A Pathogenic Triad in Chronic Cough*

Asthma, Postnasal Drip Syndrome, and Gastroesophageal Reflux Disease

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Background: Coughing may be produced by a number of different disorders in distinct anatomic sites. Chronic cough causes major functional limitation in a considerable patient population and requires careful evaluation.

Methods: Seventy-eight nonsmoking patients of both genders who complained of cough for \( \geq 3 \) weeks and had normal findings on plain chest radiographs were studied prospectively. Their histories were obtained, and physical examinations were performed. The diagnostic workup included pulmonary function tests, CT of the paranasal sinuses and chest, carbachol provocation test, fiberoptic rhinoscopy, fiberoptic bronchoscopy, and 24-h esophageal pH monitoring. The final diagnosis depended on clinical, radiologic, and laboratory findings; a successful response to therapy was required for confirmation.

Results: The causes of chronic cough were determined in all patients. Coughing was due to a single cause in 30 patients (38.5%) and multiple causes in 48 patients (61.5%). The five most important causative factors were asthma (46 patients; 58.9%), postnasal drip syndrome (PNDS; 45 patients; 57.6%), gastroesophageal reflux disease (GERD; 32 patients; 41.1%), bronchiectasis (14 patients; 17.9%), and tracheobronchial collapse (11 patients; 14.1%).

Interpretation: Asthma, PNDS, and GERD, alone or in combination, were responsible for 93.6% of the cases of chronic cough. The presence of these three conditions was so frequent that the expression “pathogenic triad of chronic cough” should be acknowledged in specialized literature. It is essential to consider pulmonary and extrapulmonary causes in order to prescribe a successful specific therapy for chronic cough.

Key words: asthma; chronic cough; gastroesophageal reflux disease; postnasal drip syndrome; sinusitis

Abbreviations: BRO = bronchiectasis; BRONCH = fiberoptic bronchoscopy; CIC = carbachol inhalational challenge; GERD = gastroesophageal reflux disease; HRCT = high-resolution CT; PFTs = spirometry with a pharmacodynamic test; PNDS = postnasal drip syndrome; RHINOS = fiberoptic rhinoscopy; TRCOL = tracheobronchial collapse

The discomfort caused by persistent cough compels a great number of people to seek medical services. Persistent cough is a symptom that can interfere with a person’s sleep, studies, and professional and social activities. It is estimated that approximately 24,263,000 visits to medical services in the United States in 1991 involved chronic cough, the most frequently mentioned illness- or injury-related reason for seeking medical care. The prevalence of chronic cough among the nonsmoking adult population ranges from 14 to 23%. Therefore, we studied 78 patients who complained of chronic cough and had normal findings on chest radiography in order to evaluate the use of an anatomic protocol, based on the location of receptors and afferent cough reflex nerve pathways, for the

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Correspondence to: Bruno Carlos Palombini, MD, PhD, Faculdão Pereira Filho, Santa Casa, Rua Annies Dias, 265, Porto Alegre, RS, 90020–090, Brazil
differential diagnosis of causative factors. This article describes the spectrum and frequency of the causes of chronic cough in the group studied, and it analyzes the results of diagnostic tests used to identify the etiology of chronic cough. The article adds the response to specific therapy as a diagnostic criterion, and ultimately identifies the group of diagnostic methods that are best able to identify the pathogenesis in the vast majority of cases of chronic cough.

**Materials and Methods**

The protocol for this study was approved by the Hospital Ethics Committee, and all patients gave their informed consent. This was a prospective, descriptive study of consecutive, unselected, immunocompetent patients who were referred to our university outpatient clinic for the evaluation of chronic cough. All patients were evaluated using a previously published diagnostic protocol.4–8

**Research Outline**

A cross-section study was performed. Patients were eligible for inclusion if they had a cough for ≥3 weeks, if they were >12 years old, and if they had normal or nearly normal findings on chest radiography. Patients who smoked were excluded.

