

J. PLEVKOVA, S. VARECHOVA, M. BROZMANOVA, M. TATAR

TESTING OF COUGH REFLEX SENSITIVITY IN CHILDREN SUFFERING FROM ALLERGIC RHINITIS AND COMMON COLD

Department of Pathophysiology, Jessenius Faculty of Medicine,
Comenius University, Martin, Slovakia

Cough associated with upper respiratory tract disorders is a common and troublesome problem in children and little is known about the etiology of this type of cough. This study examined the capsaicin cough sensitivity (CS) in children suffering from allergic rhinitis (AR) and upper respiratory tract infection (URI), comparing it with that in healthy children taken as controls (C). CS to capsaicin, spirometry, skin prick tests, and nose-throat examination were performed in 61 children grouped by the diagnosis of AR, URI, and C. The results, in order of C vs. AR vs. URI, expressed as a geometric mean ($\pm 95\%$ CI) $\log_{10} \mu\text{M}$ of capsaicin for C2 (the lowest concentration of capsaicin in $\mu\text{mol/l}$ required to induce ≥ 2 coughs) were: 1.8 (1.6–1.9) vs. 1.0 (0.8–1.2) vs. 0.48 (0.2–0.8), $P < 0.001$ and for C5 (the lowest concentration of capsaicin in $\mu\text{mol/l}$ required to induce ≥ 5 coughs) 2.9 (2.8–2.9) vs. 2.6 (2.5–2.6) vs. 2.1 (2.0–2.3), $P < 0.05$. We found that CS in children with AR, even when tested out of pollen season, was significantly heightened compared with controls. CS in children with URI was extremely high compared with both C and AR groups. We conclude that pathological processes in the nose of any etiology could cause a sensitization of the cough reflex with decreased cough threshold during asymptomatic period of AR. Cough also is enhanced by acute inflammation in the upper airways in nonatopic children.

Key words: *allergic rhinitis, children, common cold, cough sensitivity*

INTRODUCTION

Diseases of the respiratory system are very common in childhood. Cough - the main symptom of respiratory disorders - is a common reason for parents to seek medical attention (1). The coughing child with other symptoms of acute viral or bacterial infection of the airways is usually not problematic to manage. A short

course of antibiotics with a combination of antitussive/expectorant therapy appears to provide satisfactory effects. On the other hand, it is recognized that preschool and school children might suffer from acute respiratory infections approximately 6 to 8 times a school year and up to about 140 coughs daily may be considered as normal or expected in this group (1). Munyard et al (2) reported that even entirely healthy children might have about 34 coughs per day, because of cortical modulation of the cough reflex and possibility of coughing induced voluntarily.

Pediatricians often encounter cases having chronic cough lasting several weeks to months. Cough itself is not an illness but a symptom of an underlying stimulus or disease, therefore, evaluation and treatment of cough should be directed at the underlying condition rather than cough itself. The definition of persistent or chronic cough varies (>3-6 weeks) and the etiological factors vary in children from the benign to life threatening causes such as cystic fibrosis. The true prevalence of chronic or persistent cough is difficult to evaluate, given the methodological difficulties in studying cough, the poor repeatability of questions on isolated cough, unreliable reporting (compared with objective measurements), and the time effect (spontaneous resolution with time) (3).

Adult protocols emphasizing the treatment of persistent cough with medications for asthma, postnasal drip/sinusitis, and gastroesophageal reflux have been extrapolated to children (4, 5), although there is poor evidence that the same etiological factors cause persistent cough in adults and children (6, 7). There are no data that describe the spectrum of etiology of persistent cough in children; therefore, medications for asthma, steroids, and antibiotics are used in excess, with serious side effects, prior to establishment of the real underlying condition in a coughing child (8). Prominent causes of chronic cough in children include frequently recurring simple viral bronchitis, asthma, sometimes labeled as "cough variant asthma", and postinfectious cough.

