

Chronic cough and irritable larynx

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Background: Perennial rhinitis (PR), chronic rhinosinusitis (CRS), or both, asthma, and gastroesophageal reflux disease (GERD) are the most frequent triggers of chronic cough (CC). Extrathoracic airway receptors might be involved in all 3 conditions because asthma is often associated with PR/CRS and gastroesophageal refluxate might reach the upper airway. We previously found that most patients with rhinosinusitis, postnasal drip, and pharyngolaryngitis show laryngeal hyperresponsiveness (LHR; ie, vocal cord adduction on histamine challenge) that is consistent with an irritable larynx. **Objective:** We sought to evaluate the role of LHR in patients with CC.

Methods: LHR and bronchial hyperresponsiveness (BHR) to histamine were assessed in 372 patients with CC and in 52 asthmatic control subjects without cough (asthma/CC−). In 172 patients the challenge was repeated after treatment for the underlying cause of cough.

Results: The primary trigger of CC was PR/CRS in 208 (56%) patients, asthma in 41 (11%) patients (asthma/CC+), GERD in 62 (17%) patients, and unexplained chronic cough (UNEX) in 61 (16%) patients. LHR prevalence was 76% in patients with PR/CRS, 77% in patients with GERD, 66% in patients with UNEX, 93% in asthma/CC+ patients, and 11% in asthma/CC− patients. Upper airway disease was found in most (95%) asthma/CC+ patients and in 6% of asthma/CC− patients. BHR discriminated asthmatic patients and atopy discriminated patients with PR/CRS from patients with GERD and UNEX. Absence of LHR discriminated asthmatic patients without cough. After treatment, LHR resolved in 63% of the patients and improved in 11%, and BHR resolved in 57% and improved in 18%.

Conclusions: An irritable larynx is common in patients with CC and indicates upper airway involvement, whether from rhinitis/sinusitis, gastric reflux, or idiopathic sensory neuropathy. (J Allergy Clin Immunol 2010;■■■:■■■-■■■.)

Key words: Chronic cough, asthma, rhinosinusitis, laryngeal hyperresponsiveness, irritable larynx

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Abbreviations used

BHR:	Bronchial hyperresponsiveness
CC:	Chronic cough
CRS:	Chronic rhinosinusitis
CVA:	Cough-variant asthma
F _{ENO} :	Fraction of exhaled nitric oxide
GERD:	Gastroesophageal reflux disease
ICS:	Inhaled corticosteroid
LHR:	Laryngeal hyperresponsiveness
MIF ₅₀ :	Maximum midinspiratory airflow rate
PC ₂₀ FEV ₁ :	Histamine concentration provoking a 20% decrease in FEV ₁
PC ₂₅ MIF ₅₀ :	Histamine concentration provoking a 25% decrease in MIF ₅₀
PPI:	Proton pump inhibitor
PR:	Perennial rhinitis
ROC:	Receiver operating characteristic
UNEX:	Unexplained chronic cough

All the recent guidelines^{1,2} agree that upper airway diseases,³ asthma, and gastroesophageal reflux disease (GERD) are the most common triggers of chronic cough (CC). It is presumed that in patients with upper airway diseases, such as rhinitis and sinusitis, cough originates in pharyngolaryngeal receptors stimulated by the postnasal drip of inflammatory material or made hypersensitive by mucosal inflammation and damage.³ In asthmatic patients cough likely originates from stimulation of intrathoracic airway receptors, and in patients with GERD, it likely originates from stimulation of esophageal receptors. However, an involvement of upper airway receptors is a possibility in both asthmatic patients because rhinitis, sinusitis, or both are common comorbidities⁴ and in patients with GERD because the refluxate often reaches the larynx and might go up to the rhinopharynx. Moreover, in asthmatic patients no clear relationship has been demonstrated between cough-receptor sensitivity and bronchial responsiveness,⁵ and persistence of cough has been reported, even after achieving good asthma control with inhaled corticosteroids (ICSs).⁶

In the upper airway there are many sensory nerve receptors⁷ that are central to protecting the lungs from exogenous noxious agents. An important defensive reflex is the laryngeal chemoreflex, which in the newborn consists of vocal cord adduction and apnea aimed at preventing the aspiration of liquids,⁸ whereas in the adult it consists of cough and airway constriction. The nociceptive nerve endings involved in these reflexes are unmyelinated, unencapsulated C-fibers and myelinated Aδ-fibers,⁹ which lay beneath and between the mucosal epithelial cells of the epiglottis, aryepiglottic folds, and interarytenoid space.

