



Idiopathic chronic cough and organ-specific autoimmune diseases: a case–control study[☆]

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Received 13 February 2003; accepted 1 October 2003

KEYWORDS

Chronic cough;
Idiopathic chronic cough;
Autoimmune disease

Summary The marked female predominance in cases of idiopathic chronic cough and its association with mild chronic lymphocytic airway inflammation suggests an underlying autoimmune process. We set out to test the hypothesis that idiopathic chronic cough is associated with other organ-specific autoimmune diseases in a case–control study. Twenty-two patients with idiopathic chronic cough and 65 community-matched controls for age and sex who responded to a self-administered questionnaire were asked about the presence of autoimmune disease, other medical problems and drug history. All subjects were invited to have a blood test for an autoimmune screen. Thirteen out of 22 (59%) patients with idiopathic chronic cough and eight out of 65 (12%) age- and sex-matched controls reported organ-specific autoimmune disease (odds ratio 8.8; 95% confidence interval 2.4–31.8, $P < 0.001$). Organ-specific autoantibodies were present in a significantly higher proportion of cases than controls (40% vs. 13%; $P = 0.047$). These findings suggest a relationship between idiopathic chronic cough and organ-specific autoimmunity.

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Introduction

Cough is one of the commonest causes of presentation to general practice. At any one time, 20% of the UK population have a troublesome cough and sufferers consume 75 million doses of over-the-counter anti-tussive medication annually.¹ Most cases are mild and self-limiting but a small

proportion have persistent troublesome cough and require specialist review. Several series have shown that a cause of persistent cough can be identified relatively simply in 80–99% of cases with most causes due to one or more of asthma, gastro-oesophageal reflux and rhinitis with post-nasal drip.^{2–4} However, in up to 20% of patients, the cough remains unexplained even after extensive investigation and treatment trials.³

Bronchoscopic studies have shown some evidence of chronic airway inflammation with a mononuclear cell infiltrate in the airway mucosa of patients with idiopathic chronic cough.⁵ The nature of the airway inflammation and the female predominance of

[☆]This study was supported by The British Lung Foundation and University Hospitals of Leicester NHS Trust.

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patients with idiopathic chronic cough suggested to us the possibility of an autoimmune process. Organ-specific autoimmune diseases are commoner in women and are associated with chronic lymphocytic inflammation in the target organ. We have tested the hypothesis that patients with idiopathic chronic cough have a higher incidence of organ-specific autoimmune disease in a case-control study.

Methods

Cough diagnostic algorithm

Patients were recruited from consecutive patients attending a specialised cough clinic run by Dr. Pavord between 1998 and 1999 which receives referrals from primary- and secondary-care largely confined to a population of 970,000 within Leicestershire. Investigations were carried out according to a standardised algorithm.² The protocol for investigation and treatment, and criteria for accepting diagnosis were as previously described.^{2,6} We defined idiopathic chronic cough as a cough lasting >3 weeks in association with normal clinical examination (including Ear Nose Throat), normal chest X-ray and CT scan, normal lung function tests, negative methacholine inhalation test (provocative concentration: PC₂₀ FEV₁ >16 mg/ml), normal peak expiratory flow variability, no sputum eosinophilia and no pathological gastro-oesophageal reflux or evidence of temporal association between cough and gastro-oesophageal reflux on 24 h oesophageal pH monitoring. Patients had normal macroscopic findings on fiberoptic bronchoscopy and all had extensive negative treatment trials including trials of inhaled and systemic corticosteroids.²

Subjects

One hundred and fifty patients were seen in our cough clinic (mean age 51 years [range 22–90], females 66%) of which 25 (17%) fulfilled our criteria for idiopathic chronic cough. The other primary causes of cough were cough-variant asthma (15%), gastro-oesophageal reflux (15%), rhinitis with post-nasal drip (13%), eosinophilic bronchitis (17%), post-viral cough (13%), chronic bronchitis and/or bronchiectasis (8%) and angiotensin converting enzyme inhibitor cough (2%). Identification of controls was carried out using the method described by Hubbard et al.⁷ Briefly, four controls

matched for age and sex were obtained for each case that responded. These controls were drawn from the list of the case patient's general practitioner and were selected randomly if more than four suitable subjects were available; if four controls of the same age were not listed with the general practitioner the age matching was widened to within 5 years.