Allergic rhinitis is the most common condition in the pediatric population, affecting 20-40 % of children (9). If this condition is treated inadequately and becomes chronic, it leads to complications in both upper and lower airways (10). This group of complications also includes asthma and chronic cough. Inflammation occurring in the upper airways could be propagated through the airway or systemic pathway into the lower airways (11). It is clear that the condition of the upper airways ultimately influences the lower airways, but what factors are responsible for the onset of inflammation in lower airways in patients with diseases of the nose and sinuses. Could that be the duration of nasal pathology, inadequate treatment, or enormous exposure to aeroallergens or other environmental factors, such as passive smoking or air pollution?

It has been reported that cough sensitivity is significantly increased in pollen sensitive subjects who suffer from seasonal allergic rhinitis during the pollen season (12). Little is known about the pathogenesis of cough that relates to upper respiratory tract disorders. The pertinent mechanisms may include post nasal drip,

nasobronchial reflex that alters breathing pattern, pulmonary aspiration of nasal contents, or increased levels of inflammatory factors in the blood (13, 14). Another factor that should be taken into consideration is central cough plasticity, which means neuronal potentiation of the cough reflex reported in adult subjects with allergic rhinitis (15).

The aim of the present study was to assess cough reflex sensitivity in children suffering from allergic rhinitis and common cold, and to compare it with that observed in healthy children. Allergic rhinitis and common cold are two major conditions strongly associated with cough, which are usually described as upper respiratory tract-related cough. Paradoxically, the pathological process is located in the nasal cavity, from which cough cannot not be elicited. The question arises of whether, and by what mechanisms, these diseases in children could influence the cough reflex sensitivity.

MATERIAL AND METHODS

Subjects

The study was approved by a local Ethics Committee and parents of all subjects gave written consent for participation in the study, after the study goals and protocol had been explained.

The study population consisted of 21 healthy children, 20 children with seasonal allergic rhinitis, and 20 children with upper respiratory tract infection (common cold) (*Table 1*). The subjects were studied during October and November of 2005, which was out of pollen season.

The characteristics of the three groups of the subjects were the following.

- healthy children with no history of atopy, allergic responses to inhaled allergens or food components, who did not suffer from acute respiratory tract disease in the past four weeks;
- children with allergic rhinitis with a characteristic history of seasonal allergic rhinitis (rhinorrhea, nasal itch, sneezing, and nasal obstruction after allergen exposure) and positive skin prick tests to pollens. At the time of the examination they were free of allergic nasal symptoms, antihistamine/decongestant therapy or other local or systemic drugs, and did not suffer from acute respiratory tract disease over the past four weeks;
- children with acute upper respiratory tract infection at the time of the investigation, who were otherwise healthy, and who had at least two of the five characteristic symptoms of common cold – rhinorrhea, nasal congestion, sneezing, sore throat, and cough with a score of ≥ 4 on a four point scale of severity (0-not present, 1-mild, 2-moderate, and 3-severe).

Exclusion criteria for all the subjects were the presence of a past history of cardiac or neonatal pulmonary problems, abnormal cardiopulmonary physical examination findings, including wheezing or abnormal spirometry (FEV1 or FVC < 80% predicted), abnormal otorhinolaryngological findings (adenoids), and in the group of children with common cold serious systemic symptoms, such as body temperature higher than 38.5°C, headache, muscle pain, or fatigue.

Study design

The subjects' characteristics were obtained through a standard questionnaire. The subjects were interviewed and examined by a pediatrician and an otorhinolaryngologist. Then, spirometry was performed to measure FEV1 and FVC, using a computer assisted spirometer (Microlab-ML 3500, Micromedical, England) in compliance with the proper standards for children. Spirometric measurements were repeated after the capsaicin single breath challenge.

Table 1. Characteristics of the subjects recruited for the study.

	Healthy controls (n = 21)	Allergic rhinitis (n = 20)	Upper respiratory tract infection (n = 20)
Age – median (IQR)	10.6 (7-15)	11.2 (6-17)	9.8 (6-15)
Boys/girls	10/11	9/11	10/10
Mean FEV1 % predicted (SE)			
Before capsaicin challenge	106.1 $\pm$ 2.4	102.1 $\pm$ 2.6	100.1 $\pm$ 1.2
After capsaicin challenge	106.3 $\pm$ 1.8	102.6 $\pm$ 2.6	99.3 $\pm$ 1.1

IQR - interquartile range, FEV1- forced expiratory volume in 1 s, SE - standard error of mean.

