Chronic cough and obstructive sleep apnoea: reflux-associated cough hypersensitivity?

Obstructive sleep apnoea (OSA) is being increasingly recognised as a cause of chronic cough. The impact of continuous positive airway pressure (CPAP) therapy and the mechanism of this association are not well understood. We describe a patient with OSA and chronic cough who responded well to CPAP. Objective and subjective assessments of cough on treatment with CPAP, off CPAP and on follow-up as well as pharyngeal pH monitoring suggest a possible mechanism for this association.

A 61-yr-old male who was a nonsmoker presented to the Hull Cough Clinic (Hull, UK) with a dry cough of 2 yrs' duration. He did not complain of associated breathlessness or wheezing or a history of post-nasal drip. He did complain of heart burn and treatment with acid-suppressive therapy in the past lead to some improvement in his cough, though it continued to be a significant problem. Previous trials of inhaled and nasal corticosteroids did not improve his cough. He did not have any comorbidities and was not on regular medications. His body mass index was 31 $kg \cdot m^{-2}$. General physical examination and examination of the respiratory system were unremarkable. A chest radiograph and spirometry were normal. On further questioning, he had a history of snoring for many years. He also complained that his sleep quality was not good and he felt somewhat sleepy in the day time. His Epworth Sleepiness Scale score was 12. This raised the clinical suspicion of OSA. Treatment with lansoprazole was initiated and a sleep study was organised.

At review, on treatment with lansoprazole, his cough was slightly better, although, like previously, it continued to be a significant problem. The sleep study confirmed the diagnosis of severe OSA, the apnoea–hypopnoea index (AHI) being 45 events$\cdot h^{-1}$. 75.3% of the events were apnoeic (72.9% obstructive, 0.8% central and 1.6% mixed) and 24.7% of the events were hypopnoeic. His mean oxygen saturation was 93.7%, the proportion of time with a saturation <90% was 5.2% and his oxygen desaturation index was 36.6 events$\cdot h^{-1}$.

He was initiated on treatment with CPAP therapy. Fixed pressure of 10 cmH_2O led to amelioration of his sleep-related symptoms as well as the chronic cough. The improvement persisted on follow-up at 1 yr. To look into the mechanism of improvement of cough with CPAP, he had several assessments on and off CPAP and at 1-yr follow-up.

Assessments were performed on treatment with CPAP, 1 week following stopping of CPAP and at 1-yr follow-up on CPAP. The patient underwent cough challenges with citric acid, completed the Leicester cough questionnaire (LCQ) and a visual analogue scale (VAS) for cough on each occasion. The LCQ scores, VAS score and citric acid challenge data are summarised in table 1. The data demonstrate an improvement in cough-related quality of life, markedly decreased VAS score for cough and reduction in cough sensitivity associated with CPAP therapy. There was no significant change in cough reflex sensitivity on stopping CPAP at onset. However, 1 yr after recommencement, the patient showed a remarkable difference in cough sensitivity. Indeed, there was no cough produced even by 1 M citric acid inhalation. We also performed 24-h airway pH study to assess the intensity of reflux using the Restech Dx-pH measurement system (Respiratory Technology Corporation, San Diego, CA, USA), which is a novel device that measures the pH of vapour in the upper airway. The pharyngeal probe detects not only liquid acid but, more importantly, aerosolised acid. The minimally invasive probe is inserted transnasally and rests just behind the soft palate for the duration of the study (usually 24–48 h); it transmits the data using wireless telemetry to a recorder attached to the patient's waist. The pharyngeal pH is assessed using a mathematical graphical model taking into account both upright and supine pH thresholds. A composite score, called the Ryan Score [1], is obtained. There was a significant difference in the Ryan Score obtained from airway pH analysis (23.66 on CPAP and 70.48 off CPAP).

OSA is characterised by recurrent episodes of upper airway narrowing during sleep with or without associated symptoms of daytime somnolence, morning headache and unrefreshing sleep. The prevalence of OSA is estimated to be 3–9% if defined as AHI >5 events$\cdot h^{-1}$ with at least one symptom of OSA syndrome [2]. We report a case of OSA who presented with cough. There were two aspects to the patient's cough. First, a chronic cough related to gastro-oesophageal reflux and secondly, cough related to OSA. There was some improvement in cough following acid suppression but the institution of CPAP

TABLE 1 Leicester cough questionnaire (LCQ) scores, visual analogue scale (VAS) score and citric acid challenge data

	Visit 1 On CPAP	Visit 2 Off CPAP	Visit 3 On CPAP at 1 yr
LCQ domains			
Physical	5.9	4.9	5.9
Psychological	6	6.1	6.1
Social	6.3	4.8	6.8
Total	18.2	15.8	18.8
Cough challenge			
C2 mM	35.7	7.81	>1000
C5 mM	42.4	40.7	>1000
VAS	4	44	2

Assessments were performed on continuous positive airway pressure (CPAP) following initiation of therapy, off CPAP for 1 week and on CPAP at 1 yr of follow up. The LCQ is a health-related quality of life measure of chronic cough and is divided into three domains. Total LCQ scores range from 3 to 21, with higher scores representing better quality of life. The VAS was a 100-mm linear scale. Cough challenges were undertaken with citric acid. C2 is the concentration of citric acid eliciting two or more coughs and C5 that eliciting five or more coughs.

produced a dramatic reduction in cough frequency and improvement in his quality of life. We have demonstrated that CPAP therapy in OSA is associated with a reduction in cough sensitivity, along with clinical improvement in cough-related quality of life. We believe that the possible mechanism of cough resolution with CPAP is through reduction of cough reflex sensitivity and improvement in reflux episodes. The baseline cough sensitivity was high but the patient had been on CPAP for only 2 months. Short-term cessation of CPAP did not cause change in cough sensitivity. However, at 1-yr follow-up, no coughs could be elicited by tussive challenge. We have previously demonstrated the disconnect between cough reflex sensitivity and symptoms [3]. We suggest in this case, cough reflex sensitivity lagged behind symptomatic improvement.