Questionnaire and blood tests

On obtaining permission to enter each case and their matched controls from their general practitioner, a questionnaire was posted to each subject's home. The questionnaire asked specifically about the presence of the following conditions: hyperthyroidism, hypothyroidism, diabetes, pernicious anaemia, Addison's disease, alopecia, vitiligo, coeliac disease, Crohn's disease, ulcerative colitis, premature menopause, autoimmune hepatitis, other medical problems and drug therapy. The presence of self-reported organ-specific autoimmune diseases was validated (in cases) by review of medical notes. The subjects were also invited to have a blood test for an autoantibody screen which included islet cell (in-house indirect immunofluorescence), adrenal (indirect immunofluorescence, Biodiagnostics Ltd, Worcestershire, UK), parietal (in-house indirect immunofluorescence), endomy-sial⁸ (indirect immunofluorescence, Binding Site Ltd, Birmingham, UK) and thyroid peroxidase autoantibodies (fluorescent ELISA system, Pharmacia Diagnostics, Milton Keynes, UK).

Analyses

Matched case-control analysis of the incidence of organ-specific autoimmune disease was done by conditional logistic regression using the EGRET computer statistical package.⁹ The effect of variables significantly associated with cough were analysed in a multivariate model. The incidence of organ-specific autoantibodies in each group were compared by χ^2 -test. The study had ethics approval from the Leicestershire ethics committee.

Results

We obtained the general practitioner's permission to contact 25 idiopathic chronic cough patients and 88 controls. Twenty-two (88%) of the cases and 65 (74%) of the controls responded to the questionnaire. The distribution of age and sex among all cases and controls, those that responded to the questionnaire and those that had an autoantibody

Table 1 Distribution of age and sex among all cases and controls identified, all respondents to the questionnaire and those who had an autoantibody screen.

	No.	Men		Women		Overall mean(sd) age (years)
		No. (%)	Mean(sd) age (years)	No. (%)	Mean(sd) age (years)	
Original sample						
Cases	25	7(28)	54.2(5.4)	18(72)	55.4(3.0)	55.1(2.6)
Controls	88	21(24)	60.9(1.6)	67(76)	58.7(1.7)	59.2(1.3)
Respondents						
Cases	22	5(23)	58.8(3.3)	17(77)	57.0(3.1)	57.5(2.5)
Controls	65	12(18)	63.3(2.1)	53(82)	55.7(1.9)	57.1(1.6)
Autoantibody screen						
Cases	15	3(20)	63.0(4.6)	12(80)	59.1(3.6)	59.9(3.0)
Controls	24	5(21)	51.6(9.6)	19(79)	52.8(2.9)	52.6(2.9)

No. = number; sd = standard deviation.

screen were similar and not statistically significant (Table 1). The median duration of cough in cases was 12 months (range 7–360 months). The response to all questions asking about organ-specific autoimmune disease is outlined in Table 2. Diseases suggesting organ-specific autoimmunity were reported by 13 cases (59.1%) and eight controls (12.3%, Table 2). Matched case–control analysis showed the difference to be highly significant (odds ratio 8.8; 95% confidence interval 2.4–31.8, $P < 0.001$). A significantly higher proportion of the cases had organ-specific autoantibodies present than controls (40% vs. 13%; $P = 0.047$; Table 2). In the cases, positive thyroid autoantibody titres ranged from 1:100 to 1:6400 (strong positive titre $> 1:100$). In general, the presence of organ-specific autoantibodies was consistent with self-reported organ-specific autoimmune disease. Four patients with explained chronic cough ($n = 125$) had organ-specific autoimmune disease or positive autotantibodies (3.2%). Unexpectedly, non-steroidal anti-inflammatory drug (NSAID) use for more than 2 months was reported more commonly by cases than controls (10 (46%) vs. 8 (12%); odds ratio 5.6; 95% confidence interval 2–18, $P < 0.01$). Both associations (autoimmune disease and NSAID use) remained significant and were essentially unchanged when analysing using a multivariate model.

Discussion

We found a significantly higher prevalence of organ-specific autoimmune disorders in patients with

Table 2 Self-reported organ-specific autoimmune disease and presence of organ-specific autoantibodies in cases and controls.

	Controls (no.)	Cases (no.)
	$n = 65$	$n = 22$
<i>Autoimmune disorder</i>		
Hypothyroidism	2	5
Hyperthyroidism	3	0
Diabetes mellitus type1	2	3
Pernicious anaemia	0	2
Celiac disease	1	1
Vitiligo and premature menopause	0	1
Vitiligo and chronic autoimmune hepatitis	0	1
Addison's disease	0	0
Inflammatory bowel disease	0	0
Alopecia	0	0
Total	8	13**
	$n = 24$	$n = 15$
<i>Autoantibodies</i>		
Thyroid peroxidase	0	4
Parietal cell	1	1
Endomysial	1	1
Islet cell	1	0
Adrenal	0	0
Total	3	6*

No. = number. * $P < 0.05$, ** $P < 0.001$.

idiopathic chronic cough. There was a similar difference in the prevalence of organ-specific autoantibodies between the two groups. These

findings support our hypothesis that idiopathic chronic cough is associated with the presence of organ-specific autoimmune disease.

