Prolonged cough presenting with diagnostic difficulty: a study of aetiological and clinical outcomes

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ABSTRACT

Introduction: Prolonged cough is a common reason for referral to a respiratory physician. Some cases of prolonged cough can be a diagnostic challenge, especially when it is not accompanied by features that suggest common aetiologies. The current study examined this group of patients so as to ascertain the final aetiological and clinical outcomes.

Methods: We performed a chart review of cases that had been prospectively identified. The inclusion criteria were cough lasting more than three weeks, normal chest radiograph, non-smoking status, no history of angiotensin-converting enzyme inhibitor use, normal physical examination and absence of suggestive features of asthma, gastroesophageal reflux disease and postnasal drip syndrome. We classified the final diagnoses into three categories: likely diagnosis; possible diagnosis; and no diagnosis established, and traced the clinical outcomes.

Results: A total of 54 patients met the study criteria. The median duration of cough was 16 weeks (range four weeks to five years), while the median age of the patients was 38 (range 18–73) years. A likely diagnosis was reached in 23 patients and a possible diagnosis, in 12 patients. Gastroesophageal reflux disease and postnasal drip syndrome were the commonest diagnoses. There were no cases of asthma. The cough improved completely in 44 patients. Three cases were lost to follow-up before an outcome could be documented.

Conclusion: In most of these cases, a diagnosis could be achieved. The cough improved in the majority of patients, including those in whom a diagnosis could not be made.

Keywords: chronic cough, prolonged cough, subacute cough

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INTRODUCTION

Non-acute or prolonged cough (duration > 3 weeks) is one of the commonest reasons for referral to a respiratory physician.[1,2] The American College of Chest Physicians recently sub-classified prolonged cough into subacute cough (duration 3–8 weeks) and chronic cough (duration > 8 weeks).[3] The main reason for this was to highlight cases of 'post-infectious cough', which usually do not last beyond eight weeks. Western literature has clearly shown that in non-smoking patients with prolonged cough, who have normal chest radiograph and are not on angiotensin-converting enzyme inhibitors (ACEIs), the commonest aetiologies are asthma, postnasal drip syndrome (PNDS) and gastroesophageal reflux disease (GERD).[4] These account for 95% of all cases of prolonged cough. Cough experts have renamed PNDS as upper airway cough syndrome, since they believe that nasal dripping alone does not account for the mechanism of cough in all these patients. Nonasthmatic eosinophilic bronchitis (NAEB), a relatively new entity, is also a fairly common cause of prolonged cough, and it is characterised by sputum eosinophilia (eosinophils > 3%) and the absence of bronchial hyper-responsiveness, usually accompanied by a response to inhaled steroids.[5]

In many such cases of prolonged cough, patients may present with 'helpful' clues in the history or physical examination that may point to any of the above three common causes. However, in a small number of patients, these features are 'silent' and hence present a diagnostic dilemma. For such patients, experts recommend further diagnostic testing or empiric therapy for either of the three main causes (asthma, PNDS or GERD). Diagnostic testing may include spirometry, methacholine challenge test (MCT), ear, nose and throat (ENT) evaluation and 24-hour oesophageal monitoring.

Our study evaluated a group of patients with silent prolonged cough, with an aim to determine the final diagnoses and clinical outcomes. To our knowledge, such a study has never been carried out in Singapore. For the rest of this article, the term 'prolonged cough' is used to refer non-acute cough.

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Table I. Patient demographics.

Characteristic	No. (%)
Median age; range (yrs)	39; 18–23
Gender	
Male	32 (59.3)
Female	22 (40.7)
Ethnicity	
Chinese	34 (62.9)
Malay	12 (22.2)
Indian	5 (9.4)
Others	3 (5.5)
Duration of cough; range (wks)	18; 4–260

Table II. Diagnostic work-up.

