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Case report

Successful use of guanfacine in a patient with chronic refractory cough: A case report

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ABSTRACT

Chronic idiopathic cough is a common and often frustrating complaint for patients as well as providers. When common etiologies of cough are ruled out and/or do not respond to usual treatments, neurogenic cough should be considered as a diagnosis of exclusion. Here, we report on a 58-year-old woman with an 8-year history of chronic, treatment-refractory cough of unknown etiology that we diagnosed as neurogenic cough and successfully treated with guanfacine monotherapy, with rapid and durable improvement in symptoms. This case was particularly challenging for a number of reasons, including a distant past smoking history and previous pneumonia, a significant psychiatric history, and a mildly deviated nasal septum and nasal osteophyte, all or some of which could have contributed to the etiology of the cough. This case illustrates that neurogenic cough should be a diagnostic consideration in patients presenting with chronic cough in whom other treatment modalities have failed, and also suggests that the therapeutic use of guanfacine in this clinical setting warrants future investigation.

1. Introduction

A cough is a reflexive inhalation and exhalation against a closed glottis resulting in the forceful expulsion of air as building pressure forces the glottis open. Cough can be classified as acute (lasting up to 8 weeks) or chronic (lasting greater than 8 weeks) [1,2]. While acute cough is often self-limited or requires minimal intervention, chronic cough is a common complaint that is often diagnostically and therapeutically challenging in the primary care, otolaryngology, pulmonology, or psychiatric settings. The cause of chronic cough is often identified as asthma, eosinophilic bronchitis, gastroesophageal reflux disease (GERD), rhinosinusitis, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, or bronchiectasis [3]. Yet, an inciting cause is frequently not found. A recent analysis of bronchial biopsies from 100 patients with chronic cough yielded 62 cases in which no definitive cause and no effective treatment could be identified [4]. Thus, many patients with chronic cough continue to suffer a refractory course, which has been shown to significantly reduce quality of life [5,6].

When objective findings are limited or equivocal, a chronic non-productive cough should raise suspicion for a diagnosis of neurogenic cough, resulting from laryngeal paresthesia, or somatic cough syndrome in patients with tic disorders, though the latter is more frequently reported in children and adolescents than adults, and generally exacerbated by contextual factors such as stress [7–10]. Yet, even with a correct diagnosis, treatment options are controversial. Non-pharmacological interventions that have demonstrated significant benefits over placebo include physiotherapy and speech and language therapy, such as laryngeal hygiene and hydration, cough suppression techniques, breathing exercises, and psychoeducational counselling [11–13]. Antidepressant medications including amytriptyline and paroxetine have been reported to show modest efficacy in some cases [14,15]. Likewise, neuromodulators such as gabapentin, pregabalin and baclofen may be helpful for a subset of patients [1,16,17]. Still, many patients are resistant to medical management of their chronic cough, which begs the need for increased research. Here, we report on a patient with an 8-year history of a chronic progressively worsening cough resistant to multiple medications that was rapidly and persistently responsive to the alpha-2-

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adrenergic agonist guanfacine monotherapy. Based on the response to treatment, we propose that this cough was likely neurogenic in origin, and that neurogenic cough can be successfully treated using guanfacine.

2. Case report

A 58-year-old Caucasian female presented to an outpatient psychiatric clinic complaining of an 8-year history of chronic progressively worsening cough. The cough was nonproductive and the patient experienced at least two coughing bouts (of 2–3 coughs each) per hour daily on presentation. The patient described the cough as worst in the morning (6:30am) and evening (8:00pm), exacerbated by singing, eating and changing positions, and improved with throat lozenges. The patient had undergone allergy testing, which revealed seasonal allergies for which she had been initiated on a trial of cetirizine without success. She had also been treated with ranitidine and lansoprazole for GERD, also without improvement in cough symptoms. She had also taken albuterol on and off for suspected asthma, again without improvement in symptoms. Other previously trialed medications had included amitriptyline, nortriptyline, imipramine, gabapentin, and lamotrigine for suspected sensory neurogenic cough, with none providing clinical benefit. Her other medications included Sudafed cough syrup (dextropmethorphan, guaifenesin, and pseudoephedrine) 1 teaspoon as needed to help with cough, esomeprazole 40 mg qd for GERD, and levetiracetam 250 mg qd for petit mal seizures, which began in her 20s.