TABLE I. Baseline characteristics of the 4 classes of patients with CC and of asthmatic control subjects without cough

	PR/CRS	GERD	UNEX	Asthma/CC+	Asthma/CC–
No.	208	62	61	41	52
Age (y)	36.8 (34.9–38.6)	40.9 (37.4–44.4)	40.8 (37.3–44.3)	40.8 (36.3–45.4)	36.9 (33.2–40.6)
Women, no. (%)	109 (52)	46 (74)	47 (77)	30 (73)	31 (59)
Smokers, no. (%)	51 (24)	16 (26)	12 (20)	9 (22)	11 (21)
Atopy, no. (%)	129 (62)	3 (5)	7 (11)	29 (71)	35 (67)
Cough VAS (mm)	3.35 (3.19–3.51)	3.53 (3.24–3.83)	3.51 (3.20–3.82)	3.84 (3.48–4.19)	1.14 (1.04–1.24)
PND, no. (%)	157 (75)	40 (54)	7 (11)	29 (71)	0 (0)
Pharyngitis, no. (%)	109 (52)	51 (82)	37 (61)	27 (66)	6 (11)
FEV ₁ % predicted	102.8 (101.1–104.4)	103.9 (101.1–106.7)	102.9 (99.2–106.6)	98.1 (94.9–101.4)	98.9 (95.6–102.4)
MEF ₅₀ /MIF ₅₀	0.91 (0.87–0.95)	0.99 (0.91–1.08)	1.06 (0.93–1.18)	0.93 (0.78–1.08)	0.83 (0.71–0.95)
BHR, no. (%)	68 (33)	10 (16)	15 (25)	41 (100)	52 (100)
LHR, no. (%)	160 (77)	48 (77)	40 (66)	38 (93)	6 (11)
PC ₂₀ FEV ₁ log (mg/mL)	1.11 (1.05–1.17)	1.31 (1.22–1.39)	1.22 (1.11–1.33)	0.45 (0.35–0.56)	0.54 (0.42–0.66)
PC ₂₅ MIF ₅₀ log (mg/mL)	0.64 (0.56–0.71)	0.75 (0.64–0.86)	0.78 (0.65–0.91)	0.34 (0.19–0.49)	1.30 (1.21–1.40)
F _{ENO} (ppb)	25.9 (19.8–32.1)	12.4 (7.2–17.5)	13.5 (9.9–17.1)	49.2 (34.6–63.7)	45.6 (28.3–62.7)

Continuous values are expressed as means and 95% CIs, where shown.

MEF₅₀, Forced midexpiratory flow; PND, post nasal drip; VAS, visual analog scale.

Stimulation of these receptors triggers a nerve impulse carried in the superior laryngeal nerve followed by an efferent impulse in the recurrent laryngeal nerve leading to vocal cord adduction.¹⁰ This reflex is heightened by laryngeal inflammation, viral infection, and frequent stimulation from acidic or other solutions.^{7,9} We previously found¹¹ that most patients with upper airway inflammatory disorders and cough have laryngeal hyperresponsiveness (LHR), which is a paradoxical inspiratory vocal cord adduction on histamine inhalation challenge that is consistent with an irritable larynx. Such reflex laryngoconstriction was reflected by a decrease in inspiratory airflow rates, particularly the maximum midinspiratory airflow rate (MIF₅₀).¹¹ Using MIF₅₀ as the marker of an irritable larynx, we subsequently found that LHR was very common in nonasthmatic patients with CC and inflammatory diseases of the upper airway,¹² particularly in those with acute exacerbation of chronic sinusitis.¹³ In such patients laryngeal dysfunction reversed after treatment with intranasal corticosteroids and appeared to be sustained by damage of the rhinopharyngeal epithelium.¹⁴

Based on these findings, we wondered whether the assessment of laryngeal responsiveness as a marker of an irritable larynx might help in evaluating the role of upper airway receptors in the pathogenesis of CC, particularly in cases in which both upper and lower airway receptors might be involved, as in asthma and GERD. We reasoned that the presence of LHR, irrespective of whether it is associated with bronchial hyperresponsiveness (BHR), would provide useful information for optimizing cough treatment.

We thus assessed laryngeal and bronchial responsiveness to histamine inhalation challenge in addition to cough diagnostic workup in consecutive patients presenting for undiagnosed CC and normal spirometry. Asthmatic patients without cough served as control subjects.

METHODS

All the consecutive patients who presented with CC as their main symptom in the period between January 2002 and June 2008 and had normal spirometric and chest radiographic results were enrolled in the study. The exclusion criteria were as follows: severe systemic illnesses; known bronchopulmonary diseases; acute respiratory tract infections in the last 2 months; treatment with

H₁- and H₂-antihistaminic, antitussive drugs, bronchodilators, oral corticosteroids, or ICSs in the last month, and current treatment with angiotensin-converting enzyme inhibitors and β -blockers. A total of 372 patients were enrolled in the study. Fifty-two steroid-naïve patients with mild persistent asthma and normal spirometric results receiving diagnoses in the same period who did not complain of cough (asthma/CC– patients) served as control subjects.

The study was approved by the ethics committee of Piemonte Region. All patients provided informed consent for the use of their data.

Study protocol

All patients underwent history and symptoms recording, physical examination, measurement of specific IgE levels for common aeroallergens, spirometry, and histamine inhalation challenge. Cough severity in the last month was rated by each patient on a 5-point visual analog scale, with 0 being no cough and 5 being the worst cough ever. Fraction of exhaled nitric oxide (F_{ENO})^{15,16} values were measured beginning from 2006, when the online nitric oxide analyzer was available (see below).

