Effect of Post-nasal Drip on Overnight-cough Frequency and Cough Pattern in Children with Asthma

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Objective: In children, post-nasal drip (PND)-induced cough is speculated. However, the relationship between PND and cough is still unclear.
Methods: During acute exacerbation of asthma, the number of overnight coughs and the cough pattern were compared in the children with atopic asthma with PND (n = 8) and the children with atopic asthma without PND (n = 27). All subjects had allergic rhinitis according to our original cough monitor.
Results: The total number of overnight coughs was significantly higher in the subjects with PND than in the subjects without PND ($P < 0.05$). In contrast, the overnight cough pattern of the subjects with PDN was found to be the same as in the subjects without PND, showing an increase in the number of coughs at the sleep onset and in the early morning.
Conclusion: Our results suggest that PND may increase the number of nighttime coughs in children with atopic asthma and allergic rhinitis. In contrast, the overnight cough pattern was the same in the two groups, suggesting that this specific cough pattern is due to allergic inflammation of the upper and lower airways.

Key words: asthma, children, cough, cough monitor, post-nasal discharge

INTRODUCTION

Cough is one of the most common symptoms in pediatric practice, and prolonged cough is also common. It is well known that childhood cough has a wide variety of causative disorders [1]. However, there are few global studies on cough diseases in children, as the mechanism and causative diseases of children are estimated to differ from those of adults [2], and the frequency varies among countries.

In contrast, as in adults [3], coughing associated with upper respiratory tract disease from the nose and sinuses to the larynx is common in children [4]. Upper airway cough syndrome (UACS) is a cough disorder associated with upper respiratory tract diseases [5]. Globally, asthma, protracted bacterial bronchitis and UACS are the most common causes of chronic cough in children [6]. UACS is not a specific disease and is diagnosed by clinical symptoms and signs related to the upper airway and the effect of antihistamines [7]. The main causative diseases of UACS are allergic rhinitis, non-allergic rhinitis and chronic nasal sinusitis [8]. Most of the diseases are associated with post-nasal drip (PND), and all of them are known to cause chronic cough.

Although there are many reports on the mechanism underlying the cough onset in UACS, the basic questions of whether or not PND itself causes coughs and how it does so remain unclear. In this study, we focused on the effect of PND, which is common in children, on the onset of cough. We used our original cough monitor [9] in children with atopic asthma with PND and evaluated the frequency of nocturnal cough and the cough pattern.

PATIENTS AND METHODS

Study subjects

In the present study, we used our cough monitoring system to measure nocturnal cough counts [9–11]. All of the subjects were pediatric inpatients at Tokai University Hospital and Tokai University Hachioji Hospital from September 2010 to December 2015. We invited all of the admitted patients with asthma exacerbation with PND to enroll in the study, and 8 children agreed (8 asthmatic children with allergic rhinitis and PND; median age, 8.0 [6.3–11.3] years, boys:girls = 4 : 4). We compared these subjects' findings with those of 27 asthmatic children with atopic asthma and allergic rhinitis without PND from our previous study. The overnight frequency of cough (number/night) and cough pattern were determined for each patient (Table 1).

Asthma was clinically diagnosed based on previous reports[12]. All asthma patients had a history of recurrent wheezing and symptom relief using β_2 agonist inhalation, and they showed bronchial hyperresponsiveness measured by the methacholine inhalation challenge [13, 14] and/or more than 12% improvement

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Table 1 The profiles of patients

	No.	Age (Years*)	Sex (m : f)	Comments**
Asthma with PND	8	8.0 (6.3–11.3)	4 : 4	postnasal drip(8) All atopic-type asthma
Asthma	27	8.0 (5.0–11.0)	14 : 13	All atopic-type asthma

*; median (first quartile, third quartile) ,
**; Numbers in parentheses indicate the number of patients.

in the FEV_1 (Forced expiratory volume in 1 second) after β_2 agonist inhalation. PND was defined as nasal discharge into the oropharyngeal cavity confirmed by the pediatrician at the time of admission.