Diagnostic work-up	No. (%)	Result
MCT	51 (94)	All negative
Spirometry	1 (1.8)	Normal
ENT referral	33 (61)	Diagnosis achieved: n = 21; allergic rhinitis: n = 11; c/c sinusitis: n = 1; GERD: n = 7; GERD + allergic rhinitis: n = 1; GERD + c/c sinusitis: n = 1
Sputum eosinophil count	3 (5.5)	All negative

MCT: methacholine challenge test; ENT: ear, nose and throat; GERD: gastroesophageal reflux disease

METHODS

We prospectively reviewed cases of prolonged cough that were referred to our respiratory clinics at the Changi General Hospital over a two-year period (June 2006 to May 2008). The following were the inclusion criteria: (a) cough > 3 weeks; (b) normal chest radiograph; (c) non-smoking status; (d) no history of ACEI use; and (e) absence of helpful clues that point to asthma (a history of dyspnoea or wheezing with physical examination showing rhonchi), PNDS (a history of runny nose, blocked nose, nasal dripping, itchy nose, sneezing or constant throat clearing with physical examination showing 'cobblestoning' of pharyngeal mucosa) or GERD (a history of heartburn and acid regurgitation). However, the diagnostic approach and treatment were left to the individual physician and were not protocolised.

A chart review of these patients was then performed. In our laboratory, a negative MCT indicated a provocative concentration of methacholine > 16 mg/ml producing a 20% decrease in forced expiratory volume in one second (FEV1). Sputum eosinophilia was defined as > 3% eosinophil concentration in the sputum. We examined the diagnostic work-up ordered and grouped the final diagnoses into three categories: (1) likely diagnosis, where there was objective evidence (e.g. a positive MCT or sputum eosinophilia), clinical evidence (positive nasal or laryngeal endoscopy findings) or a history suggestive of a preceding viral upper respiratory illness with spontaneous resolution of symptoms; (2) possible diagnosis, where the diagnosis was less certain in patients who responded to a targeted therapeutic trial; and (3) no diagnosis established. We also looked at the clinical outcomes in this group of patients. Improvement or resolution was defined as the complete disappearance of symptoms. A waiver of consent was obtained from the hospital ethics committee.

RESULTS

The patient demographics are shown in Table I. A total of 54 patients (32 male, 22 female) aged 18–73 years met the study criteria (Table II). The duration of cough was 4–260 weeks. 37 patients had a chronic cough (duration > 8 weeks) at the time of presentation. The diagnostic steps taken by the physician included ordering an MCT, spirometry or sputum eosinophil count, referral to ENT (for endoscopy) or starting empiric therapy (Table II). 18 patients were started on empiric treatment (for asthma: inhaled steroids or inhaled steroids combined with long-acting beta-agonists; GERD: proton pump inhibitors with or without domperidone; and PNDS: nasal steroids with antihistamines). Response was observed in ten patients. Some form of diagnosis (likely or possible) was reached in 35 (67%) patients (Table III). Dual diagnoses were noted in two patients. GERD and PNDS were the commonest diagnoses, each occurring in 17 patients. In one patient who was morbidly obese (120 kg), the cough disappeared when he lost 20 kg after being prescribed an appetite suppressant. One patient who had a newly diagnosed anxiety disorder reported resolution of the cough after receiving psychiatric treatment (probable psychogenic cough). A history suggestive of a preceding viral upper respiratory illness was obtained in two patients, suggesting a likely diagnosis of postinfectious cough. Among the 54 patients, we did not encounter a single case of asthma. 51 patients had a negative MCT, one had a normal spirometry but failed to respond to a trial of inhaled steroids, one defaulted follow-up and one had spontaneous resolution of cough.

Out of the 54 patients, four were lost to follow-up (Table III). A diagnosis had been established in two of these four patients; however, they defaulted clinic visits before a response to therapy could be ascertained. 44 patients reported an improvement in cough, while three patients with a likely diagnosis did not respond to the therapy. In the no diagnosis group, the cough

Table III. Final diagnosis and outcome.

Diagnostic group	No. of patients				
	Total	Defaulted	Improved	No improvement	Spontaneous resolution
Likely diagnosis	23	2	18	3	-
PNDS*	12				
GERD	7				
Postinfectious cough	2				
GERD + PNDS	2				
Possible diagnosis	12	-	12	-	-
GERD	9				
PNDS*	2				
Psychogenic cough	1				
No diagnosis	19	2	-	4	13

* PNDS included cases of allergic rhinitis and chronic sinusitis.
PNDS: postnasal drip syndrome; GERD: gastroesophageal reflux disease

spontaneously resolved in 13 patients (median duration of cough was eight weeks). Spontaneous resolution of cough was observed in ten of the 17 patients who initially presented with cough lasting less than eight weeks.