Based on clinical data, the following conditions were diagnosed.

First was persistent rhinitis diagnosed according to the Allergic Rhinitis and Its Impact on Asthma guidelines,¹⁷ with or without increased IgE for a perennial aeroallergen.

Second was chronic rhinosinusitis (CRS),^{17,18} defined by a more than 12-week history of 2 or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior, posterior, or both) with or without facial pain/pressure/fullness and reduction or loss of sense of smell. Patients with such symptoms were referred for nasal endoscopy and for computed tomographic scans to confirm paranasal sinus disease.

Third was GERD, which was diagnosed as a primary cause of cough in nonasthmatic patients without PR and CRS who complained of typical symptoms, such as heartburn and regurgitation, and had positive results on ambulatory 24-hour esophageal pH monitoring.¹⁹ The monitoring was performed with a dual-channel antimony pH catheter connected to an ambulatory recorder Mark III Digitrapper (Synectics Medical, Inc, Chicago, Ill). All the patients were examined by a single experienced otorhinolaryngologist blinded to the results of pH monitoring. GERD-related laryngitis was diagnosed when at least 2 symptoms of hoarseness, globus pharyngeus, dysphagia, throat clearing, or soreness were combined with endoscopic evidence of at least 2 of the following: subglottic edema, posterior laryngitis, or laryngeal diffuse edema or hyperemia.²⁰

Fourth was unexplained cough,²¹ which was diagnosed when no trigger for cough could be demonstrated.

Finally was mild persistent asthma,²² which was diagnosed in patients with normal spirometric results and BHR associated with 1 or more of the following

TABLE II. Results of multinomial logistic regression, with PR/CRS as the comparison class, expressed as odds ratios and 95% limits

Class	OR	Lower limit	Upper limit	P value
GERD				
Atopy	0.03	0.01	0.10	<.0001
BHR	0.39	0.17	0.89	.024
LHR	1.16	0.53	2.53	.705
UNEX				
Atopy	0.06	0.03	0.16	<.0001
BHR	0.77	0.37	1.62	.488
LHR	0.61	0.30	1.27	.188
Asthma/CC+				
Atopy	1.42	0.63	3.22	.392
BHR	80.64	10.59	614.00	<.0001
LHR	1.09	0.27	4.44	.900
Asthma/CC−				
Atopy	1.15	0.39	3.39	.797
BHR	132.95	32.46	544.57	<.0001
LHR	0.01	0.00	0.03	<.0001

symptoms: wheezing, accessional dyspnea, and chest tightness. BHR was diagnosed with histamine challenge when the histamine concentration causing a 20% decrease in FEV₁ was 8 mg/mL or less.²³

Based on these diagnostic criteria, each patient was allocated to one of the following classes: perennial rhinitis (PR)/CRS, GERD, asthma with cough (asthma/CC+ patients), and unexplained chronic cough (UNEX). Patients with asthma (ie, BHR and symptoms) who were not troubled by cough in the last 8 weeks (cough visual analog scale score <2; asthma/CC− patients) served as control subjects.

Lung function tests. Lung volumes and flow-volume loops were measured by using the computerized spirometer BAIRES (Biomedin, Padova, Italy). Forced vital capacity, FEV₁, forced midexpiratory flow, and MIF₅₀ were calculated from the best of 5 reproducible curves. Reference values were obtained from European Respiratory Society guidelines.²⁴

Histamine challenge. Histamine challenge was performed to assess bronchial and laryngeal thresholds, as previously described.¹² Histamine was delivered in doubling concentrations, starting from 0.5 mg/mL up to 32 mg/mL by using a compressed air nebulizer controlled by a breath-actuated dosimeter (MEFAR MB3; Markos, Monza, Italy). Each concentration was inhaled by taking 5 slow vital capacity breaths from the nebulizer. After each set of inhalations, FEV₁ and flow-volume loops were recorded, and the best of 3 trials was selected. MIF₅₀ was used as the index of laryngeal narrowing because we previously found that it reflects the decrease in cross-sectional glottic area during histamine challenge.¹¹ The challenge was stopped when a 20% FEV₁ decrease was obtained or the highest histamine concentration was reached. The histamine concentration provoking a 20% decrease in FEV₁ was the bronchial threshold (PC₂₀FEV₁) and that provoking a 25% decrease in MIF₅₀ was the laryngeal threshold (PC₂₅MIF₅₀). BHR and LHR were defined when the thresholds were equal or less than the 8 mg/mL histamine concentration.

F_{ENO} measurement. F_{ENO} values were measured according to American Thoracic Society/European Respiratory Society recommendations²⁵ by using a nitric oxide chemiluminescent analyzer (Sievers NOA 280; Sievers, Boulder, Colo) with a sampling flow rate of 50 mL/s. F_{ENO} values were calculated on an end-expiration plateau sustained for at least 3 seconds. The mean value of 3 consecutive acceptable trials was computed.

