

Urine Leukotriene E4 Levels in Children with Nonspecific Isolated Chronic Dry Cough

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Chronic cough is the most common complaint during childhood. Various pathophysiologic mechanisms may cause cough. Knowledge of the mechanisms underlying chronic cough plays an important role in the choice of treatment to evaluate the role of leukotrienes in children with nonspecific isolated chronic dry cough. The patient group consisted of children with isolated chronic dry cough persisting for >4 weeks and the control group included healthy children. Medical histories were elicited and physical examinations were performed, then respiratory function testing was done and chest X-rays were obtained. Patients were given inhaled corticosteroid. The urine leukotriene E4 (uLTE4) levels in the patient and control groups was measured by enzyme immunoassay. The patient group included 55 patients, 25 of them were males between 6 and 12 years old. The control group included 25 healthy children between 6 and 12 years old, 12 of them were males. There were no pathologic findings on physical examinations, pulmonary function testing, and chest X-rays. The complaints of cough in 50 patients were resolved after treatment. The median level of uLTE4 was 73.1 ng/mmol creatinine (range, 15.59–787.55 ng/mmol creatinine) in the patient group, and 64.2 ng/mmol creatinine (range, 12–282 ng/mmol creatinine) in the control group. No significant difference was detected between the 2 groups with respect to age, gender, and uLTE4 levels. Different pathophysiologic mechanisms are known to influence nonspecific isolated chronic dry cough. Various mechanisms, other than leukotrienes, may also give rise to dry cough.

Introduction

CHRONIC COUGH is a common problem and the reason for many doctor visits in childhood. It is defined lasting longer than 4 weeks according to the American College of Chest Physicians (ACCP) guideline;¹ however, it is defined longer than 8 weeks according to the British Thoracic Society guideline.² For chronic cough, both guidelines recommend the assessment of a patient with history, physical examination, chest X-ray, and pulmonary function tests. In an otherwise healthy child, if these assessments are normal and no specific disease pointers, chronic cough is divided into 2 groups (wet and dry cough) according to ACCP guidelines. Antibiotics are recommended for wet coughs, whereas inhaled steroids are recommended for dry coughs. A dry cough is also known as a nonspecific isolated cough. If the patients' cough resolved with inhaled corticosteroids, their diagnosis is labeled as asthma-like disease or asthma.^{1,3}

Pinpointing the underlying cause of a cough or having knowledge of the pathologic mechanism underlying a cough plays an important role in the selection of treatment. Recently, several studies have been conducted regarding the

inflammatory mechanisms underlying the physiopathology of acute and chronic coughs.^{4,5}

Airway inflammation is a common finding of cough-associated diseases, such as asthma, rhinosinusitis, gastroesophageal reflux disease, or nonasthmatic cough.^{6,7} Leukotrienes (LTs) are important lipid mediators released by inflammatory cells, such as macrophages, neutrophils, eosinophils, and mast cells, which are synthesized in the cell wall from arachidonic acid by arachidonate 5-lipoxygenase.^{8,9} LTC₄, LTD₄, and LTE₄ are known as cysteinyl leukotrienes (Cys-LTs), which have been reported to play an important role in asthma. The pulmonary metabolism of Cys-LTs *in vivo* results in a rapid and exclusive formation of LTE₄ without further conversion and is recovered in the urine as LTE₄ (2%–6%). Measurement of Cys-LTs in urine is more advantageous than measurement in blood. Therefore, the urine leukotriene E4 (uLTE4) level can be used as an appropriate biomarker for the measurement of Cys-LTs.^{10–13} Chandhuri et al.¹⁴ demonstrated increased levels of Cys-LTs, LTB₄, eosinophilic cationic protein (ECP), PGE₂, and IL-8 in induced sputum from subjects with chronic coughs. In addition, they noted that exhaled NO, CO, and ECP were significantly suppressed after 2 weeks of inhaled fluticasone. Cai et al. investigated the relationship

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between uLTE4 levels and clinical response to antileukotriene treatment in patients with asthma. They showed that the mean uLTE4 level from the responders was higher than from the nonresponders.¹⁵

In addition, LTs have been reported to be involved in the pathophysiologic mechanism by affecting neurogenic pathways in chronic cough.¹⁶

We hypothesize that LTs have an important role in chronic isolated nonspecific dry cough. The aim of this study was to evaluate the level of uLTE4, which is the final product of LTs in children with chronic isolated nonspecific dry cough.

Materials and Methods

This study was conducted between January and December 2007 at the Dr Behcet Uz Child Hospital. The demographic characteristics of the patients (duration and nature of cough, personal or family history of atopy, and passive smoking exposure) were elicited by medical history. The presence of specific findings was evaluated during physical examination. Pulmonary function tests (PFTs) were performed and chest X-rays were obtained.

The patient group consisted of isolated chronic cough lasting >4 weeks and with normal PFTs and chest X-rays. The patients who had chronic recurrent infections, family or personal histories of atopy, wet coughs, a history of smoke exposure, and pathologic physical findings (growth and developmental retardation, finger clubbing, cardiac and pulmonary auscultation findings) and signs supporting the presence of upper airway cough syndrome (UACS) were excluded from the study. Urine samples were taken and inhaled corticosteroid (Budesonide 200 µg twice a day) was given. After 2–4 weeks of treatment, they are questioned about their symptoms; no more urine samples were taken during control visits for comparison.