**Diagnostic Procedures**

The research protocol included the following procedures: present and past medical history; physical examination; plain chest radiography; high-resolution CT (HRCT) of the chest; HRCT of the paranasal sinuses; blood workup; sputum test (bacteriology and cytology); fiberoptic rhinoscopy (RHINOS); skin tests for inhalable antigens; spirometry with a pharmacodynamic test (PFTs [the pharmacodynamic test being a response to fenoterol inhalation]) or carbachol inhalational challenge (CIC); 24-h esophageal pH monitoring; and fiberoptic bronchoscopy (BRONCH). Because the project consisted of a formal protocol aimed at the quantification of the accuracy of several tests, we decided to use all of the tests in each patient.

**Pretreatment Diagnostic Criteria**

Criteria were established according to the literature for the presumptive diagnosis of postnasal drip syndrome (PNDS),4,9,10 asthma,11–13 gastroesophageal reflux disease (GERD),14,15 bronchiectasis (BRO),16,17 and tracheobronchial collapse (TRCOL).18,19 as causes of chronic cough.

PNDS was considered present when the patients described the feeling of having something dripping down their throats or if they mentioned the need to clear their throats often (throat-clearing sign).

Asthma was considered present when the patients presented with the following: episodic wheezing, dyspnea, and/or coughing, and auscultation showed the presence of wheezing; a reversible airflow obstruction demonstrated by pulmonary function tests (diminished FEV1 ≥12% from baseline, and improvement of the obstruction after using the bronchodilator fenoterol, even in the absence of wheezing); or positive results from CIC with normal results from PFTs, and no wheezing. The diagnosis of asthma was not accepted in patients who had presented with an acute respiratory infection in the 2 months preceding the examination.

GERD was considered present when the patients complained of heartburn, burning, and/or a sour taste in the mouth; when barium esophagography demonstrated a reflux of barium to the middle of the esophagus or higher, with or without the previous condition; or when the patients had abnormal esophageal pH even in the absence of GI complaints, with or without one or both of the conditions above.

BRO was considered present when the patients presented with cough and expectoration for a long time (years). Hemoptysis could also be present as an associated symptom, and coughing usually occurred with the change in lateral decubitus, or when the patient assumed the recumbent position. BRO was also diagnosed when an aspect of infiltration along bronchovascular bundles was noted on chest radiography, with or without the previous condition, or when patients demonstrated BRO on chest CT, with or without one or both of the conditions above.

TRCOL was considered present when the patients presented with a nonproductive cough that was difficult to control or relieve, was usually accompanied by suffocation, and did not respond to any treatment tried previously; or when BRONCH revealed expiratory collapse in the trachea and/or main bronchi, at a grade of ≥50% while coughing.

**Posttreatment Diagnostic Criteria**

Treatment was considered successful when the cough was controlled and/or disappeared after treatment. The final diagnosis of the causes of the cough required both fulfillment of the pretreatment criteria and the disappearance of cough after specific treatment.

Treatment of each condition described was administered according to the literature.6,17,20–24

If more than one disorder was involved as the cause of coughing, the effect of therapy on the most prominent clinical condition was observed before another condition was treated. In such cases, the patients were followed for at least 1 year; the last eight patients were followed for 6 months. No patient received nonspecific/symptomatic therapy.

The final diagnosis of the causes of the cough required that the pretreatment criteria be fulfilled and that the cough be stopped after specific treatment. The specific treatment for PNDS depended on its etiology, which was identified based on clinical criteria, otolaryngologic evaluation, sinus HRCT, and/or RHINOS.

Allergic rhinitis was treated mainly with topical beclomethasone and occasionally with a decongestant and antihistamine; when possible, precipitating environmental factors were avoided. Sinusitis was treated with a combination of antibiotics, decongestants, and systemic steroids; in cases refractory to aggressive clinical treatment, the patients underwent endoscopic surgery. Asthma was usually treated with systemic and topical steroids; during coughing episodes, the patients also used bronchodilators. When there was some contraindication to using systemic steroids, only topical beclomethasone was used. GERD was treated with nonpharmacologic measures (bed blocks, weight loss, avoidance of alcohol, chocolate, and caffeine) and with pharmacologic treatments (H2 blockers), which were administered for at least 90 days; H2-blocker therapy could be extended up to 160 days. BRO was treated with antibiotics and respiratory physiotherapy; patients were instructed to continue this treatment after discharge from the hospital. The diagnosis of TRCOL was considered an exception. Measures that did not include aggressive intervention (the use of continuous positive airway pressure) or surgery (airway segment resection, or use of stents internal or external to the airway) were utilized in some cases. The number of patients was too small to allow quantification.
Statistical Analysis