Treatment

Cough severity and airway responsiveness were reassessed after treatment of the disorder deemed to be the primary trigger of the cough by using the following protocols:

- Patients with PR were reassessed after 1 month's treatment with a second-generation H₁-antihistamine drug.¹⁷
- Patients with CRS were reassessed after 1 month's therapy with nasal saline irrigation and 25 µg per nostril of intranasal fluticasone or equivalent

TABLE III. Classification of patients within any class: Observed versus predicted by means of multinomial logistic regression analysis based on atopy, BHR, and LHR

Observed	Predicted					Correct percentage
	PR/CRS	GERD	UNEX	Asthma/CC+	Asthma/CC−	
PR/CRS	188	0	16	0	4	90.4
GERD	49	0	12	0	1	0
UNEX	42	0	16	0	3	26.2
Asthma/CC+	39	0	0	0	2	0
Asthma/CC−	7	0	1	0	44	84.6
Overall	76.7	0	10.6	0	12.7	58.5
predicted percentage						

The rows are the predicted and the columns are the observed numbers of subjects in each class. Any given observation was assigned to the group having the highest probability computed by means of linear combination of parameters (see the Methods section). For multinomial logistic regression, the predicted class is the one with a probability higher than the ratio 100/number of classes. In a perfect model all the cases should be on the diagonal, and the overall correct percentage should be 100%.

administered twice daily.¹⁸ Acute exacerbations, which were observed in 18 patients, were treated with a 2-week course of amoxicillin-clavulanate (clarithromycin in 2 cases of penicillin allergy).²⁶

- Patients with GERD were reassessed after 3 months' treatment with 40 mg/d of the proton pump inhibitor (PPI) omeprazole.¹⁹
- Patients with UNEX were reassessed after a month-long empiric trial of an H₁-antihistamine plus 40 mg/d omeprazole.^{1,2}

In patients who received H₁-antihistamines, the histamine challenge was scheduled for 1 week after drug withdrawal.

Statistical analysis

Statistical analysis was performed with the STATA10 package (StataCorp, College Station, Tex).^{27,28}

Mean values of lung function tests, histamine thresholds, and F_{ENO} values were calculated for patients in each of the 4 CC classes (ie, PR/CRS, GERD, UNEX, and asthma/CC+) and for asthma/CC− control subjects and compared by using ANOVA.

Multinomial logistic analysis, also known as polytomous logistic regression, with the "mlogit" procedure was used to assess in which observed diagnostic category the predicted diagnoses were classified. Class (PR/CRS, GERD, UNEX, asthma/CC+, and asthma/CC−) was used as the dependent variable, with atopy, LHR, and BHR as the predictive variables. F_{ENO} values were excluded from the analysis because they were available in only 120 patients. PR/CRS was used as the reference class for statistical analysis because rhinitis and sinusitis are recognized to be the most common triggers of CC.^{1,2}

The predicted probability of being in a particular class was computed by using the following formula:

$$P_{ij} = \frac{e^{\sum_{k=1}^K \alpha + \beta_{kj} X_{kji}}}{\sum_{j=1}^J \frac{e^{\sum_{k=1}^K \alpha + \beta_{kj} X_{kji}}}{e^{\sum_{k=1}^K \alpha + \beta_{kj} X_{kji}}}},$$

where i is defined as cases, j is defined as category, and k is defined as independent variables.

Classification tables were computed by using a linear combination of parameters across categories as the $n \times n$ tables for multinomial logistic regression, which tally correct and incorrect estimates, to assess the validity of each test or test combination to distinguish one class from the others. The cutoff of 0.5 was used as the positive outcome threshold. The predicted diagnostic class was compared with the observed class as the reference category in terms of sensitivity and specificity.

