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Chronic cough in upper airway diseases

J.B. Watelet [a,*], T. Van Zele [a], G. Brusselle [b]

[a] *Department of Otorhinolaryngology, Ghent University Hospital, De Pintelaan 185, B-9000 Ghent, Belgium*
[b] *Department of Respiratory Medicine, Ghent University Hospital, De Pintelaan 185, B-9000 Ghent, Belgium*

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Summary
Background: The epidemiological, pathophysiological and clinical links between upper and lower airways are nowadays clearly demonstrated. Most of asthmatics are suffering from rhinitis while up to 40% of rhinitic patients have asthma. Asthmatics and COPD patients are also prone to develop concomitant chronic rhinosinusitis (CRS).

This study aimed to determine the predictive value of cough for concomitant asthma in patients suffering from upper airway diseases.
Methods: This cross-sectional study described a group of 143 consecutive patients suffering simultaneously from common upper and lower airway disorders. Both ENT-specialists and respiratory physicians consecutively examined the patients in Ghent University Hospital from October 2004 till October 2006. This study was based on the demographic characteristics, upper and lower airway conditions.
Results: Forty-seven percent of the patients included in the study were males and the mean age of studied population was 43.6 years. The major complaint was chronic cough. When present, patients with chronic cough have an increased risk of suffering from a concomitant asthma in both allergic rhinitis (OR = 5.8) and CRS with nasal polyps (OR = 10.4), but not in CRS without polyps.
Conclusions: Chronic cough was found to be a key symptom of associated asthma in allergic rhinitis and CRS with nasal polyps. Interestingly, chronic cough in CRS without nasal polyps did not show the same predictive value: this suggests different pathophysiological mechanisms.

Introduction

Cough is an essential protective physiological mechanism that prevents foods, liquids, dusts and chemicals from reaching the lower airways, but it is also a symptom of many inflammatory diseases of the respiratory tract.[1]

Chronic cough, defined as lasting for more than 8 weeks,[2,3] is reported by 3–40% of the general population[3]

* Corresponding author. Tel.: +32 9 332 2332; fax: +32 9 332 4993.
E-mail address: jeanbaptiste.watelet@ugent.be (J.B. Watelet).

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and has an important impact on quality of life.[4] A European study showed that 30% of the patients had nocturnal cough, 10% a productive cough and another 10% a non-productive cough.[5] Together with asthma and gastroesophageal reflux disease.[6] postnasal drip syndrome (PNDS) (induced by all types of rhinitis and rhinosinusitis) is one the most common causes of chronic cough.[7] When considering all types of cough, the upper airways cough syndrome (UACS), previously referred to as PNDS, has been shown to be the principal cause of cough, especially when associated with common cold,[8] but this condition usually results in an acute type of cough. When considering chronic cough, an etiology can be determined in 88–100% of cases. This high rate of accurate diagnosis implies a higher chance to successful treatment.[2]

However, chronic cough can be related to more than one disease. Three or more simultaneous causes have been described in up to 42% of patients.[9,10] Moreover, in patients with chronic cough, neither the patient's description of his or her cough in terms of its character or timing, nor the presence or absence of sputum production should be used to rule in or rule out a diagnosis or to determine the clinical approach.[11]

The difficulty in daily practice is to clinically differentiate an upper airway cough syndrome from a chronic cough generated by an associated lower airway disease.[12,13] The association of symptoms is of little clinical value and physical findings are rarely conclusive.[14]

The aim of this study was to calculate the predictive value of chronic cough for concomitant asthma in patients suffering from upper airway diseases.

Materials and methods

Description of study

This cross-sectional study recruited consecutive outpatients suffering from chronic upper airway symptoms. At the moment of consultation, the patients should present one or more lower airway symptoms for being included in the study. They were systematically examined by both ENT-specialists and pneumologists at the Ghent University Hospital from October 2004 till October 2006. The data collection was focused on demographic characteristics, upper airway conditions, lower airway status, other co-morbidities and smoking status. Both frequency and severity of the upper and lower airway symptoms were considered. The primary complaint was defined as the most troublesome symptom or the symptom having led to consultation. In the studied population, patients suffering from chronic cough were distinguished from those without chronic cough. Chronic cough was defined as cough lasting for at least 8 weeks.[2] Severity of cough was graded by the patient into mild, moderate and severe. Mild was defined as occurrence of symptom interfering neither with daily or work activities nor with sleep. Moderate was considered if interference with activities without necessity of treatment. Severe was defined as the occurrence of symptom with dependence of medication to function.

