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A cough that won't go away: Evaluation and treatment in 2 patients

A 65-YEAR-OLD MAN presents with a dry, nonproductive cough, which he has had for 10 months. He describes it as very intrusive, as it limits his effectiveness in his work. He says the cough is worse when he laughs, walks up stairs, or talks for more than 15 seconds at a time. He says he has mild postnasal drainage but feels this does not cause the cough. He denies heartburn or reflux. He does not cough when eating or drinking or at night.

His medical history is unremarkable. He has never smoked. He is on no medications. He takes a daily multivitamin. He has no known history of allergies.

A second patient, a 48-year-old woman, presents with a similar history of nonproductive cough for 8 months. She is embarrassed to attend social functions, as her cough often causes urinary incontinence. Her coughing sometimes wakes her up at night.

Her medical history is notable only for hypertension, which is well controlled with hydrochlorothiazide 25 mg once daily. She takes no other medications and has never smoked. She denies heartburn or other symptoms of reflux. She does not cough when eating or drinking. She has no known history of allergies.

Vital signs in both patients are within normal limits, and lung auscultation reveals no wheezing, crackles, or rales in either patient.

FIRST STEP IN EVALUATION

1 Based on the available information, what is the most appropriate next step for these patients?

- ☐ An extensive history
- ☐ Chest radiography
- ☐ Nasal endoscopy
- ☐ A pulmonary workup

While all of the above are important in the diagnosis of chronic cough, collecting an extensive history is a crucial first step to rule out the most common causes of chronic cough and should always be done (Table 1). In particular, one should find out:

Is the patient taking an angiotensin-converting enzyme (ACE) inhibitor? These drugs are a common treatment for hypertension and are well known to cause a persistent dry cough.¹

Does the patient have occupational exposure to allergens?

Does the patient smoke?

Are there symptoms of underlying disease? These can include:

- Wheezing and shortness of breath, indicating asthma
- Heartburn and regurgitation, indicating gastroesophageal reflux disease (GERD)
- Nasal discharge and phlegm, indicating postnasal drainage or untreated sinusitis
- Hemoptysis, chest pain, and weight loss, possibly indicating lung cancer.²

Two patients present with similar symptoms, but different causes and treatment

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TABLE 1

Causes of chronic cough

Common causes

Angiotensin-converting enzyme inhibitor use
Asthma
Chronic obstructive pulmonary disease
Gastroesophageal reflux disease
Upper airway cough syndrome (eg, sinusitis, rhinitis)

Uncommon causes

Foreign body aspiration
Pneumonia
Lung cancer
Tuberculosis
Bronchitis
Sarcoidosis
Idiopathic pulmonary fibrosis

Diagnostic tests

Common diagnostic tests such as chest radiography, nasal endoscopy, laryngoscopy, spirometry with bronchodilator testing, and exhaled nitric oxide measurement can also be used to detect some of the less apparent causes of chronic cough.

Chest radiography will not reveal the most common causes of cough, but it is important in detecting foreign body aspiration and lung diseases such as pneumonia, lung cancer, and tuberculosis.

Nasal endoscopy is warranted in patients who report postnasal drip. Cough from postnasal drip, otherwise known as upper airway cough syndrome (UACS), is the most common cause of chronic cough seen in respiratory clinics, contributing to 26% to 87% of US cases.^{2,3} UACS is characterized by a feeling of nasal secretions at the back of the throat, resulting in a persistent urge to clear the throat. Causes include allergic rhinitis, nonallergic rhinitis, bacterial sinusitis, and allergic fungal sinusitis. It is unknown how often the patient's description of symptoms correlates with actual confirmatory findings on endoscopy.

Importantly, GERD can present with upper respiratory symptoms and can mimic UACS.³

Laryngoscopy can identify laryngeal irritation from chronic cough, evidence of reflux disease, and sinonasal pathology.

Spirometry can noninvasively uncover evidence of asthma and chronic obstructive pulmonary disease, both of which can cause chronic cough. Cough due to asthma can be classified as cough-variant asthma, in which cough is the sole symptom; cough-predominant asthma, which can include dyspnea and wheezing; and cough that persists despite therapy with corticosteroids and beta agonists.^{4,5}

Of note, while variable airflow obstruction is classically detected in asthmatic patients, some patients exhibit no abnormal spirometry results.^{6,7} Therefore, additional pulmonary tests are often needed, such as methacholine challenge and fraction of exhaled nitric oxide (FeNO) measurement.

