chronic unexplained cough describe a preceding viral infection and following this develop a chronic cough. It may be that the lymphopenia seen in this group of patients is as a result of a prior viral infection. Furthermore, there is a strong associated with lymphopenia and both systemic and organ specific autoimmunity. Lymphopenia results in homeostatic peripheral T cell expansion which is distinct from normal T cell responses, and can result in T cell proliferation in response to self-antigens, leading to the development of organ specific auto-immune disease. It is possible that the peripheral blood lymphopenia and the BAL lymphocytosis are indicative of an airway specific autoimmune process. The physiological, radiological and pathological features of the airway disease seen in association with chronic inflammatory disorders have not been extensively investigated. It has been suggested that they are due to a low grade obliterative bronchiolitis analogous to that seen in chronic rejection in lung transplant recipients or chronic graft vs. host disease in bone marrow transplant recipients. Unexplained chronic cough is particularly prevalent in menopausal women perhaps because CD-4 positive T-cell numbers increase in the lung at this time.

In conclusion, we have shown that a small majority of patients with unexplained chronic cough who consented to a further assessment at least 7 years after the first have persistent morbidity due to cough. Patients with unexplained chronic cough also had an abnormally rapid decline in FEV₁ and around 10% developed spirometric features of COPD. Our findings raise the possibility that unexplained chronic cough is due to a persistent damaging airway process and suggest that this condition could be regarded as a risk factor for developing COPD.
Conflict of interest statement

We wish to confirm that there are no conflict of interest associated with publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed.

We confirm that ethical approval of all relevant bodies has been obtained and that such approvals are acknowledged within the manuscript.

References