In this study, all asthmatic participants received hospital treatment for asthma exacerbation according to the judgment of a pediatrician. The medical treatment provided in the hospital during this study corresponded to the Japanese Childhood Asthma Guideline 2012 [15]. The severity of acute asthma exacerbation can be divided into three groups [12, 15], and all participants in this report showed a moderate level of asthma exacerbation. Patients with symptoms of respiratory tract infections, such as a fever, were excluded from the study by the attending physician in order to focus on the effect of PND on childhood nocturnal cough.

The atopic patients were diagnosed with a positive allergic family history, and their reaction to common environmental allergens (house dust mites, grass, Japanese cedar pollen, pets) administered via the skin prick test and/or positive findings for a specific IgE antibody was recorded. All participants were atopic and received treatments (leukotriene receptor antagonist, n = 2, inhaled steroid and leukotriene receptor antagonist, n = 6). No patients received oral or corticosteroid injection in the emergency room before admission. The patients were only admitted to our hospital after it was determined that recurrent β_2 agonist inhalation was ineffective, and systemic steroid therapy was subsequently administered to the asthmatic patients who needed it.

Allergic rhinitis was diagnosed based on the characteristic clinical symptoms and the results of the allergic test. All cases had perennial and seasonal allergic rhinitis. PND was considered to be caused by allergic rhinitis and was determined by multiple pediatricians confirming oral PND at admission. At the time of this study, there were no complaints of rhinorrhea from the subjects in either the group with or without PND. GERD was not seen in any cases.

Approval was obtained from the Tokai University Hospital Institutional Review Board for Clinical Research (project approval number: 09R-141), and written informed parental consent was obtained for each child prior to the study.

Novel cough monitoring system

Our novel cough monitoring system consisted of a high-resolution microphone (EM167NM2, Primo Co., Tokyo, Japan), a highly-sensitive accelerometer (S18; Primo Co.) and a recorder (R-09HR; Roland Co., Hamamatsu, Japan) [9–11]. The software program used to calculate the number of cough sounds and the accelerometer were originally developed by our laboratory. A personal computer was used to perform the calculations.

Counting cough using the cough monitoring system

The cough events generated typical audio and accelerometer signals [9]. The microphone was placed at the second intercostal space in the mid-clavicular line, and the accelerometer was placed in the center of the abdomen between the navel and the sternal notch. A single eight-hour overnight recording session produces a set of files containing a total of four gigabytes of data, which can be archived using compact card-type memory. In addition, the cough index calculated by the microphone and accelerometer signals can be differentiated from others noises due to speech, crying, friction and snoring. The analysis of the signal related to cough-specific abdominal muscle movement and the simultaneous characteristic sound improves the accuracy of detection.

After completing an eight-hour recording, the stored data were transferred to a personal computer. The analysis software program automatically tagged explosive coughs when the sound signal and abdominal movement exceeded our pre-determined thresholds [9–11].

Data analyses

In this study, all cough data were analyzed using an original software program. The data were expressed as the median (first quartile, third quartile). The statistical analyses were conducted using a statistical software package (Grah Pad Prism version 8.4.3 for Mac; GraphPad Software, San Diego, CA, USA). A non-parametric analysis of variance (Dunn's multiple comparisons test following the Kruskal-Wallis test) was used to determine the presence of a significant difference between individual groups. The Mann-Whitney U-test was used to evaluate the difference between the two groups. P values of < 0.05 were considered to be statistically significant.

To analyze the time-dependent cough frequency pattern, we performed a polynomial trend line analysis for the evaluation of cough frequency patterns using a software program (Excel® for Windows; Microsoft, Redmond, WA, USA).

RESULTS

Total nocturnal cough count

An 8-h measurement of the number of coughs during sleep (10 pm to 6 am) was successfully performed in all participants. In the children with PND, the total number of overnight coughs was 137.5 ±