Descriptive statistics were used to analyze the data. Contingency tables were used to evaluate the usefulness of the diagnostic tests. The “gold standard” adopted was a specific therapeutic response during the 12-month follow-up period, once the pre-treatment diagnostic criteria had been fulfilled. The sensitivity, specificity, and positive and negative predictive values of the tests were evaluated. The $\chi^2$ test and Fisher’s Exact Test were applied for the statistical analysis of data. The minimum level of significance adopted was 0.05.

RESULTS

Seventy-eight patients were studied: 27 were male (36%) and 51 were female (64%). The mean ± SD age was 57 ± 16.7 years (range, 15 to 81 years). The mean ± SD history of cough was 72 ± 96.4 months (range, 1 to 480 months). The mean ± SD number of physicians previously seen was 7.4 ± 8.8 per patient. A total of 666 diagnostic tests were performed (mean, 8.5 tests per patient).

A diagnosis was established in all 78 patients. The therapeutic success rate was 93.6%, i.e., 73 of the patients who underwent the proposed treatment achieved resolution or significant improvement of the symptom. The mean ± SD number of times that patients were seen at the clinic or otherwise contacted (over a period of 2 to 480 days) was 2.7 ± 2.3 times, with a mean ± SD of 79.7 ± 92.6 days before a specific diagnosis became definitive based on the treatment response. The time period that was required for a successful treatment of the cough increased with the number of causal factors, with a mean ± SD of 35.2 ± 36.9 days (range, 2 to 120 days) for a single cause; 79.1 ± 75.9 days (range, 2 to 330 days) for two causes; and 141.6 ± 133.7 days (range, 12 to 480 days) for three causes or more.

Of the five patients who continued to cough, three patients had severe TRCOL, one patient had a retrosternal goiter, and one patient had a middle lobe syndrome. Surgery was indicated for all five patients, but it was not performed because they refused to submit to the procedure.

As Table 1 shows, the $\chi^2$ test and Fisher’s Exact Test confirmed an association between the final diagnosis of chronic cough and each test except for spirometry. With the $\chi^2$ test, no association was found between the results of the skin tests, the number of eosinophils in peripheral blood and sputum, and the presence of asthma/rhinitis as a cause of chronic cough ($\chi^2 = 2.54; p > 0.05$).

The causes of chronic cough were determined in all 78 patients (100%). Cough was due to a single cause in 30 patients (38.5%) and to multiple causes in 48 patients (61.5%). The total number of causes identified in the sample was 151. The percentage of cases presenting one, two, three, and four causative factors is shown in Figure 1.

The five most frequent etiologic conditions seen in all patients studied are indicated in Figure 2; these factors account for 96.2% of the cases of chronic cough. Asthma was detected in 46 patients (58.9%), PNDS in 45 patients (57.6%), GERD in 32 patients (41.1%), BRO in 14 patients (17.9%), and TRCOL in 11 patients (14.1%).

One or more components of the three most common factors (asthma, PNDS, and GERD) were found in the 48 patients who presented with multiple causal factors. Twenty-five (83.3%) of the 30 cases having isolated causative factors were also related to components of this triad. Only five patients (16.7%) presented with causes different from those listed in the triad previously mentioned.

Because of the high incidence of association between the three factors, the expression pathogenic triad of chronic cough will be used throughout this article. The participation of pathogenic triad components in the various combinations of causal factors is as follows: 35 patients (44.8%) presented with a single component of the triad, 26 patients (33.3%) had two components, and 12 patients (15.4%) had all three components. Figure 3 illustrates the number of patients who presented with each component of the pathogenic triad of chronic cough.