The patient's family history was noncontributory. Her social history was remarkable for sexual abuse from ages 11 to 18. She had subsequently developed posttraumatic stress disorder (PTSD), for which she is currently undergoing psychotherapy and group therapy for survivors of sexual abuse. She reported a 10 pack-year smoking history twenty years ago, but denied alcohol or other substance use. She works as a medical technician.

The patient had been seen by two pulmonologists in February 2011 for evaluation of suspected pneumonia. She reported that levofloxacin and azithromycin prescribed at the time had mildly improved her cough, but that it worsened and returned to baseline soon after completion of the antibiotic regimen. Evaluation of pulmonary function and airway anatomy was conducted in March 2011, after resolution of the pneumonia. On examination, the patient's lungs were clear bilaterally without wheezes or adventitious sounds. Spirometry revealed a moderate obstructive pattern with good bronchodilator response, with normal total lung capacity and normal diffusion capacity. A chest x-ray was read as negative for pathology. The patient underwent bronchoscopy, which revealed a normal appearing larynx, subglottic area, and trachea, and brochoalveolar lavage was negative for fungal or bacterial pathogens.

The patient was subsequently referred to an otolaryngologist for follow-up evaluation of sinus, pharyngeal and laryngeal pathology. Nasopharyngoscopy was performed, which revealed a normal larynx with normal vocal cord mobility and no mass lesions present. Her nasal exam demonstrated no evidence of purulent discharge. A mildly deviated nasal septum was noted. The patient was referred for a noncontrast multislice CT of the sinuses, which revealed patent sinuses, no mucoperiosteal thickening, clear frontal sinus drainage pathways and clear sphenoethmoidal recesses. Bowing of the nasal septum to the right was noted, and a posterior osteophyte was identified between the inferior and middle nasal turbines. The frontal, ethmoid, maxillary, and sphenoid sinuses were clear. There was no mucoperiosteal thickening. Frontal sinus drainage pathways were patent. The sphenoethmoidal recesses were clear. There were no air fluid levels noted. The bones surrounding the sinuses including the lamina papyracea, fovea ethmoidalis, and cribriform plate were intact. The osteomeatal complexes were patent bilalterally. Bilateral calcification of the trochlear apparatus on the orbit was present. In spite of septal deviation and the presence of a posterior osteophyte, it was felt that sinus pathology was unlikely to be the underlying etiology of the patient's chronic cough, and therefore septoplasty to correct the septal deviation was not recommended. The patient was subsequently referred to psychiatry for follow-up.

Based on the cough's refractory nature and lack of responsiveness to other medical treatments, a presumptive diagnosis of neurogenic cough was made in July 2016. Given the lack of responsiveness to first/second line agents for neurogenic cough, the patient was initiated on a trial of guanfacine, an alpha-2-adrenergic agonist, which has shown moderate benefit in reducing tic symptoms in patients suffering from tic disorders [18,19] and experimental evidence in blocking sensory nerve output [20]. Oral guanfacine monotherapy 1 mg bid was started empirically, with follow-up at 3 weeks for reassessment. At follow-up the patient reported a marked reduction in cough frequency to ~4 bouts per day. At this appointment, the dose of guanfacine was increased to 1.25 mg bid but was poorly tolerated, causing dizziness, sedation, tremor, and shortness of breath. The initial dose was restarted with good response at two-week and 7-month follow-up, with cough occurring ~4 times per day, more commonly during the evening than in the morning. At 14-month follow-up, the patient reported that her cough had been well-controlled at a 2 mg bid dose, but had led to episodes of dizziness and hypotension (self-measured blood pressure 90/40), and so she had adjusted to a 1 mg tid dose (8:00am, 2:00pm, 8:00pm). At this dose, the patient reported the frequency of her cough as ~10 bouts (~20–30 coughs) per day on average, equally during daytime and nighttime. At this visit, the patient completed the Leicester Cough Questionnaire (LCQ), reporting domain scores of 5.4 (physical), 4.9 (psychological), 6 (social) and a total score of 16.2. Subjectively, she described markedly improved quality of life since beginning guanfacine therapy, with improved functioning. She stated that the cough was initially debilitating, would often embarrass her, limited her speaking ability, often almost caused her to vomit, and led to thoughts of suicide. At present, she describes her cough as much more mild, never causing her embarrassment or episodes of near-vomiting. She is able to speak and teach without interruption, and no longer experiences suicidal thoughts.