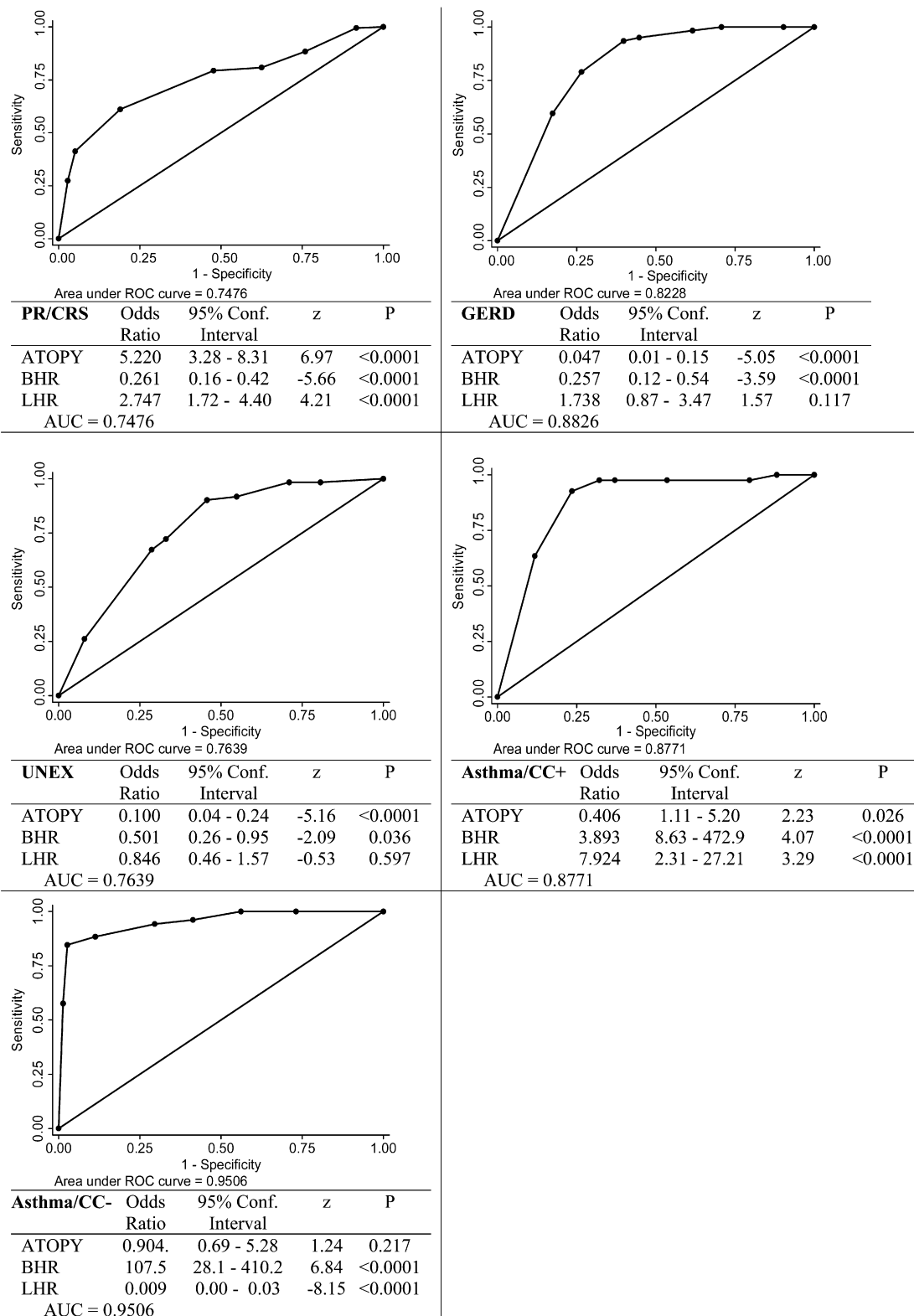


FIG 1. Receiver operating characteristic (ROC) curves plotting the true-positive rate (sensitivity) in function of the false-positive rate (100-specificity) for different cutoff points of a parameter. The area under the ROC curve (AUC) measures how well a parameter can distinguish between diagnostic classes. In the asthma/CC+ class an AUC of 0.87 means that a randomly selected subject from this class has a test value larger than that for a randomly chosen subject from another class 87% of the time.

Receiver operating characteristic (ROC) curves were plotted to evaluate the validity in terms of combined sensitivity and specificity of the tests used to discriminate each class from the others. The area under the curve, which summarizes this measure, was computed for each class.

The main characteristics of the examined subjects were compared within diagnostic classes by means of 1-way ANOVA. The effects of treatment were assessed by means of generalized random intercept model analysis with subject as panel indicators and assuming treatment (nested within diagnostic class) as a within-subject fixed effect. The estimated means were compared within diagnostic classes and between pre-post treatment with the least significance difference method to correct the significance level for multiple comparisons, when indicated. For each test, a *P* value of less than .05 was deemed significant.

RESULTS

According to the diagnostic criteria, the distribution of the 372 patients within each class was as follows: PR/CRS, 208 (56%) patients, 123 with PR and 85 with CRS; GERD, 62 (17%) patients, 51 with laryngeal involvement; UNEX, 61 (16%) patients; and asthma/CC+, 41 (11%) patients, 39 (95%) with persistent rhinitis, sinusitis, or both.

The general characteristics of the patients in the 4 CC classes and of the 52 asthma/CC− control subjects are compared in Table I. The most significant differences were that patients with PR/CRS and asthma/CC− patients had lower mean age and lower prevalence of female sex and that asthmatic patients, with or without cough, had the lowest PC₂₀FEV₁ and the highest F_{ENO} values. LHR was present in most patients with CC, irrespective of the cause, but was uncommon in asthmatic control subjects without cough. Among patients with GERD, LHR was found in 48 (94%) of the 51 patients with evidence of laryngitis and in none of the 11 patients without laryngeal involvement.

The results of multinomial logistic regression analysis with PR/CRS as the reference class are reported in Table II in terms of odds ratios. The GERD class was characterized by low risk of having atopy and BHR, the UNEX class by low risk of atopy, and both the asthma/CC+ and asthma/CC− classes by increased risk of BHR. The asthma/CC− control class was characterized by low risk of LHR.

