

Pearls and pitfalls in the diagnosis of cough variant asthma

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ABSTRACT

Cough alone may sometimes be the sole presenting symptom of asthma. Patients experience cough without wheeze or shortness of breath and with normal baseline pulmonary function test results. These patients do, however, demonstrate bronchial hyperreactivity. They also respond to specific traditional asthma therapy. These patients are considered to have a specific asthma phenotype: cough variant asthma (CVA).

In prospective studies of patients with chronic cough, an average of 25% have CVA. Patients have chronic cough, normal baseline pulmonary function tests, positive bronchial inhalation challenge results, and response to specific asthma therapy. What makes these patients cough is still unknown. The cough reflex is complex. The specific cause of cough in CVA may be similar to cough mechanisms seen in typical bronchial asthma.

All therapies for typical bronchial asthma have been successful in controlling cough in patients with CVA. The overall prognosis of CVA is excellent, with most patients requiring chronic inhaled corticosteroid therapy.

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Cough, wheeze, and shortness of breath are common symptoms of bronchial asthma. On occasion, cough alone may herald an acute asthma attack in patients with a known history of bronchial asthma. Cough as the sole presenting symptom of bronchial asthma has been described.¹ The initial patients complained of cough but did not wheeze or have shortness of breath. Results of a physical examination and baseline pulmonary function testing were normal. The studies did not demonstrate reversibility, but all the patients demonstrated bronchial hyperreactivity and responded to specific asthma therapy.¹ Patients who meet the above criteria are now considered to have a specific phenotype: cough variant asthma (CVA).

Prospective studies of patients with chronic cough (>8 weeks' duration) demonstrate that, on average, 25% of adults with a chronic cough have CVA. In these studies, all the patients had an isolated chronic cough (usually dry; occasionally minimal sputum), normal baseline pulmonary function test results, positive bronchial inhalation challenge results, and response to specific asthma therapy (β -agonists, leukotriene modifiers,

and corticosteroids). The condition exists less commonly in children.² Laboratory data varied in most studies.³ Sputum eosinophilia, elevated immunoglobulin E levels, and exhaled nitric oxide vary and cannot be used as specific diagnostic tests.^{4–6}

What makes these patients cough is still unknown. Theories include regional bronchoconstriction,⁷ inflammation, upregulated cough receptors' sensitivity, and heightened vagal activity. The cough reflex is complex.⁸ It consists of peripheral receptors, afferent nerves, a "cough center" in the medulla, and efferent nerves. The receptors are found in the upper airway and sinuses, hypopharynx, ears, glottis, trachea, bronchial tree, pleura, esophagus, stomach, and pericardium. They are heavily concentrated in the glottis and in airways >2 mm. Receptors include slowly adapting fibers (C fibers, slowly adapting receptors [SARS]) located in epithelial surfaces and stimulated by bradykinin, serotonin, protons, nicotine, capsaicin (*via* substance P), ozone, and adenosine. These receptors activate ion channels, transient receptor potential vanilloid type 1 and type 4, and transient receptor potential ankyrin type 1, and lead to depolarization of afferent nerves: vagus glossopharyngeal and trigeminal nerves.

Rapidly adapting receptors are located in the larynx, trachea, and extrapulmonary sites. They are mechanically stimulated and sensitive to protons and to hypo- and hypertonic solutions. Given this complex interaction among receptors, ion channels, and afferent nerves, no specific cause of cough has been identified in CVA, and it may be similar to cough mechanisms in typical bronchial asthma. Nonallergic eosinophilic bronchitis (NAEB) is a

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condition less commonly encountered and that mimics CVA.⁹ Patients present with an isolated chronic cough, do not demonstrate airway reversibility, have a negative bronchial inhalation challenge results, and always have sputum eosinophilia or bronchial alveolar lavage eosinophilia. Patients may demonstrate increased sensitivity to capsaicin; these patients respond to corticosteroids, inhaled or oral, but not to other asthma medications; and they demonstrate a persistent need for corticosteroid therapy.

THERAPY

All therapies for typical bronchial asthma have been successful in controlling cough in patients with CVA. In the original publication,¹ oral β -agonists were used and, when stopped, the cough came back. Other studies support the use of oral bronchodilators.¹⁰ Montelukast was studied in 14 patients with CVA in a double-blind placebo-controlled protocol of montelukast versus placebo,¹¹ given over a 4-week period. There was a significant decrease in cough with montelukast versus placebo (70% versus 20%). Inhaled corticosteroids remain the treatment of choice but have not been prospectively studied against other asthma therapies. Oral corticosteroids may be used for exacerbations but are rarely needed chronically.

PROGNOSIS

Overall, the prognosis of CVA is excellent, with most patients requiring chronic inhaled corticosteroid therapy (ICS). There are few prospective studies that looked at the prognosis of CVA. In 42 patients with CVA, treatment of ICS plus long-acting β_2 -agonist (LABA) vs LABA was continued for 12 weeks. Medications were stopped, and the patients were observed for 24 weeks. Sputum eosinophils decreased in the subjects on ICS-LABA. Symptoms increased in both groups when the medications were stopped.¹²

In a 4-year retrospective study of 42 patients with CVA, 20 patients were treated with ICS and 22 patients were treated, in a nonrandomized protocol, with bronchodilators (inhaled β -agonist or long-acting theophylline).¹² Thirteen of the 42 patients developed wheezing; 3 of the 20 patients on ICS therapy developed wheeze, and, of the 20 patients who received ICS, 17 did not develop wheezing.¹³ This retrospective analysis indicates that anti-inflammatory agents protected against the development of typical asthma symptoms.¹³

CONCLUSION

Chronic cough, without wheeze or shortness of breath, commonly presents as a sole manifestation of asthma. Physical examination and pulmonary function tests are often normal. When challenged with cholinergic agents or histamine, patients demonstrate bronchial hyperreactivity. Patients respond to typical bronchial asthma therapy, bronchodilators, or inhaled or oral corticosteroids.

Pearls

- CVA is common in adults, less common in children
- Diagnosis is simple: chronic cough, positive bronchial inhalation challenge result, and response to asthma therapy
- Excellent long-term prognosis

Pitfalls

- If a patient fits the diagnostic criteria yet does not respond to therapy, look for alternative coexisting etiology (upper-airway cough syndrome, gastroesophageal reflux disease, bronchiectasis)
- CVA should not be confused with nonallergic eosinophilic bronchitis (negative bronchial inhalation challenge result)
- Oral prednisone is rarely used chronically but may be needed for an exacerbation
- The exact mechanism of the cough is unknown

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