3. Discussion

Here, we report a case of chronic refractory cough of 8-years duration treated with the alpha-2-adrenergic agonist guanfacine. To our knowledge, this is the first demonstration that alpha-2-adrenergic agonism, which has been used in the treatment of tic disorders with some success [19], and shows experimental evidence for blocking sensory nerve conduction [20,21] may be a viable option for patients with unremitting cough without an identified etiology, which we diagnosed as neurogenic cough. Neurogenic cough is believed to arise as a sensory neuropathy, which may be due to laryngeal irritation, and has been reported following viral upper respiratory tract infection (URTI) [22]. However, even for patients who lack a clear URTI history or for those who are resistant to treatments targeting more common causes of cough, neurogenic cough should be considered, and may be the result of a sensory neuropathy. Another diagnostic consideration is a tic disorder, characterized by sudden, repetitive, stereotyped motor movements or vocalizations. Several distinct tic disorders are recognized in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), including Tourette disorder, persistent (chronic) motor or vocal tic disorder, provisional tic disorder, unspecified tic disorder, and other specified tic disorder (https://www.psychiatry.org/psychiatrists/practice/dsm). Importantly, vocal tics can also include somatic cough syndrome, although these are more commonly found in children/adolescents than adults [23]. A previous study that included patients with all tic disorders found that guanfacine was safe and effective to treat tic symptoms in these patients [18]. In light of the patient's lack of responsiveness to multiple alternative medical therapies, we explored guanfacine as a possible therapeutic agent. Given our patient's age, historical factors, and dramatic response to guanfacine, we conclude that her cough was likely neurogenic in origin. Alpha-2-adrenergic

agonists have been shown to act peripherally to block action potential conduction in peripheral nerves, as well as centrally to increase vagal tone [20,24]. We hypothesize that one or both of these mechanisms may be responsible for our patient's symptom responsiveness.

A chronic cough (lasting greater than 8 weeks in duration) can have multiple potential causes, the most likely of which is infection [25]. Therefore, on a patient's initial presentation, one should be immediately suspicious of infectious etiologies such as pharyngitis, bronchitis, or pneumonia. However, the list of other possibilities includes, but is not limited to the following: pulmonary disorders such as asthma, COPD, bronchiectasis, idiopathic pulmonary fibrosis and eosinophilic bronchitis, gastrointestinal disorders such as GERD, cardiac disorders such as congestive heart failure (CHF), autoimmune disorders such as sarcoidosis, and medication reactions [26,27]. In particular, angiotensin converting enzyme (ACE) inhibitors can cause cough in up to 19% of patients who take them [28,29]. Carcinoma and tuberculosis are important diagnoses to rule out in the setting of red flags (e.g. weight loss, chronic night sweats, hemoptysis). The physical exam should focus on checking the pharynx and listening to the heart and lungs. The most common radiological study to order is a chest x-ray, looking for pneumonia or other pulmonary lesions, and if necessary a chest CT, which is helpful in identifying lung lesions and mediastinal abnormalities such as sarcoidosis, and pleural or pericardial effusions. In cases for which cardiac sources are being considered, electrocardiography and echocardiography may be appropriate.

With regard to the present patient, several objective findings made this case particularly challenging. In particular, there is sparse and controversial evidence that nasal septal deviation or osteophytes contacting the lateral wall of the nose may induce or be associated with cough [30,31]. However, in our experience, septoplasty to try to relieve cough is effective in less than 50% of cases. Likewise, the previous distant smoking history, moderate obstructive pattern on spirometry, and previous pneumonia all raised suspicion for pulmonary causes of cough. However, the lack of responsiveness to any treatments for the above conditions invited the possibility that a neurogenic cause may have been at least partially responsible.

In conclusion, the positive response to guanfacine in this patient with a chronic refractory cough of unknown etiology strongly suggested a diagnosis of neurogenic cough and also encouraged us that others suffering a similar course may also benefit from this treatment. For our patient, her cough was dramatically improved with minimal side effects at a 3 weeks and 7 months post-treatment, but by 14 months the effective dose also led to hypotensive episodes, requiring dose adjustment. We acknowledge that the side effect profile, dosing considerations, and careful patient selection should all be further investigated and discussed with patients prior to initiating treatment. Future research should also strive to implement serial cough questionnaires (e.g. the LCQ) in addition to monitoring cough frequency in order to establish a symptomatology baseline and to formally track response to therapy.

Disclosures

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Conflicts of interest

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