Methacholine challenge is classically used to assess for bronchial hyperreactivity. However, it has been shown to be a poor diagnostic tool for chronic cough and is only recommended when no other obvious causes exist.^{8,9}

FeNO measurement. Guidelines from the American Thoracic Society state that adult patients with low FeNO (< 25 ppb) likely have either noneosinophilic or no airway inflammation. In contrast, a high FeNO (> 50 ppb) implies uncontrolled or deteriorating eosinophilic airway inflammation.¹⁰

In a study by Yi et al,¹¹ a cutoff of 31.5 ppb or higher was found to have a sensitivity of 54%, a specificity of 91.4%, and a positive predictive value of 89.3% for corticosteroid-responsive cough. Possible causes in patients with high FeNO include atopic asthma, eosinophilic bronchitis, and COPD with a mixed inflammatory phenotype.¹⁰ As a result, patients with a measurement of 31.5 ppb or higher are more likely to benefit from oral steroids, transitioning to inhaled corticosteroid treatment.^{12,13}

CASES CONTINUED

Both patients undergo detailed questioning, chest radiography, nasal and laryngeal endoscopy, and pulmonary workup. In each patient, the history is unremarkable and chest radiographs are clear. Neither reports any sensation of nasal

Upper airway cough syndrome is the most common cause of chronic cough seen in respiratory clinics

drainage, nor does nasal endoscopy find remarkable results. Laryngeal examinations show no evidence of inflammation or pathology.

Although both patients have normal spirometry results, our female patient has an FeNO of 56 ppb, while our male patient has 10 ppb. As a result, our female patient is started on inhaled corticosteroid treatment. When she comes back for follow-up 1 month later, she reports that her cough is almost completely gone.

Does our male patient have GERD?

With all other common causes of chronic cough such as asthma, UACS, and lung disease ruled out, it may be useful to consider GERD as the underlying cause of our male patient's chronic cough, even though he has no gastrointestinal symptoms. Irwin et al¹⁴ reported that 9 (75%) of 12 patients with GERD-related chronic cough had no gastrointestinal symptoms.

However, evidence supporting GERD treatments for chronic cough is controversial at best. A Cochrane review of 19 studies found insufficient evidence that GERD treatment was useful in the treatment of chronic cough.¹⁵ Similarly, guidelines from the American College of Chest Physicians note that proton pump inhibitors lack efficacy when a workup of GERD is negative, and so they recommend against using these agents in this situation. However, they do recommend them for chronic cough caused by GERD, and they also state that drugs may be given to treat coexisting conditions, such as proton pump inhibitors to treat GERD, as long as they are used at a stable dose.¹⁶

Nevertheless, cough is common in GERD, we cannot rule out GERD even if 24-hour monitoring yields negative results,¹⁷ and proton pump inhibitors pose a low level of risk. Therefore, we decide on a trial of a proton pump inhibitor for our patient.

Four months later, the patient returns, visibly agitated, and states that the proton pump inhibitor has not helped his cough at all. At this juncture, we make the diagnosis of unexplained chronic cough, also known as chronic refractory cough, as a diagnosis of exclusion.

Of note, although the most likely cause is neurogenic cough, this is not synonymous with unexplained chronic cough.

TREATMENT FOR UNEXPLAINED CHRONIC COUGH

2 What is the first-line treatment for the patient at this point?

- ☐ Neuromodulators
- ☐ Behavioral cough suppression therapy
- ☐ Superior laryngeal nerve block
- ☐ Codeine or another opioid
- ☐ Laryngeal botulinum toxin injection

Neuromodulators for chronic cough

Neuromodulators are most often the first-line treatment for unexplained chronic cough. Although this is an off-label use, these drugs are thought to lessen the increased neural sensitization that underlies many cases of chronic cough.¹⁶ Currently, there is evidence that amitriptyline, gabapentin, pregabalin, tramadol, and baclofen may benefit chronic cough patients.^{18,19}

In a randomized trial in 62 patients receiving gabapentin or placebo, Ryan et al²⁰ found that the gabapentin group demonstrated significantly improved cough-specific quality of life compared with the placebo group (number needed to treat 3.58; $P = .004$). On the other hand, 10 (31%) of the 32 patients receiving gabapentin experienced adverse effects vs 3 (10%) of the 30 in the placebo group. The most common adverse effects were, in order of frequency, nausea and stomach pain, dizziness, fatigue, dry mouth, and confusion.

As such, gabapentin is an effective and well-tolerated treatment in chronic cough, and several prospective case series and cohort studies support its efficacy.^{21,22}

Similarly, the effectiveness of amitriptyline was assessed in a single randomized clinical trial²³ in 28 patients randomized to receive either amitriptyline or codeine-guaifenesin. Eleven (73%) of the 15 patients in the amitriptyline group achieved a complete response, compared with none of the patients in the codeine-guaifenesin group, indicating that amitriptyline may also be an effective treatment in chronic cough.

Lastly, a single randomized crossover study of baclofen in 2 patients,²⁴ a pilot case series of tramadol,²⁵ and a retrospective cohort study of pregabalin²⁶ demonstrated efficacy of these medicines.