Therefore, in this series, 93.6% of the patients had at least one of the triad components. In addition, it

<table>
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<tr>
<th>Tests</th>
<th>No.</th>
<th>TP</th>
<th>TN</th>
<th>FP</th>
<th>FN</th>
<th>SENS, %</th>
<th>SPEC, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Sinus CT</td>
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<td>35</td>
<td>19</td>
<td>9</td>
<td>0</td>
<td>100</td>
<td>87</td>
<td>90</td>
<td>100</td>
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<tr>
<td>Rhinoscopy</td>
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<td>35</td>
<td>13</td>
<td>12</td>
<td>3</td>
<td>92</td>
<td>52</td>
<td>75</td>
<td>81</td>
<td>&lt;0.001</td>
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<tr>
<td>PFTs</td>
<td>78</td>
<td>34</td>
<td>26</td>
<td>6</td>
<td>34</td>
<td>26</td>
<td>81</td>
<td>66</td>
<td>43</td>
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<tr>
<td>CIC</td>
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<td>34</td>
<td>18</td>
<td>5</td>
<td>0</td>
<td>100</td>
<td>78</td>
<td>87</td>
<td>100</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chest CT</td>
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<td>15</td>
<td>46</td>
<td>3</td>
<td>0</td>
<td>100</td>
<td>94</td>
<td>93</td>
<td>100</td>
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<td>Esoph pH</td>
<td>70</td>
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<td>32</td>
<td>6</td>
<td>0</td>
<td>100</td>
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<td>&lt;0.001</td>
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*Esoph pH = 24-h esophageal pH monitoring; TP = true positive; TN = true negative; FP = false positive; FN = false negative; SENS = sensitivity; SPEC = specificity; PPV = positive predictive value; NPV = negative predictive value.
can be stated within a 95% confidence interval that among the patients with chronic cough at least 89.02% are expected to present with at least one of the three components.

**DISCUSSION**

Several published studies of the differential diagnosis of chronic cough have employed similar protocols. These studies included chest radiography, sinus radiography, pulmonary function tests, methacholine inhalational challenge, biochemical laboratory tests, BRONCH, and esophageal pH monitoring. In the present study, we added RHINOS, sinus HRCT, and chest HRCT. We believe that RHINOS should be included routinely, as recent articles in the literature have quoted the presence of postnasal secretion as the most prevalent pathogenic factor of chronic cough. Sinus HRCT was included because of the discrepancy observed between the findings of sinus HRCT and sinus radiography. We included chest HRCT primarily to detect BRO.

The mean of 8.5 diagnostic tests per patient is higher than the mean number of tests performed in other studies. The therapeutic success rate of 93.6% is similar to that cited in other publications, which show a therapeutic success rate variation of 86 to 98%. The mean duration of cough was 72 months, with a broad range of durations, which is greater than the mean duration mentioned in other studies, with a per-patient mean of 7.4 physicians seen previously.

It is important to stress that the objective of the present study was not to analyze treatment effectiveness, but rather to identify the causes of chronic cough. Although the basic diagnostic criteria for diseases include objective findings, we considered the specific therapeutic response during follow-up to be part of the final diagnosis. We also employed the subjective analysis given by the patient, as have other authors.

The most common single causes of chronic cough were PNDS, GERD, and asthma. This finding is in accordance with other published studies, as illustrated in Figure 4. In 1981, Irwin et al looked for the causes of chronic cough in their patients and concluded that cough was due to PNDS in 29% of the cases, to asthma in 25% of cases, and to GERD in 10% of cases. In 1990, Poe and Israel reported the following causes: asthma, 33% of cases; PNDS, 28%; “postinfectious syndrome,” 11%; and GERD, 6%. In a 1990 study, Irwin et al found PNDS in 41% of cases; asthma, 24%; and GERD, 21%. A previously reported study of ours showed PNDS in 33.3% of cases; GERD, 26.7%; and asthma, 23.3%. From these four studies, a clinical profile emerged that predicted when PNDS, asthma, and/or GERD was the cause of chronic cough. In the vast majority...
of cases, these three conditions were responsible for chronic cough in nonsmoking patients who were not taking angiotensin-converting enzyme inhibitors and had normal findings on chest radiography.