Allergic rhinitis was defined and classified into intermittent or persistent following the ARIA classification[15,16] while asthma was defined and classified following the GINA classification 1995.[17] Asthma is defined as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment. The clinical diagnosis of asthma was prompted by symptoms such as episodic breathlessness, wheezing, cough, and chest tightness. Measurements of lung function (spirometry or peak expiratory flow) provided an assessment of the severity of airflow limitation, its reversibility, and its variability, and provided confirmation of the diagnosis of asthma. Asthma was classified by severity based on the level of symptoms, airflow limitation, and lung function variability into four categories: intermittent, mild persistent, moderate persistent, or severe persistent. Chronic rhinosinusitis with and without NP were defined following the EAACI position paper EP^{3}OS.[18,19] The Lund–MacKay scores were used for staging abnormalities on CT scan of sinuses. Gastroesophageal reflux (GER) was evoked when a preliminary diagnosis was established by gastro-enterologists or when symptoms of pyrosis, dysphagia were present with endoscopic inflammation of the posterior laryngeal commissure and with reduction of symptoms with proton pump inhibitors.[6,20] A complete otorhinolaryngological examination, CT scan of paranasal sinuses, allergy tests (skin prick tests or RAST), chest auscultation and lung function tests were performed in all patients for confirmation of the diagnosis.

Patients with pathologies such as vocal cord dysfunction, chronic laryngitis, daily use of angiotensin-converting enzyme inhibitors, post-intubation pharyngolaryngeal pathology, and pharyngolaryngeal tumors were excluded from this study.

The local Ethics Committee of the Ghent University Hospital has been informed of the study.

Statistical analysis

For comparison of frequencies, the Chi-square test was used in the univariate analysis; if the frequency in a subgroup was lower than 5 the Fisher's Exact test was used. To calculate the odds ratios (ORs) a logistic regression was used to determine the influence of independent variables on cough. Differences were regarded as statistically significant if $p < 0.05$.

Results

A total of 143 consecutive patients were recruited for this study, from which 12 were excluded for chronic laryngitis ($n = 4$), vocal cord dysfunction ($n = 3$), daily use of angiotensin-converting enzyme inhibitors ($n = 3$), post-intubation pharyngolaryngeal pathology ($n = 1$), and pharyngolaryngeal tumors ($n = 1$). One hundred thirty-one patients having concomitant nose and lung complaints were finally considered as eligible for this study. The

demographic profile of the total group was 53% females and 47% males, with a mean age of 43.6 years (range 16–74 years) (Table 1).

Description of the most frequent upper and lower airway symptoms

The most frequently reported complaints were cough, nasal congestion, postnasal drip and rhinorrhea. Of the 131 patients, 58 (44.2%) experienced cough lasting more than 8 weeks as a main reason for consultation. Nasal congestion was reported in 49.6% of the patients. Anterior rhinorrhea and postnasal drip were found in 42.7% and 38.9% of patients, respectively.

In the 58 patients with chronic cough, 55% were females. The mean age was 46.4 years (range 16–83 years). The most frequently associated symptoms within this group were postnasal drip (41.3%), nasal congestion (39.6%) and rhinorrhea (37.9%). In lesser extent, headache (25.8%), sneezing (15.5%) and pharyngeal irritation (15.5%) were present.

Severity of cough estimated by patient varied from moderate to severe. Mild, moderate and severe cough were found in 5.2%, 67.2%, and 27.6%, respectively. Only in a minority of patients, there was nocturnal cough (20%) with a mild to moderate grade of severity. A productive cough was reported by 46.7%. If a productive cough was present, the presence of purulence was equally distributed (50% purulent and 50% non-purulent). No correlation was found between chronic cough and patient's feeling of postnasal drip.

Description of the most frequent upper and lower airway diseases

Allergic rhinitis was present in 66 patients (50.3%). The most frequent sensitization profiles were against house dust mites (83%), pollens (56.9%) and pets (56.9%) isolated or in association. CRS was found in 21 patients (16.0%), while NP was found in 14 cases. The remaining patients, even if presenting upper airway symptoms, were not found to have any chronic nasal or sinus diseases but, in this group, endoscopic features of GER were found in 15.2% of them. Patients with NP were found to have significantly higher Lund–MacKay CT scan scores than those with CRS ($p = 0.01$) or AR ($p < 0.0001$). In patients presenting nasal disorders, up to 8.6% had associated GER.

Serum total IgE was found increased in AR when compared to CRS and NP but the difference did not reach a statistically significant difference. Finally, regarding the serum absolute eosinophilia, AR and NP patients were found with higher amount and trend for significant difference when compared with CRS ($p = 0.07$ and $p = 0.08$, respectively). The percentage of serum eosinophilia was not different between the groups even if the trend of higher level in NP was found (Table 1).