As a result, neuromodulators are currently seen as an efficacious treatment for unex-

Some patients with asthma have normal results on spirometry

plained chronic cough and should be one of the first considerations for this patient, given his lack of benefit from a multispecialty work-up.²¹ A major limitation of this treatment approach is that we cannot predict the patient in front of us will respond to any particular medication at any given dose or frequency.

Behavioral therapy is also indicated

Consultation with a speech pathologist who has expertise in behavioral cough suppression therapy is also indicated. Behavioral therapy is usually done concurrently with drug treatment, though patients may respond to one or the other, or to both, to varying degrees.

Behavioral cough suppression therapy is a good option for patients with unexplained chronic cough and is recommended by current guidelines.¹⁶ It is hypothesized that behavioral therapy, given by a speech-language pathologist, effectively reduces cough sensitivity, improves voluntary control over cough, and reduces laryngeal muscle tension. Additionally, there may be an element of placebo response. Behavioral cough suppression intervention involves education, strategies to control cough, vocal hygiene training, and psychoeducational counseling.²⁷

A single randomized controlled trial²⁸ in 87 patients with chronic cough found that those receiving a speech pathology intervention demonstrated greater reduction in cough, breathing, voice, and upper airway symptom scores compared with a placebo group ($P < .001$ for all scores). In total, 88% of participants in the treatment group achieved successful outcomes, compared with 14% in the placebo group ($P < .001$).

Behavioral cough suppression therapy by a speech pathologist would be an appropriate and likely effective intervention for our patient.

Superior laryngeal nerve block

Hypersensitivity of the superior laryngeal nerve has been implicated as a possible cause of neurogenic cough, also known as cough hypersensitivity syndrome.²⁹ Cough can be triggered by actions that stimulate the superior laryngeal nerve such as talking, laughing, and swallowing, and by exposure to strong smells.

Superior laryngeal nerve block is an emerging office-based treatment, but it is unknown how many injections are needed for cough suppression.³⁰ This is a good option for

patients who develop diminished responses to neuromodulator therapy or who cannot tolerate adverse effects of this drug class.

In a retrospective study³⁰ of 18 patients treated with percutaneous blockade of the internal branch of the superior laryngeal nerve, cough severity index scores decreased significantly afterward, and 15 of the 18 patients reported cough improvement. Duration of benefit seems to be 2 to 3 months; however, it is unknown if patients are definitively “cured” after a series of injections or if they require extended long-term treatment. More data will provide more clarity. To our knowledge, there have been no blinded, randomized studies to assess the effectiveness of this treatment.

Superior laryngeal nerve block may be an effective, low-risk, low-cost treatment for neurogenic cough. However, because there is currently less evidence for this treatment vs other treatments such as neuromodulators or behavioral cough suppression therapy by a speech pathologist, we are hesitant to pursue this before trying the other treatments.

Botulinum toxin injections

Botulinum toxin type A is another agent thought to lessen laryngeal hypersensitivity and hyperactivity.³¹

A case series in 4 patients treated with botulinum toxin injection found that all patients experienced significant cough relief afterward, and that a median of 7 injections was sufficient to achieve complete resolution.³¹ In a study of 22 patients,³² 11 (50%) reported greater than 50% improvement in cough severity or symptoms after the first injection. No patients experienced adverse effects.

Small studies show that botulinum toxin injection has efficacy similar to that of superior laryngeal nerve block but with the undesirable effects of a weak voice and mild dysphagia. However, most studies have been observational, limiting the quality of evidence. Patient selection and long-term outcomes require further investigation.

Opioids

Morphine and codeine have a long history of use as centrally acting cough suppressants. Similarly, tramadol has been anecdotally successful in chronic cough and warrants further research. In the only published prospective case

**Patients with
FeNO $\geq$ 31.5 ppb
are more likely
to benefit from
oral steroids**

series, all 16 patients reported improvement in cough symptoms, and validated assessment tools showed significant improvement in cough severity.²⁸ However, these medications have significant adverse effects such as constipation and drowsiness, and the risk of addiction.³³

Yancy et al,³⁴ in a systematic review and meta-analysis comparing opioids and placebo, found that the standardized mean difference of cough severity with opioids was 0.55 (95% confidence interval [CI] 0.38–0.72; $P < .0001$) and the difference in frequency was 0.57 (95% CI 0.36–0.91; $P = .026$), indicating a medium effect size. However, while there have been more studies of opioids as cough suppressants than the other options listed, Yancy et al noted that the studies are generally of low quality and may not be accurate indicators of efficacy.³⁴

CASE CONTINUED

After discussing treatment options with the patient, we decide to start a trial of gabapentin. This drug is typically started at a dose of 300 mg at bedtime, and then adding a dose every 5 to 7 days to a maximum dose of 300 mg 3 times daily.