Measurement of the cough reflex sensitivity

The measurement of cough sensitivity to inhaled capsaicin was carried out according to the modified method described by Chang et al (16). Each subject inhaled the aerosol of a control solution (physiological saline), followed by progressively increased concentrations of capsaicin solutions (pungent extract from the red pepper) from 1.23 to 1250 μ mol/l prepared *ex tempore* from a stock solution. Capsaicin was obtained from Sigma (St. Louis, MO) and the aerosol was prepared by a ProvoJet nebulizer (Ganshorn Medizin Elektronik, Niederlauer, Germany). Penetration of aerosol particles into the airways during 400 ms of inspiration was ascertained by computer driven nebulization. The number of capsaicin-induced coughs was counted manually during 30 s after nebulization. The measures of capsaicin cough sensitivity (CS) were the lowest concentration of capsaicin required to induce ≥ 2 coughs (C2) and ≥ 5 coughs (C5).

Data analysis

Descriptive statistical methods were used to summarize the data obtained. The values of the cough reflex sensitivity were grouped, $\log_{10}$ transformed, and then expressed as a geometric mean with 95% confidence interval. Differences between groups were further analyzed using ANOVA (multiple comparison testing) and Kruskal-Wallis tests. Linear correlations were analyzed between the nasal symptom scores and cough reflex sensitivity in the common cold group. $P < 0.05$ was considered as statistically significant.

RESULTS

The mean capsaicin C2 concentration (the cough threshold) was 68.3 μ mol/l (41.3-80.0; 95% CI) in the healthy children, which was significantly higher than the 11.05 μ mol/l (7.0-19.5) obtained in subjects with allergic rhinitis evaluated out of pollen season, and, therefore, without nasal symptoms ($P < 0.001$). The cough threshold for subjects with common cold complaining about nasal symptoms and cough was 3.02 μ mol/l (0.61-6.2) (different from the allergic rhinitis group at $P < 0.001$). Similar data were obtained for the capsaicin C5 concentration (Table 2) ($P < 0.05$). Based on this data it is clear that capsaicin CS was significantly increased in the allergic rhinitis group and extremely enhanced in the common cold group.

A positive correlation between the symptom severity and CS in the common cold group (*Fig. 1*) also was found, but it should be taken into consideration that the objective evaluation of symptom severity could not be entirely precise as it was performed with children.

DISCUSSION

The aim of the present study was to test the cough reflex sensitivity in children suffering from allergic rhinitis and common cold. CS is defined as the lowest concentration of a tussive substance that induces a defined cough response (17). This parameter reflects neurophysiological properties of the afferent nerve endings in airways that mediate cough. These properties (irritability, sensitivity) could be changed due to pathophysiological processes in the airways, nasal cavity (12, 18), esophagus (19), or in the whole organism (atopy) (20). Sensitization of the nerve endings is a consequence of peripheral cough plasticity and it can manifest as increased capsaicin CS.

Table 2. Cough reflex sensitivity in the experimental groups studied.

	Healthy controls (n = 21)	Allergic rhinitis (n = 20)	Upper respiratory tract infection (n = 20)
Cough reflex sensitivity (geometric mean with 95% CI; $\mu\text{mol/l}$ of capsaicin)			
C2	68.3 (41.3-80.0)	11.1 (7.0-19.5)**	3.02 (0.6-6.2)**
C5	737 (680-760)	358 (320-397)*	150 (111-196)*
Cough reflex sensitivity ($\log_{10}$ transformed; $\mu\text{mol/l}$ of capsaicin)			
C2	1.8 (1.6-1.9)	1.0 (0.8-1.2)**	0.5 (0.2-0.8)**
C5	2.9 (2.8-2.9)	2.55 (2.5-2.6)*	2.1 (2.0-2.3)**

Asterisks denote differences from the preceding group; * $P < 0.05$ and ** $P < 0.001$.