At the level of lower airways, asthma was diagnosed in 55% of the patients. No significant difference concerning absolute and percentage of FEV_1 and FEV_1/FVC scores was observed between the groups. Chronic obstructive pulmonary disease was found in three patients, and emphysema in one. Bronchiectasis was diagnosed in 14 patients (11.3%), from which three were diagnosed on lung X-rays and 11 on high resolution CT scan.

Table 1 Demographic data, atopic status, lung function, serum IgE concentrations and blood eosinophilia. The *p*-values are calculated in comparison with patients without the disease. *$p < 0.0001$ with AR and $p = 0.012$ with CRS.

Parameter	Total (including GER)	AR	CRS	NP
n	131	66	21	14
Age: mean (range)	43.6 (16–74)	40.9 (16–74)	48.9 (21–74)	48.7 (28–70)
Gender ratio: males (%)	47	42.4	45	71.4
BMI: mean (range)	26.9 (17–37)	26.7 (17–36)	28.5 (17–37)	25.2 (19–30)
Smoking				
Never (%)	65.4	70.4	60	50
Former (%)	23.5	20.4	33.3	25
Current (%)	11.1	9.2	6.7	25
Total Lund–Mackay CT scan sinus score: mean (range)	6.5 (0–12)	4.7 (0–10)	5.4 (1–10)	16.0 (2–24)*
Co-morbidities				
Asthma (%)	53	57.6	30	71.4
Atopy (%)	57.6	100	30	42.8
After bronchodilator:				
FEV_1 abs	2.8 (1.5–4.2)	2.8 (1.8–4.2)	2.3 (1.5–2.9)	3 (2.3–4.2)
$FEV_{1\%}$	85.2 (61–124)	85.5 (61–124)	83.7 (69–98)	85.6 (65–101)
FEV_1/FVC Mean (range)	65.1 (44–88)	67 (44–88)	67.1 (59–76)	57.8 (44–77)
Eosinophilia				
Absolute	409 (10–2728)	399.4 (10–2728)	360.9 (10–2143)	522.2 (40–2143)
Percent Mean (range)	5.1 (0.1–34)	5.2 (0.1–34)	4.1 (0.1–25)	6.3 (0.5–22)
Serum tot IgE mean (range)	476.4 (4.4–8170)	622 (4.4–8170)	138.4 (4.8–525)	262.6 (13–889)

Table 2 Odd ratios (OR) and their confidence interval (CI) for having concomitant asthma in patients suffering from AR, CRS and NP with or without associated chronic cough. NB: when in italics: not significant.

Patients	Cough	OR for asthma (CI)	*p*-value
Allergic rhinitis	No	3.3 (1.2—8.6)	$p = 0.02$
	Yes	5.8 (1.7—19.6)	$p = 0.005$
Chronic rhinosinusitis without NP	No	*0.7 (0.2—2.2)*	*p = 0.6*
	Yes	*0.3 (0.04—2.9)*	*p = 0.4*
Chronic rhinosinusitis with NP	No	*2.0 (0.5—9.3)*	*p = 0.5*
	Yes	10.4 (11—100.8)	$p = 0.03$

Identification of the most frequent causes of chronic cough in upper and lower airway diseases

In the chronic cough group, AR was present in 46.5% and asthma in 31%. CRS was found in 12% of patients and NP in 8.6%.

Calculation of the predictive value of chronic cough for concomitant asthma in patients suffering from upper airway diseases

A patient with AR in absence of cough had a significant 3.2 higher risk of associated asthma than a patient without AR ($p = 0.02$). If cough was present concomitantly with AR, the risk increased 5.8 fold higher than in patients without AR and cough ($p = 0.004$). Moreover, a patient with NP without cough had a 2 fold higher risk of associated asthma when compared to patients without NP (not significant) while, in a patient with concomitant NP and chronic cough, the risk to have concomitant asthma is 10 fold higher than in patient without NP and cough ($p = 0.03$) (Table 2). Interestingly, chronic cough in CRS was not significantly associated with higher percentage of concomitant asthma.

The sensitivity of chronic cough in AR for having concomitant asthma reached 82% but poorly specific (51.9%). The sensitivity and specificity of chronic cough in the group of NP were respectively 77% and 80%. But, in this group, the positive predictive value was 97.5% (Table 3).

Discussion

In this series of patients complaining of both upper and lower airway symptoms, chronic cough was found to be the most frequent reason for consulting. In this study, patients with upper airway diseases when associated with chronic cough were found to be more prone to have a concomitant asthma. Interestingly, this risk in association was different in function of the upper airway disease: NP and AR associated with chronic cough are more likely to have a concomitant asthma when compared to CRS. These findings were in line with the observed difference in eosinophilia between the diseases. Considering the high positive predictive of chronic cough, asking for cough should be considered as an essential step during history taking in upper airways disorders. All patients suffering from chronic upper airway diseases and persistent cough should be systematically screened for the presence of asthma.