Additionally, it is important to stress the identification of 14 patients with BRO (17.9%) and 11 patients with TRCOL (14.1%). Radiologically hidden cases of BRO have been described in the literature.32,33 In 1990, Irwin et al6 identified BRO as a cause of persistent cough in 4% of cases. TRCOL should be considered in patients with chronic cough and/or asthma that is refractory to broad medical treatment. BRONCH is the direct method most often used to confirm the diagnosis of TRCOL.18

The frequent association among the components of the pathogenic triad of the chronic cough are worthy of special consideration. In 1981, Irwin et al4 published a study in which the association between PNDS and asthma was detected in 18% of cases. In their second study in 1990,6 a multicausal pathogenesis was identified in 26% of patients studied. In 1993, Pratter et al7 described factors of multiple association in 29% of a series of 45 patients studied. If the results of the clinical evaluation suggest more than one diagnosis, or if treatment of a single cause fails, all possibilities should be investigated. Unless all causes are treated, the cough will continue, as usually happened in our patients when they were treated only for cough due to asthma.34 In the studies mentioned, the most common combinations of diagnoses were PNDS and asthma; PNDS and GERD; asthma and GERD; and PNDS, asthma, and GERD.

Considering these findings, we reviewed the literature for several possible mechanisms that might explain these interactions. Among the mechanisms by which sinus disease may induce or exacerbate diseases of the lower respiratory tract are aspiration of purulent material21,35 or reflex bronchoconstriction.22,36

Some accounts27-34 have stated that the act of coughing can make asthma worse, so the cough caused by PNDS and GERD could maintain or exacerbate cough due to asthma. Such associations help explain the pathogenesis of either bronchoconstriction or coughing, since the primary causative factors, as well as the receptors and the afferent pathways and their hypothetical function, are mostly the same.24

With regard to the pathogenesis of chronic cough from GERD, two theories have been presented to explain this possible relationship: (1) microaspiration to the airways (the reflux theory)38,39; and (2) acid reflux to the distal esophagus (the reflex theory).40,41 It can be speculated that GERD might make PNDS worse by a vagal reflex mechanism.42

Our results indicate that at least 89.0% of patients with chronic cough may be expected to have at least one of the triad components; other data from the medical literature support these findings, and the presence of at least one of the triad components varies from 72 to 100%.6,7,25,43 For this reason, we suggest using the term pathogenic triad of chronic cough to stress this association.

CONCLUSION

Several conclusions regarding the study of chronic cough appear to be important based on our findings.

The concept of an anatomic protocol focused on evaluating the location of receptors and afferent pathways of coughing is still valid. The five most important causal factors of chronic cough were asthma, PNDS, GERD, BRO, and TRCOL. These conditions were responsible for 96.2% of cases of chronic cough. Single causes of coughing were present in 38.5% of cases in the series, and we were surprised by the phenomenon of multicausality found in 61.5% of our sample.31 The presence of asthma, PNDS, GERD, and the interactions among these conditions were so frequent that we suggest the introduction in literature of the recognition of the expression pathogenic triad of chronic cough. The three diagnostic tests used to diagnose the component factors of the pathogenic triad of chronic cough were sinus HRCT, CIC, and esophageal pH monitoring. It should be stressed that several additional tests were important in detecting other relatively frequent factors: chest HRCT to diagnose BRO, and BRONCH to detect TRCOL.

We wish to stress that our protocol to evaluate chronic cough may not be the most cost-effective one, and that this is an important issue that will need to be addressed in the future. It remains to be determined how to best evaluate cost-effectiveness in managing patients with chronic cough. As stated in the recently...
published, evidence-based Cough Consensus Panel Report of the American College of Chest Physicians,44 "since the committee was not aware of any studies that specifically addressed the role of empiric therapy as a diagnostic aid or any cost analyses that related to different ways of managing cough, no specific sections in this document deal with these issues."

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