The analysis of the agreement between predicted and observed classification of patients within each class is shown in Table III. The agreement was good only for the PR/CRS and asthma/CC− classes and was very poor for all other classes. Actually, most patients with UNEX, patients with GERD, and asthma/CC+ patients were reclassified into the PR/CRS class.

Fig 1 reports the ROC curves for each class computed by using the variables that best distinguished one class from the others (ie, atopy, BHR, and LHR). The highest area under the ROC curve was found in both the asthmatic classes with and without cough, whereas the lowest area under the ROC curve was found in the PR/CRS class.

Effect of treatment

The asthma/CC+ class was excluded from the analysis because almost all these patients had rhinitis, sinusitis, or both so that the treatment for asthma with ICSs could not be separated from that for PR/CRS. The 172 nonasthmatic patients examined after treatment were 111 with PR/CRS (55 with PR and 56 with CRS), 14 with GERD, and 47 with UNEX. As shown in Table IV, the baseline characteristics of the patients who completed follow-up were similar to those of the overall patients reported in Table I.

TABLE IV. Comparison among baseline data of the 3 groups of patients examined after treatment

Variable	PR/CRS	GERD	UNEX
No.	111	14	47
Age (y)	37.5 (35.0-40.0)	55.1 (48.8-61.5)	40.0 (36.1-43.7)
Women (%)	54.1 (44.8-63.1)	64.3 (37.6-84.3)	80.9 (67.1-89.7)
Smokers (%)	28.8 (21.2-37.9)	7.1 (1.0-37.0)	21.3 (11.8-35.2)
Atopy (%)	58.6 (49.2-67.3)	14.3 (3.6-42.7)	8.5 (3.2-20.6)
PND (%)	79.3 (70.7-85.8)	64.3 (37.6-84.3)	4.3 (1.1-15.5)
Cough VAS	3.78 (3.61-3.95)	4.21 (3.70-4.73)	3.83 (3.55-4.11)
FEV ₁ predicted	101.9 (99.5-104.3)	99.4 (82.0-116.7)	103.2 (96.9-109.5)
MEF ₅₀ /MIF ₅₀	0.91 (0.85-0.97)	0.93 (0.74-1.12)	1.12 (1.00-1.23)
PC ₂₀ FEV ₁ log (mg/mL)	0.96 (0.86-1.05)	1.37 (1.21-1.53)	1.28 (1.17-1.39)
PC ₂₅ MIF ₅₀ log (mg/mL)	0.44 (0.35-0.54)	0.64 (0.35-0.93)	0.75 (0.59-0.90)
BHR (%)	43.2 (34.9-53.5)	7.1 (1.1-47.2)	14.9 (7.5-29.5)
LHR (%)	89.2 (81.9-93.8)	78.6 (50.6-92.9)	68.1 (53.6-79.8)

Values are expressed as means and 95% CIs, where shown.

MEF₅₀, Forced midexpiratory flow; PND, post nasal drip; VAS, visual analog scale.

After treatment, laryngeal and bronchial thresholds were significantly improved in all the classes, particularly in the PR/CRS class (Table V). Cough was improved or resolved in 105 (95%) of the patients with PR/CRS, in 11 (79%) of the patients with GERD, and in only 18 (36%) of the patients with UNEX.

BHR reversed with the sole treatment of PR/CRS or GERD but without ICSs in 32 (57%) of the 56 patients with pretreatment BHR. Of the 24 patients with persistent BHR, 2 were lost to follow-up, and 22 (18 with PR/CRS and 4 with UNEX) were considered to have asthma and were examined after 1 month's treatment with ICSs.¹⁶ ICS treatment (Table VI) produced a significant improvement of cough and of both bronchial and laryngeal thresholds, so that only 2 patients had persistent BHR and LHR.

DISCUSSION

The results of this study indicate that an irritable larynx is very common among patients who present with CC as the main symptom. In fact, most of the 372 patients with CC examined showed LHR, consisting of a dose-dependent decrease in inspiratory flows during histamine challenge. In 164 (44%) patients LHR was the only functional abnormality and would have been missed by recording FEV₁ as the response variable.

In agreement with the literature,^{1,2,29} the most common triggers of CC were persistent rhinitis and chronic sinusitis, which were found in 56% of the patients, followed by GERD, which was found in 17%. Asthma-associated cough had a rather low prevalence (11%), and this was probably due to the selection of patients with cough as the main presenting symptom and with normal lung function test results.