Resolution of cough with CPAP has been demonstrated in a case series of four patients who had objective cough recording and LCQ scores obtained pre- and post-CPAP therapy [4]. There was a significant improvement in both parameters in all patients. However, inhalational cough challenge was not performed in any of the patients.

Cough associated with OSA is probably under-recognised as there are only limited studies with small numbers of patients evaluating the prevalence of OSA as a cause of chronic cough. In a retrospective review, 44% of patients with chronic cough had OSA with 93% demonstrating significant improvement in cough with CPAP [5]. However, it is difficult to ascribe this benefit solely to CPAP as the majority of these patients had multiple therapeutic interventions for their cough. In a prospective series of 108 patients being evaluated for sleep disordered breathing, co-existent cough was documented in 33% [6]. Our case report evaluates the effect of CPAP on cough in a prospective and systematic manner and looks at a possible mechanism of this association.

The aetiology of cough in OSA could be multifactorial. First, OSA is associated with heightened cough sensitivity similar to patients with eosinophilic bronchitis. Obesity, a known risk factor for OSA, as well having as an association with chronic cough, is known to be associated with airway inflammation. This heightened cough sensitivity seen in OSA is likely to be related to cough receptor sensitisation secondary to increased inflammatory mediators in the upper airways and airway epithelial damage [7]. Furthermore, sensory dysfunction at upper airway correlates with the degree of OSA as measured by AHI and oxygen desaturation [8]. We propose that the mechanism of this airway inflammation is through reflux as there is evidence of a high prevalence of gastro-oesophageal reflux disease in patients with OSA and commencement of CPAP results in improvement in transthoracic pressure and reflux [9]. Secondly, there is objective evidence of impaired swallowing in OSA, which could predispose these patients to reflux, microaspiration and cough [10].

To our knowledge, this is the first clinical demonstration of reversibility of cough reflex sensitivity in OSA with CPAP therapy. This case highlights an interesting association and mechanism of chronic cough with OSA, likely to be under-recognised in cough clinics as a cause of chronic cough. Furthermore, it emphasises the value of thorough and systematic clinical evaluation in the management of patients with chronic cough.

Shoaib Faruqi, Ahmed Fahim and Alyn H. Morice
Dept of Cardiovascular and Respiratory Studies, Castle Hill Hospital, University of Hull, Cottingham, UK.

Correspondence: S. Faruqi, Dept of Cardiovascular and Respiratory Studies, Castle Hill Hospital, University of Hull, Castle Road, Cottingham, HU16 5JQ, UK. E-mail: sfaruqi@doctors.net.uk

Statement of Interest: None declared.

REFERENCES

1 Ayazi S, Lipham JC, Hagen JA, *et al.* A new technique for measurement of pharyngeal pH: normal values and discriminating pH threshold. *J Gastrointest Surg* 2009; 13: 1422–1429.
2 Jennum P, Riha RL. Epidemiology of sleep apnoea/hypopnoea syndrome and sleep-disordered breathing. *Eur Respir J* 2009; 33: 907–914.
3 Morice AH, Menon MS, Mulrennan SA, *et al.* Opiate therapy in chronic cough. *Am J Respir Crit Care Med* 2007; 175: 312–315.
4 Birring SS, Ing AJ, Chan K, *et al.* Obstructive sleep apnoea: a cause of chronic cough. *Cough* 2007; 3: 7.
5 Sundar KM, Daly SE, Pearce MJ, *et al.* Chronic cough and obstructive sleep apnea in a community-based pulmonary practice. *Cough* 2010; 6: 2.
6 Chan KK, Ing AJ, Laks L, *et al.* Chronic cough in patients with sleep-disordered breathing. *Eur Respir J* 2010; 35: 368–372.
7 Paulsen FP, Steven P, Tsokos M, *et al.* Upper airway epithelial structural changes in obstructive sleep-disordered breathing. *Am J Respir Crit Care Med* 2002; 166: 501–509.
8 Nguyen AT, Jobin V, Payne R, *et al.* Laryngeal and velopharyngeal sensory impairment in obstructive sleep apnea. *Sleep* 2005; 28: 585–593.
9 Teramoto S, Ohga E, Matsui H, *et al.* Obstructive sleep apnea syndrome may be a significant cause of gastroesophageal reflux disease in older people. *J Am Geriatr Soc* 1999; 47: 1273–1274.
10 Teramoto S, Sudo E, Matsuse T, *et al.* Impaired swallowing reflex in patients with obstructive sleep apnea syndrome. *Chest* 1999; 116: 17–21.

DOI: 10.1183/09031936.00025012