We do not prescribe speech therapy for this patient, as he lives far from the nearest center and is unwilling to commit the necessary time.

At 1-month follow-up, he states that he is satisfied, as his cough has significantly improved.

IF GABAPENTIN DOES NOT WORK

3 During this visit, the patient asks what else might have been done if his trial of gabapentin had not worked.

- ☐ Try another neuromodulator
- ☐ Adjust the dose of gabapentin
- ☐ Try a different class of medications
- ☐ Enroll in a clinical trial of future therapies

Several studies have shown that it may be necessary to adjust the dose or type of neuromodulator multiple times to achieve maximal effect; adjustments and titration should be attempted before switching to another neuromodulator. But if no clinical response is seen after several weeks of gabapentin 300 mg 3 times a day, further escalation of the dose is unlikely to help.

Again, it is difficult to predict who will respond to what neuromodulator at what dose.

In addition, a significant number of patients develop tachyphylaxis, ie, a diminished response to previously efficacious treatment. A recent retrospective review of amitriptyline in patients with idiopathic cough noted that it is necessary to titrate or restart the medication for cough control in many patients.³⁵ Moreover, a retrospective review found a 35% incidence rate of tachyphylaxis in patients treated with neuromodulators.³⁶ Increasing the neuromodulator dose may help these patients, but the clinician should periodically weigh the possible benefits.¹⁶ Current guidelines recommend that physicians assess risks and benefits of gabapentin treatment and adjust accordingly every 6 months.¹⁶

Maximal therapeutic response is often achieved by 1 to 3 months, and patients undergoing subsequent trials of different neuromodulators show success rates less than 33%.³⁶ However, this does not mean that trying additional neuromodulators is futile: 40% of patients who ultimately experience success do so after the first neuromodulator trial. Importantly, successful treatment may take up to 5 trials in some patients; therefore, prescribing another neuromodulator should not be ruled out.³⁶

If the patient does not respond to neuromodulators or wishes to pursue other options, it may be beneficial to recommend a trial of an opioid, behavioral cough suppression therapy, laryngeal botulinum toxin injections, or superior laryngeal nerve block. Chlorpheniramine, a first-generation antihistamine that crosses the blood-brain barrier, may also have positive effects. These therapies all have evidence supporting their use and should not be ruled out before attempting more extreme interventions.

Experimental treatments

Research into novel treatments for refractory chronic cough is focused on blocking cough arising from various etiologies while minimizing adverse effects.

Recently, the class of P2X3 receptor antagonists has shown promise in achieving this goal. P2X3 receptors are ion channels located on vagal nerve fibers innervating the airways; blocking these receptors is thought to widely suppress neurogenic cough stimuli. P2X3 receptor antagonists have moved from preclinical studies to phase 2b clinical trials.

Gabapentin is an effective, well-tolerated treatment in chronic cough

In the most recent phase 2b clinical trial,³⁷ in 253 patients, a P2X3 receptor inhibitor was found to significantly inhibit 24-hour cough frequency with an estimated change in awake cough frequency of -37% (95% CI -53.3% to 14.9%; $P = .003$). However, the most common side effect, taste disturbance, occurred in 81% of patients on the maximum dose of the P2X3 receptor inhibitor.³⁷

Future trials will need to explore pharmacologic and dosing changes to minimize these adverse effects. As these trials continue to move forward, there is hope for new, better therapies for chronic cough patients like ours.

CASE CONCLUSION

At a 6-month follow-up visit, our male patient reports that his cough is completely resolved. He then begins tapering off his medications, and 18 months after starting his gabapentin regimen, he returns cough-free and successfully weaned off the medication.

TAKE-AWAY POINTS

Unexplained chronic cough (also known as chronic refractory cough) is common, imposes a large healthcare burden, and can adversely

affect quality of life.

While the exact cause of chronic refractory cough is unknown, there are evidence-based treatment options.

A thorough and complete history may be able to uncover the underlying problem in a large number of patients.

The most common causes of chronic cough include asthma (and other lung diseases), UACS, and GERD. Testing for these underlying conditions should be pursued before establishing a diagnosis of unexplained chronic cough.

Neuromodulators have proved to be efficacious in the treatment of unexplained chronic cough and should be first-line therapy. Behavioral cough suppression therapy administered by a speech pathologist also shows efficacy and should be offered either in conjunction with other treatments or by itself.

Clinical response to neuromodulators and cough suppression therapy varies widely. Adjustments to the dose or type of neuromodulator may be required to achieve the desired effect.

Numerous alternative therapies have shown promise in treating unexplained chronic cough. More research is warranted toward developing the ideal treatment.

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