The prevalence of irritable larynx was high in all the cough classes, so that data analysis failed to demonstrate a discriminating capacity of LHR for any trigger of cough (Table II). We were surprised by this finding because based on our prior observations,¹¹⁻¹⁴ we expected to find that LHR was a characteristic of rhinosinusitis. The reason for such a low specificity of LHR for patients with PR/CRS was probably the high prevalence of upper airway disorders in all the other cough classes. In fact, rhinitis, sinusitis, or both, as well as LHR, were found in almost all the asthmatic patients with cough and were uncommon in asthmatic patients without cough. Because BHR together with wheeze,

TABLE V. Effect of treatment within each class

	PR/CRS (n = 111)			GERD (n = 14)			UNEX (n = 47)		
	Before	After	P value	Before	After	P value	Before	After	P value
Cough VAS	3.78 (3.61-3.95)	1.73 (1.57-1.88)	<.0001	4.21 (3.76-4.66)	2.14 (1.62- 2.66)	<.0001	3.83 (3.56-4.10)	3.51 (3.18- 3.84)	.001
FEV ₁ (L)	3.39 (3.22-3.55)	3.41 (3.26-3.58)	NS	3.03 (2.59-3.47)	3.01 (2.56-3.46)	NS	3.19 (2.96-3.41)	3.17 (2.95-3.40)	NS
MEF ₅₀ (L/s)	4.40 (4.13-4.67)	4.56 (4.30-4.82)	.002	4.06 (3.58-4.54)	4.22 (3.75-4.69)	NS	4.15 (3.84-4.46)	4.10 (3.65-4.56)	NS
MIF ₅₀ (L/s)	5.16 (4.85-5.48)	5.51 (5.20-5.83)	<.0001	4.75 (3.95-5.55)	5.18 (4.22-6.15)	NS	4.55 (4.10-5.00)	4.52 (4.06-4.99)	NS
PC ₂₀ FEV ₁ log (mg/mL)	0.96 (0.87-1.05)	1.23 (1.16-1.30)	<.0001	1.37 (1.23-1.51)	1.50 (1.41-1.59)	<.0001	1.28 (1.18-1.39)	1.31 (1.21-1.41)	NS
PC ₂₅ MIF ₅₀ log (mg/mL)	0.44 (0.35-0.54)	1.19 (1.12-1.26)	<.0001	0.64 (0.39-0.89)	1.27 (1.08-1.47)	<.0001	0.75 (0.60-0.89)	0.81 (0.68-0.94)	NS
BHR, % (no.)	43 (48)	17 (19)	<.0001	7 (1)	0 (0)	NS	15 (7)	11 (5)	NS
LHR, % (no.)	89 (99)	19 (21)	<.0001	79 (11)	21 (3)	.01	68 (32)	62 (29)	NS

Values are expressed as means and 95% CIs, where shown. Note: Patients with UNEX were empirically treated with an H₁-antihistamine plus omeprazole.^{1,2}
MEF₅₀, Forced midexpiratory flow; VAS, Visual analog scale.

TABLE VI. Effect of adding ICSs in the 22 patients with persistent cough and BHR after treatment of the underlying cause of cough

	(A) Baseline	(B) After cough treatment	P value, A vs B	(C) After ICSs treatment	P value, B vs C	P value, overall
Cough VAS	3.50 (3.14 to 3.86)	2.82 (2.46 to 3.18)	<.05	1.32 (0.96 to 1.68)	<.05	<.01
PC ₂₀ FEV ₁ log (mg/mL)	0.30 (0.18 to 0.42)	0.56 (0.44 to 0.68)	<.05	1.07 (0.95 to 1.19)	<.01	<.01
PC ₂₅ MIF ₅₀ log (mg/mL)	-0.01 (-0.18 to 0.16)	0.65 (0.48 to 0.81)	<.01	1.10 (0.94 to 1.27)	<.05	<.01
BHR, % (no.)	100 (22)	100 (22)	NS	9 (2; 2.4 to 34.0)	<.05	<.05
LHR, % (no.)	100 (22)	73 (16; 56.3 to 93.4)	<.05	9 (2; 2.4 to 34.1)	<.01	<.01

Values are expressed as means and 95% CIs, where shown.
VAS, Visual analog scale.

dyspnea, and chest tightness were the prerequisites for asthma diagnosis, these findings suggest that, at least in patients with mild asthma, the trigger of CC is coexistent upper airway disease rather than bronchial disease. As a support to this hypothesis, asthmatic patients without cough were discriminated by the absence of LHR and upper airway disease (Table II).

Upper airway disease was common also in the GERD class, as documented by the high prevalence of pharyngolaryngeal symptoms, with endoscopic evidence of laryngitis (82%) and postnasal drip (54%). This is in agreement with the observation of Theodoropoulos et al³⁰ that upper respiratory tract symptoms are very common in patients with GERD and are related to the number of reflux episodes. In this regard we previously found that in patients with GERD-related cough, both laryngitis and LHR were closely related to GERD severity and resolved with omeprazole.³¹ In the present study the finding that LHR was present only in patients with evidence of laryngitis suggests that the irritable larynx was sustained by laryngopharyngeal reflux. Unfortunately, we did not perform upper airway pH monitoring to evaluate whether acid reflux did actually reach the upper airway. However, even with this method, the diagnosis of laryngopharyngeal reflux is still controversial.³²