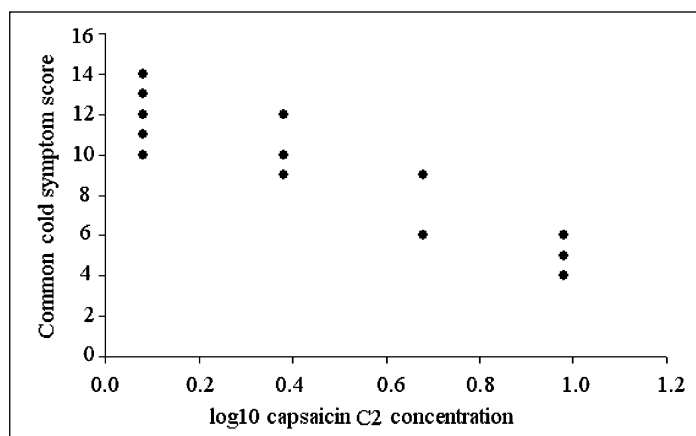


Fig. 1. Correlation between the symptom severity and capsaicin cough sensitivity in the group of children with common cold.

Cough associated with upper respiratory disorders is a common and troublesome problem and it is surprising that little is known about the etiology of this type of cough. It is assumed that the normal, protective reflex of cough is exaggerated in some way, so it occurs spontaneously instead of in response to food or fluid entering the airway (21). There are several studies that have reported that cough response is potentiated in patients suffering from allergic rhinitis whether tested during the pollen season or out of it (12). CS also is increased during experimentally induced obstruction and hypersecretion of the nasal cavity with the use of intranasal histamine challenge in healthy adults and adult subjects with allergic rhinitis (15, 22). The issue, however, has remained unresolved in children, who appear to be the target group that frequently suffers from upper respiratory tract disorders of various etiology.

The major finding of the present study is that CS in children with allergic rhinitis, but remaining out of pollen exposure and having no nasal symptoms, is significantly increased compared with healthy controls. This result is in general agreement with our previously published data (12), but the subjects of the present work were not tested during the pollen season. It can be expected that the capsaicin CS also should be enhanced during the pollen season due to exposure to aeroallergens of natural origin and the development of nasal symptoms secondary to allergic inflammation of the nose and sinuses. In these subjects, tested out of pollen season, the cough response could be exaggerated due to atopy (21), since all of the present subjects were atopic, or due to allergic inflammation of lower airways that "works" at a subclinical level. There were no overt symptoms from the lower airways, but discrete inflammatory changes could be deduced from an increased number of eosinophils in the induced sputum of allergic subjects. Such eosinophilic inflammation may be a precursor of asthma development, and its early recognition and treatment could prevent the onset of asthma in subjects with allergic rhinitis.

We further found that CS is extremely increased in children suffering from common cold and that there is a positive correlation between the severity of nasal symptoms obtained at the time of investigation and cough reflex sensitivity in those children. This enhancement of the cough response could be ascribed to nasal obstruction and overproduction of nasal fluids, leading to a postnasal drip. Another possible explanation of increased cough reflex sensitivity in common cold children is that viruses, and possibly also medications used, targeting the respiratory system are able to unmask receptor sites after disruption of the surface active phospholipid barrier with sensitization of the reflex.

We can summarize that cough reflex sensitivity is increased in children with allergic rhinitis, even tested out of pollen season and, therefore, remaining asymptomatic, and in those suffering from common cold accompanied by typical nasal symptoms. Enhancement of the cough sensitivity positively correlates with the nasal symptom severity in common cold. These observations are of clinical interest and merit further investigation.

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Author's address: J. Plevkova, Department of Pathophysiology, Jessenius School of Medicine, Comenius University, 26 Sklabinská St., 03753 Martin, Slovakia; phone: +421 43 4238213, fax: +421 43 4134807. E-mail: plevkova@jfmfmed.uniba.sk