The definition of chronic cough as lasting for more than 3 weeks[9] includes often the post-infectious cough, which has a benign course and requires mostly no treatment. As a consequence, we preferred the definition stating that cough should last for more than 8 weeks.[2,3] In approximately 95% of cases in immunocompetent patients, chronic cough results from asthma, conditions of the nose and sinuses, gastroesophageal reflux disease, chronic bronchitis, bronchiectasis, eosinophilic bronchitis or the use of angiotensin-converting enzyme inhibitors.[2]

When considering asthma, Dicpinigaitis reported that asthma is present in 24—29% of non-smoker patients with chronic cough and should be considered as potential etiology in any of them.[21] Moreover, cough can be the only sign of asthma in up to 57% (cough variant asthma).[2,22] On the other hand, upper airway diseases are known to play a role in asthma and rhinitis is considered as a risk factor for asthma.[15,23,24] Chronic rhinosinusitis is regularly associated with asthma, particularly in adult-onset asthma[25] and severe steroid-dependent asthma.[26]

Regarding the participation of upper airways in chronic cough, some data are also available. The differential diagnosis of UACS includes isolated or associated sinusitis and rhinitis (allergic, non-allergic, infectious, vasomotor, drug- or irritant-induced).[9,27] The exact role played by chronic rhinosinusitis and its degree of involvement are still debated. The major difficulties are linked to a poor specificity of symptoms[11] and clinical signs.

Chronic rhinosinusitis is suspected as primary etiology in 8—81% of chronic cough patients.[1] Kastelick et al. found rhinosinusitis to be the causative factor in 80% of patients with chronic cough,[28] but another study claims that postnasal drip is the cause of chronic cough in up to 81% of patients.[29]

However, as demonstrated in this study, patient's feeling of postnasal drip was not correlated with chronic cough, as already suggested by O'Hara.[30] A cobblestone appearance of the oropharyngeal mucosa or presence of mucoid secretions on the posterior pharyngeal wall are not specific and not always present, even when a history of postnasal drip is reported by the patient.[31] Furthermore, it has been suggested that chronic rhinosinusitis with or

Table 3 Sensitivity, specificity, positive and negative predictive values of chronic cough as predictor for asthma.

Patients	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Cough + allergic rhinitis	84.4	51.9	67.5	73.7
Cough + nasal polyposis	72.2	80.0	97.5	21.0

without postnasal drip can cause coughing and may be a marker of disease in the lower airways.[3] In a questionnaire to patients with chronic rhinosinusitis or polyps, Fokkens revealed that only 60% of them had postnasal drip, whereas 74% coughed. In patients without asthma, the figures dropped to 51% and 65%, respectively (unpublished data, reported in 3). Finally, chronic cough has been also described in the patient with AR, especially when AR is associated with chronic rhinosinusitis.[32]

The pathogenesis of cough from UACS remains unclear but there is a suspicion of mechanical stimulation of the afferent limb of the cough reflex in the upper airway, stimulation of cough receptors located in the hypopharynx or larynx by aspirated secretions from the sinuses or a more sensitive cough reflex in the upper airways.[33,34] Airway wall remodelling and local release of growth factors have been suspected to heighten the cough reflex.[35,36]

Even if the study was performed on a population recruited in a tertiary setting, this study supports the view that chronic cough in upper airway diseases must be considered as a marker of lower airway disorder. If, in upper airway diseases, chronic cough possesses a positive predictive value for having concomitant asthma, a difference in probability was observed between AR, CRS and NP. Chronic cough in CRS was never found to be predictive of an association with asthma. These findings suggest that the nature of background inflammation should be determinant in the occurrence of cough, especially of chronic cough. This hypothesis was already proposed by ten Brike et al., when they described the involvement of eosinophils in this process.[26] Eosinophils are key effectors in the pathogenesis of allergic rhinitis and chronic rhinosinusitis with NP, but not in chronic rhinosinusitis without NP.[37] Interestingly, in our study, a trend of increased eosinophilia was found for absolute eosinophilia in serum in both AR and NP when compared to CRS. Further explorations taking into account the local eosinophilia and the degree of eosinophil activation are requested.

Conclusions

In this cross-sectional analysis of patients with both upper and lower airway symptoms, chronic cough was found to be a key marker of associated asthma in AR and NP. Interestingly, chronic cough in CRS did not show the same positive predictive value. These findings suggest a different inflammatory background or defensive mechanisms in this condition. Finally, this study points out the importance of a multidisciplinary approach of patients suffering from concomitant upper and lower airway disorders.

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Conflict of interest statement

The authors do not have any financial, personal, academic and intellectual conflict of interest related to the article or the research described. This study was not supported by any sponsorship.

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