DISCUSSION

Prolonged cough can be a highly troublesome symptom and could lead to significant morbidity, decrease in the quality of life and even life-threatening consequences.[6,7] A prompt diagnosis may provide tremendous relief to the patient. Our study examined a difficult subgroup, i.e. patients who presented with no suggestive features of the commonest causes of prolonged cough. Our findings were similar to those of Western studies, in which GERD and PNDS were reported to be very common aetiologies. The diagnosis of GERD was either by laryngeal endoscopy or after a response to empiric therapy. The classical endoscopy findings of GERD were laryngeal or vocal cord oedema and erythema. None of the patients were subjected to 24-hour oesophageal pH monitoring, which is the gold standard test, although it is rarely done in conventional practice. Also, it could miss the diagnosis in cases of non-acid reflux. We did not encounter a single case of asthma. It is unclear why our study group differed from Western populations in this regard. One postulation may be possible ethnic differences in cough aetiologies.

International guidelines by the American College of Chest Physicians, The American Thoracic Society and The European Respiratory Society recommend performing a spirometry (with pre- and post-bronchodilator response testing) as the first step to diagnose cough-variant asthma and then proceeding to do a bronchial provocation test if the spirometry is normal. However, our findings suggest that a diagnosis of asthma is very unlikely in our local population if the patient has no suggestive features of asthma. In light of these findings, we opined that ordering an initial pre- and post-spirometry in such cases would be a waste of time and resources; hence, we recommend proceeding directly to an MCT to eliminate the diagnosis of asthma. Since baseline spirometry is done as the first step during an MCT session and patients with low FEV1 are prevented from bronchoprovocation challenge, this practice should be a safe one. In the patient whose cough improved with obesity treatment, we assume that the mechanism was possibly due to a reduction in gastroesophageal reflux. Morbid obesity has well been documented to be associated with reflux disease.[8]

Although testing for NAEB was ordered in three patients (sputum eosinophils), we did not prescribe empiric therapy (with inhaled steroids) for NAEB to any of the patients. If the three patients who received inhaled steroids as part of empiric therapy for asthma were in fact cases of NAEB, then we should have seen an improvement in their cough. However, all three failed to respond. It could be argued that some of the patients in the 'possible' group (who seemingly responded to empiric therapy) may in fact be cases of postinfectious cough that improved spontaneously and not due to the therapy. However, the median duration of symptoms of this group was 12 weeks, which makes that possibility unlikely (since most cases of postinfectious cough resolve within eight weeks).

Psychogenic or habit cough, a poorly defined entity, rarely causes chronic cough in adults who suffer from anxiety or depression, as was the case in one of our patients.[9] We failed to reach a diagnosis in 19 patients, of which the cough spontaneously resolved in 13 cases. We can only postulate that these 13 patients may have

been subclinical cases of postinfectious cough, since the median duration of cough in this group was eight weeks. Postinfectious cough follows viral or other upper respiratory tract infections, (mycoplasma, chlamydia, pertussis) and may last for 3–8 weeks.[10] Two of the 19 patients defaulted further follow-up. The remaining four patients were subjected to some degree of testing: MCT (n = 3); spirometry (n = 1); ENT evaluation (n = 4); sputum eosinophilia (n = 2); trial of inhaled steroids (n = 2); and omeprazole trial (n = 1). It could be argued that more detailed testings, such as 24-hour pH monitoring or computerised imaging of the paranasal sinuses, could have increased our diagnostic yield. Moreover, the cough did not improve in three patients whose diagnosis had been established, a finding we cannot fully explain. The possibilities are an error in diagnosis, multiple aetiologies, inadequate therapy or the presence of non-acid GERD. Spontaneous resolution of cough was noted in ten of the 17 patients who initially presented with cough lasting less than eight weeks. These patients were likely to be cases of postinfectious cough (although a history of preceding upper respiratory tract infection was obtained in only two cases). Hence, it may be a reasonable option for physicians to observe these patients with non-chronic cough for a few weeks to allow spontaneous recovery.

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