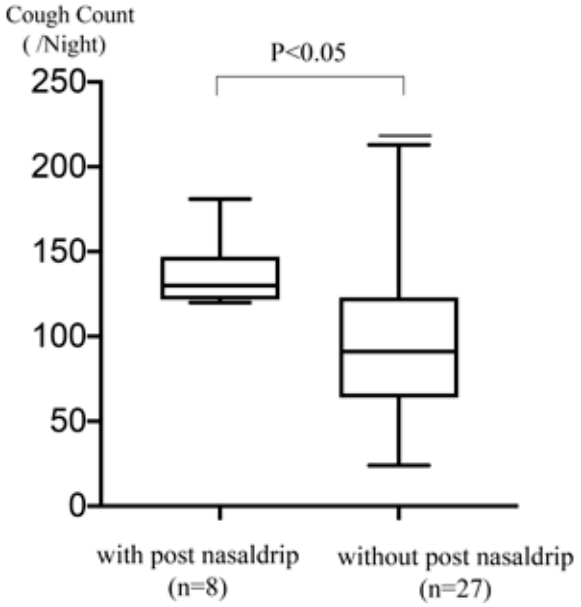

Fig. 1 The cough frequency in asthmatic children with and without PND

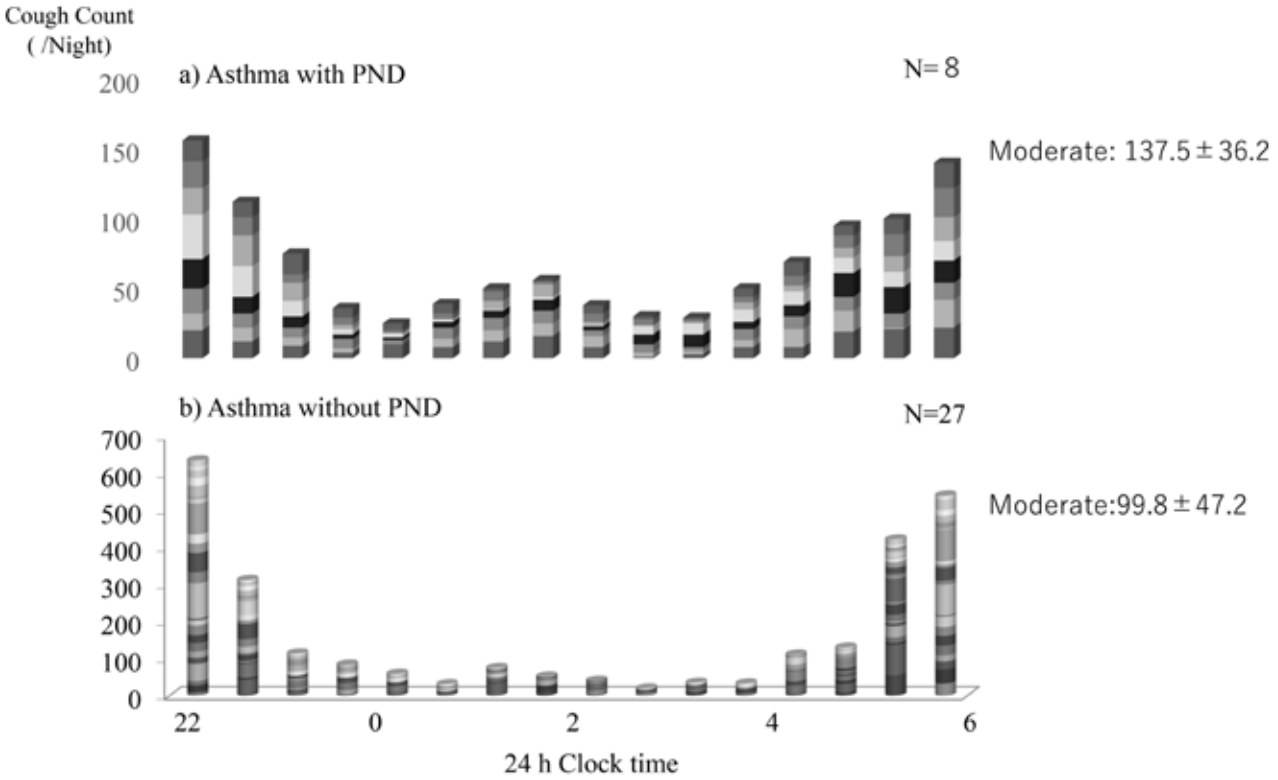

Fig. 2 The overnight cough pattern in asthmatic children with and without PND

36.2. This result was significantly higher than that of children without PND (99.8 ± 47.2/night) ($p < 0.05$) (Fig. 1).

Overnight pattern of cough frequency

For the evaluation of time-dependent cough patterns, the number of coughs every 30 minutes was calculated and shown in the figure (Fig. 2). A visual evaluation showed that the patients with PND coughed more frequently at all times than the patients without PND. In contrast, the pattern of nighttime cough in children with PND was similar to that in children without PND.