The controls represented a randomly selected group and were not excluded if they had a cough, smoked or had relevant occupational exposure. This was to ensure that we were not selecting a healthy group with an artificially lower prevalence of potential causative factors such as organ-specific autoimmune disease. As with all case-control studies, our findings might be influenced by recall bias in controls. However, the drug histories from controls did not suggest under-reporting of autoimmune disorders. Furthermore, the prevalence of organ-specific autoimmune disease seen in the control population was greater than expected from general population surveys (3–8%)^{10,11} and from the explained cough group (3.2%), suggesting that if anything, there was over-reporting of autoimmune disease in controls. Another possibility is that the cases may have different health behaviour, increasing the likelihood of seeking medical help and receiving a diagnosis of organ-specific autoimmune disease. However, the significantly higher prevalence of objective markers of organ-specific autoimmunity in cases suggests this is not the sole explanation for the association although we cannot discount the possibility that the increased prevalence of NSAID use is due to this mechanism.

This is a small study, so we were not able to compare the strength of association between different organ-specific autoimmune disorders and idiopathic chronic cough. Larger studies are required to investigate the possibility that particular types of autoimmune diseases are associated with cough. Autoimmune thyroid disease was the most prevalent organ-specific autoimmune disorder in cases with idiopathic chronic cough. On the basis of our findings, we cannot exclude the possibility that the association is exclusively due to a link between autoimmune thyroid disease and idiopathic chronic cough. Chronic cough has been reported as a presenting feature of thyroiditis in two patients.¹² In both, the cough improved following treatment of the inflammatory thyroid disorder and was thought to be due to a local irritative effect of the inflamed thyroid. It is possible that local effects of a goitre are responsible for cough in some patients. A more general link between treated autoimmune thyroid disease and increased respiratory morbidity is supported by our recent findings of increased prevalence of respiratory symptoms¹³ and unexplained fixed airflow obstruction¹⁴ in non-smoking patients with treated autoimmune hypothyroidism.

The lungs and many of the organs involved in organ-specific autoimmune disorders share com-

mon embryological origins as foregut derivatives and it is possible that homing of activated T cells into the pulmonary compartment as well as the primary site of autoimmune inflammation may cause airway wall inflammation and cough. Similar mechanisms are thought to be responsible for the lymphocytic airway inflammation seen in inflammatory bowel disease.¹⁵ Our recent description of a case of chronic cough associated with bronchoscopic evidence of lymphocytic broncho-alveolitis which resolved following treatment of coeliac disease¹⁶ and our finding of increased broncho-alveolar lymphocyte counts in a cohort of patients with idiopathic chronic cough provides some support for this mechanism.¹⁷ An alternative and intriguing mechanism is that the cough might be due to a hitherto unrecognised autoimmune bronchitis and that the association with other diseases simply reflects the well-recognised association between different organ-specific autoimmune diseases. The failure of the cough to respond to corticosteroids in the treatment trials our patients were subjected to is not surprising since autoimmune hypothyroidism, pernicious anaemia, insulin-dependent diabetes mellitus and other organ-specific autoimmune disorders differ from systemic autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis in that they do not typically respond to corticosteroids.¹¹

Unexpectedly, we identified long-term NSAID use in more cases than controls, independent of the presence of autoimmune disease. This difference was identified as a result of a post hoc analysis and was not a primary outcome so we are cautious about interpretation of these data. The association is at first slightly surprising since prostaglandins are thought to be endogenous tussive mediators¹⁸ and NSAIDs have been shown to inhibit Angiotensin Converting Enzyme Inhibitor chronic cough.¹⁹ However, the net effect of NSAIDs on airway prostaglandin production is far from clear and it is possible that in certain circumstances these drugs alter airway prostaglandin production so as to have a protussive effect. An alternative possibility is that NSAIDs cause airway inflammation, perhaps involving a similar mechanism to NSAID-induced colitis.²⁰ Finally, we cannot exclude the possibility that patients used these drugs to ameliorate the musculoskeletal complications of coughing.

In conclusion, we have identified a relationship between idiopathic chronic cough and organ-specific autoimmune disease. Further studies are required to investigate this relationship in more detail, determine whether it is associated with airway inflammation, investigate the mechanisms involved and test this hypothesis that other

unexplained airway conditions are caused by similar mechanisms.

Acknowledgements

We thank Professor John Britton for assistance with the statistics. We also thank Carole Heubeck, Ivy Rushby, Alison Conway and Bernadette Donaghy with assistance in venesection and collecting questionnaires. This study is supported by The British Lung Foundation and University Hospitals of Leicester NHS Trust. Surinder Birring is a British Lung Foundation Clinical Research Fellow.

Conflicts of interest: none

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