Inclusion criteria were as follows: the presence of chronic dry cough; the absence of atopy or other specific diseases based on history and physical examination; lack of exposure to active or passive smoking; and normal PFT and chest X-ray findings.

The control group consisted of healthy children who were admitted to the hospital for health check-up. The children in the control group had no history of chronic cough, and no family or personal history of atopy. Further, the children in the control group were of the same age as the children in the patient group, and had normal findings on physical examination.

The uLTE4 levels were determined with a commercial enzyme immunoassay kit according to the protocol of the manufacturer (Cayman Chemicals, Ann Arbor, MI) and standardized against urinary creatinine levels. The results were expressed as ng/mmol of creatinine. The LTE4 assay had 50% sensitivity and 100% specificity according to the manufacturer.

Written informed consent was obtained and the study was approved by the Ethics Committee of Behcet Uz Childrens Hospital.

In the patient and control groups, urine samples were obtained and evaluated to exclude the presence of infections and kept at –80°C until assayed.

Statistics

The data were analyzed using SPSS 11.0. The data are presented as the median. Control and patient groups were

TABLE 1. CHARACTERISTIC FINDINGS OF PATIENT AND CONTROL GROUPS

	Patient group (n=55)	Control group (n=25)
Year ^a	8 (6–12)	9 (6–12)
Male (%)	25 (45%)	12 (48%)
Duration of cough ^a (week)	7 (5–10)	
uLTE4 ^a (ng/mmolcreatinin)	73.1 (15–787)	64.2 (12–282)

^aMedian, min-max.

uLTE4, urine leukotriene E4.

compared using the Mann–Whitney *U*-test. A *P* < 0.05 was considered to be statistically significant.

Results

We evaluated 450 children with chronic cough between January and December 2007 at the Dr Behcet Uz Child Disease and Surgery Education and Research Hospital. One hundred thirty-five patients were diagnosed with nonspecific isolated dry cough. Fifty-five patients were randomly selected for this pilot study.

The patient group consisted of 55 children with a median age of 8 years (range, 6–12 years), and included 25 males (48%). The control group consisted of 25 healthy children with a median age of 9 years (range, 6–12 years). The median duration of chronic cough in the patient group was 7 weeks (range, 5–10 weeks) (Table 1).

Medical histories and physical examinations were evaluated in the patient and control groups. In addition, PFTs were performed and chest X-rays were obtained from the patient group. There were no pathologic PFT or abnormal chest X-ray findings. Inhaled corticosteroids (Budesonide 200 µg twice a day) were given to all the patients and they were re-evaluated after 2–4 weeks of treatment; 50 of the patients had a decrease in cough frequency.

In the patient group, the median level of uLTE4 was 73.1 ng/mmol creatinine (range, 15.59–787.55 ng/mmol creatinine), and 64.2 ng/mmol creatinine (range, 12–282 ng/mmol creatinine) in the control group. No significant difference existed between the 2 groups with respect to uLTE4 levels (*P* > 0.05; Fig. 1).

Discussion

Chronic cough is one of the most common complaints in children. In the absence of findings that would support a diagnosis, a differential diagnosis is difficult to establish, which in turn leads to uncertainty in treatment. Prospective studies have shown that most common causes of cough in children >6 years of age were asthma/asthma-like disease, prolonged bacterial bronchitis, and UACS.^{17,18} Guidelines for chronic cough have recommended the evaluation of physical examination, PFTs (if necessary, bronchodilator response also should be evaluated), and chest X-ray findings.^{1,2} If those investigations are normal, patients had only dry chronic cough with otherwise well child is recommended empirical anti-asthmatic therapy. If the patient's symptoms are resolved, it is labeled as asthma-like/asthma disease or cough variant asthma (CVA). We only evaluated patients with isolated chronic dry cough and who were given inhaled steroid treatment. We ruled out asthma and UACS based on

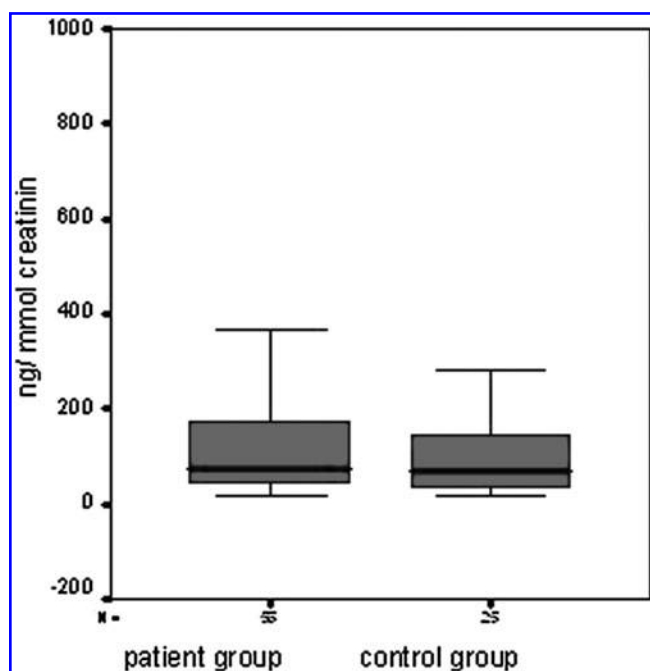


FIG. 1. Urine leukotriene E4 levels in the patient and control group.