An irritable larynx was also found in most patients with UNEX, who had no evidence of upper airway disease. In the absence of a demonstrable trigger of cough, we might suppose that in these patients cough was an expression of "sensory hyperreactivity,"³³ a condition in which airway symptoms are induced by scents, chemicals, and capsaicin inhalation. Sensory neuropathy involving the superior or recurrent laryngeal nerve has been documented in patients with chronic unexplained cough.³⁴ Our findings suggest that an irritable larynx might be revealed by histamine inhalation challenge. Unfortunately, histamine, although listed among nonspecific stimuli in international guidelines,^{23,35} is not

routinely used in bronchoprovocation challenges, either in Europe or the United States. In our opinion histamine should be preferred to methacholine in the assessment of cough because it is much more effective in stimulating the nociceptive sensory nerves involved in cough.^{36,37}

Similar to LHR, atopy or BHR did not optimally discriminate cough classes (Tables II and III). This was probably due to the fact that different triggers share some characteristics and that the triggers of cough might be multiple. As an example, atopy discriminated PR/CRS from GERD and UNEX but not from the 2 asthma classes. BHR, which is considered the hallmark of asthma, was present also in 33% of the patients with PR/CRS, in 16% of the patients with GERD, and in 25% of the patients with UNEX, even in the absence of asthmatic symptoms. This raises the crucial question of whether these patients might have cough-variant asthma (CVA).³⁸⁻⁴² Because the diagnosis of CVA assumes the absence of upper airway disorders,³⁹⁻⁴³ the only patients who could have CVA in our series were the patients with UNEX and BHR.

The sharing of characteristics among different cough classes caused a disagreement between the predicted and observed classification of patients, particularly asthma/CC+ patients and patients with GERD, most of whom turned up in the PR/CRS class (Table III). In other words, the *a posteriori* classification based on diagnostic tools was quite different from the *a priori* classification, outlining the difficult clinical approach to CC. Indeed, the inclusion of 24-hour pH monitoring among the predictive variables would have improved the classification of GERD, and the inclusion of F_{ENO} would have improved the classification of asthma/CC+ patients.^{15,16} F_{ENO} values, although available only in one third of the patients, were significantly increased in the asthma classes (Table I).

The results of the ROC curve analysis, as shown in Fig 1, demonstrate that combining the 3 predictive variables of BHR, LHR,

and atopy improved the ability of the model to discriminate each class from the others in terms of sensitivity and specificity. The area under the ROC curve was greater than 0.7 for each class and was highest (approximately 0.9) for the asthma classes.

Bearing in mind that the ultimate confirmation of a diagnosis is the response to therapy,³ we reassessed patients after treatment of the presumed trigger of cough. Asthma/CC+ patients were excluded because they needed ICSs, which would have obscured the effect of treatment of upper airway disease on both symptoms and airway responsiveness. As shown in Table V, treatment produced a significant improvement of cough and of laryngeal and bronchial histamine thresholds. The maximum effect was found in the PR/CRS class, where treatment resolved LHR in 78 of 99 patients and BHR in 29 of 48 patients. This finding suggests that in 60% of the patients, BHR was triggered by upper airway receptors made hypersensitive by rhinitis and sinusitis, which is in agreement with our prior findings.¹⁴ Cough and airway thresholds were also significantly improved in the GERD class by means of PPI treatment, whereas in the UNEX class empiric PPI and antihistamine treatment was totally ineffective. Only in 14% of the patients, 18 with PR/CRS and 4 with UNEX, did cough and airway hyperresponsiveness persist after treatment. We can suppose that at least the patients with PR/CRS had unrecognized asthma but had not yet experienced symptoms. In most of these patients with PR/CRS, the addition of ICSs resolved cough, BHR, and LHR.

In conclusion, our findings indicate that patients who present with CC often have an irritable larynx, which can be revealed by means of histamine inhalation challenge as a dose-dependent decrease in maximum inspiratory airflow rates. Such LHR is sustained by inflammation and damage of the upper airways but might also be an expression of idiopathic sensory neuropathy. The evaluation of LHR might help in the assessment of CC to identify the involvement of upper airway receptors. In patients with GERD-associated cough, LHR suggests the presence of laryngitis possibly related to laryngopharyngeal reflux. The diagnosis of irritable larynx might also help in improving cough treatment. In patients with asthma-associated cough, LHR points to coexistent rhinitis or rhinosinusitis, suggesting an important therapeutic target¹⁷ that is often disregarded by pneumologists. Our findings indicate also that an irritable larynx might sustain bronchoconstrictive reflexes in patients with rhinitis or rhinosinusitis and no asthmatic symptoms. In these patients BHR might reverse with the sole treatment of upper airway disease, with no need for ICSs, which would be preferred only when symptoms and airway hyperresponsiveness persist.

Key messages

- Patients with CC often have irritable larynx, which can be diagnosed by a decrease in inspiratory airflow rate caused by paradoxical vocal cords adduction on histamine inhalation challenge (LHR).
- LHR is a marker of upper airway involvement irrespective of the trigger of CC, whether rhinitis or sinusitis, gastroesophageal reflux reaching the larynx, or unexplained laryngeal sensory neuropathy.
- LHR can be used as an objective tool to evaluate the response to cough treatment.

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