An analysis of the cough frequency patterns showed four 2-h sections of cough count numbers per person (1, just after falling asleep; 2, midnight; 3, before daylight; and 4, just before waking up) (Fig. 3a). The number of coughs per section in each case is compared as a percentage of the number of coughs per night in each case. In the patients with PND, the median of rates of coughing overnight in sections 1, 2, 3 and 4 were 32.8%, 12.7%, 13.8% and 34.2%, respec-

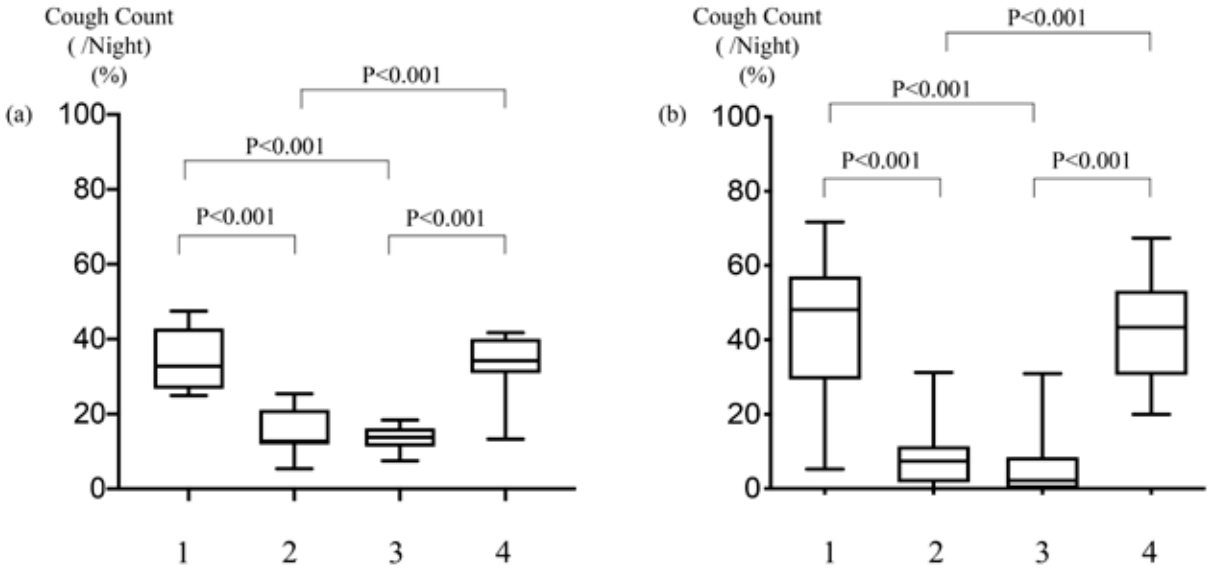

Fig. 3 The time-dependent cough frequency in asthmatic children with and without PND

tively. In the patients without PND, the median of rate of coughing overnight in sections 1, 2, 3 and 4 were 43.2%, 8.0%, 5.4% and 43.5%, respectively (Fig. 3b). Both with and without PND, the number of coughs in sections 1 and 4 was higher than the number of coughs in sections 2 and 3 and showed similar patterns ($p < 0.001$ and $p < 0.001$ respectively).

DISCUSSION

The prevalence of allergic rhinitis in children is reportedly 40% [16]. The problems of allergic rhinitis in children is that the number of patients has increased in recent years, and that it gradually develops even in younger children. Therefore, in the field of chronic cough, the number of patients with chronic cough associated with allergic rhinitis is considered to be increasing in both adults as well as children.