the history, physical examination, PFTs, and chest X-ray findings. There were no abnormality in their PFTs, chest X-ray, and physical examination. The presence of bronchial hyperactivity and atopy are important in the differential diagnosis of asthma, but are not diagnostic. Especially, the demonstration of airway hyperresponsiveness in a child with nonspecific cough is unlikely to be helpful in predicting the later development of asthma or the response to asthma medications.^{19,20} Although it is difficult to assess reflux disease as a cause of chronic cough in children, gastroesophageal reflux disease (GERD) seldom causes chronic cough in children.^{18,21} We did not evaluate GERD with any diagnostic tests. In our study, most of the patient complaints were resolved after treatment with inhaled corticosteroids. It may be suggested that the diagnosis be asthma-like disease or (CVA). In addition, we could not evaluate bronchial hyperactivity and atopy with a prick test or specific IgE.

Cys-LTs [LTC₄, LTD₄, and LTE₄] play an active role in the pathogenesis of asthma. In addition, their levels might be increased in nonallergic asthma patients such as passive exposure to smoke or virus-induced wheezing.^{22,23} They cause edema by increasing vascular permeability, and are also responsible for the mucous secretions, bronchoconstriction, and cellular infiltration seen in asthma clinics. Selective Cys-LT receptor antagonists are effective in some asthma patients.²⁴

In chronic cough, LTs have been reported to be effective in the pathophysiologic mechanism by affecting neurogenic pathways.¹⁶ By demonstrating the role of LTs in chronic cough, the antitussive effect of the LT receptor antagonist was investigated. Spector and Tan²⁵ reported significant improvement in cough with the use of montelukast in 14 patients with CVA. In another study conducted by Kita et al.,²⁶ 48 patients with CVA were separated into 3 groups. One group was treated with clenbuterol ($n=16$), the second group was treated with montelukast ($n=13$), and the last group was

treated with clenbuterol plus montelukast. Improvement in cough was achieved in the latter 2 groups in comparison with the former group. In the same study, montelukast was not effective in 19 patients with atopic cough. Another study investigated the clinical, physiological, and anti-inflammatory effects of montelukast in patients with CVA. They shown that montelukast significantly decreased the cough, sputum eosinophil count, and cough sensitivity, whereas pulmonary function, airway responsiveness, and sputum mediator levels remained unchanged.²⁷

Kopriva et al.²⁸ evaluated the efficacy of montelukast treatment in 22 children with chronic nonproductive cough persisting >3 weeks. A decrease in the frequency of cough was achieved in 14 children (68%) on the third day, and completely resolved in 3 weeks. However, the findings that may be associated with atopic disease in the patients might have been effective based on the response to treatment. The same study pointed out that the patients with higher eosinophilic cationic protein levels were more responsive to treatment.²⁸

The Cochrane database showed that there are not a sufficient number of studies that support the efficacy of montelukast in the treatment of chronic cough, and that the existing research does not support its efficacy.²⁹

In the current study, we did not evaluate the effect of inhaled steroids; however, we observed that patient coughs decreased after 2–4 weeks of inhaled steroid treatment in the study period. We did not use any control tools, but their symptoms (during day, night, and exercise-induced cough) were questioned in control visits.

In the literature, we could not find any study that had evaluated uLTE₄ levels in children with isolated chronic nonproductive cough. In this study, we evaluated the uLTE₄ levels in children with isolated chronic nonproductive cough. No significant difference existed between the patient and control groups with respect to uLTE₄ levels. This finding suggests that there are factors other than LTs accounting for cough. It is also possible that although uLTE₄ levels are normal, the receptor may be too sensitive. Moreover, LTs may have an important role in some patients with chronic cough as in some asthmatic patients. Furthermore, when the levels of uLTE₄ are normal, this may indicate that the efficacy of leukotriene receptor antagonists (LTRAs) on chronic nonproductive cough is not sufficient. In addition, isolated chronic nonproductive cough may be different from asthma in several aspects and have a different pathophysiology. This was a pilot study, and further studies are needed to confirm the results indicated in this study.

Acknowledgments

The uLTE₄ level was measured in the Hacettepe University and the Pediatric Allergy and Immunology laboratory; so, we thank them.

Author Disclosure Statement

This study was done at the Dr Behcet Uz Child Disease and Surgery Education and Research Hospital, Department of Pediatric Allergy. There is no conflict of interest. An honorarium grant or other form of payment was not given to any author to produce the manuscript. All authors have significantly contributed to the work, approved the final manuscript, and taken full responsibility for the manuscript.

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Received for publication April 17, 2013; accepted after revision June 10, 2013.