Allergic rhinitis is characterized by a significant amount of nasal discharge. As infants and children have an immature immune function, they often suffer from infectious sinusitis [16], resulting in an observation of viscous, white- or green-colored nasal discharge. Therefore, in children, not only inflammation of the airway mucosa but also direct cough-receptor stimulation of PND is presumed to underlie cough caused by allergic rhinitis.

However, there are many unclear points regarding the relationship between PND and cough onset. For this reason, we selected asthmatic children with PND thought to be caused by allergic rhinitis. The characteristics of their cough were evaluated using an original cough monitor [9], and we compared the data with same-age asthmatic patients without PND.

It is interesting that the frequency of overnight cough was significantly increased in the subjects with PND. This suggests that PND may directly stimulate cough receptors in the larynx and trachea to induce coughing [17]. However, in 2006, the evidence-based clinical practice guidelines from the American Thoracic Medical Association (ACCP) stated that PND caused by various diseases was unlikely to directly cause coughing [7]. The mechanism by which PND induces cough is unclear, as is whether or not inflammation of the upper respiratory tract directly stimulates cough receptors and whether or not PND causes cough independently. Thus, the previously used term PND syndrome (PNDS) is considered inappropriate [18].

For these reasons, in recent years, the term UACS has been proposed from a broader perspective [5]. All of our subjects have allergic rhinitis, and it seems that they can be diagnosed with UACS [19]. The mechanism underlying the onset of cough caused by PND have been fervently discussed. PND including pathogens can reportedly flow downstream and cause acute or chronic laryngitis or bronchitis, resulting in cough, and secretions can directly stimulate cough receptors in the larynx [7, 20]. Nakajima *et al.* reported that cough was significantly prolonged in subjects with allergic rhinitis and subjects with PND in their study of adult cough variant asthma and cough-predominant asthma [21]. Although the mechanism is not the same as in adult patients, aspiration of secretions from the mucosa can be a considerable coughing stimulus for children.

Regarding the pattern of overnight cough, it has been shown that even asthmatic children with PND have a characteristic U-shaped pattern in which coughing occurs frequently just after falling asleep and just before waking up, similar to the pattern in asthmatic children without PND. We used a cough monitor to study overnight cough in children with respiratory illness using a cough monitor [9]. In children with acute bronchitis and acute pneumonia, there was no significant occurrence of cough during sleep [10]. Patients with acute bronchiolitis also had higher cough numbers than those with asthma; however, no clear time-dependent cough pattern was found [11]. Whooping cough and psychogenic cough have an original cough pattern that is clearly different from the above-mentioned diseases [22, 23].

Since all subjects in this report had allergic rhinitis and atopic asthma, it is possible that type 2 allergic inflammation from the upper to the lower respiratory tract is involved in the establishment of the cough pat-

tern [24]. Although there are few reports in this field, it has been pointed out that the increase in TRPV1 associated with sensory nerves is the cause of UACS in children [25]. It is interesting that the increase in TRPV1 is influenced by the history of asthma and the increase of mucosal secretion. These results may be associated with the generation of a cough pattern specific to atopic asthma with allergic rhinitis, as we showed here. In this respect, in non-allergic rhinitis/sinusitis, the inflammation is limited to the upper airway, and the overnight pattern may differ from that of atopic asthma [26]. We plan to compare the overnight cough pattern of UACS with that of allergic rhinitis/sinusitis in a future study.

This study is limited by the number of cases being too small. Even when children were hospitalized, it was not easy to collect data with a cough monitor all night. Furthermore, as we wanted to select and compare typical UACS, strict criteria for children had to be set. In addition, the fact that an examination by an otolaryngologist expert was not conducted this time and the lack of consideration of the association between PND and upper airway infection also left ambiguity in the assessment. In addition, this study was limited to cases requiring hospitalization and compared with a group matched for age and severity of asthma exacerbation. However, it is important to investigate the effect of asthma symptoms on the development of cough. In the future, we would like to study the asthmatic children with PND and without PND during the stable state of asthma for comparison.

Even now, there are only a few reports of UACS in the pediatric field, and there has been no objective study of cough in UACS. Thus, it was difficult to compare our results with previous reports. According to a study of chronic cough associated with hyper cough syndrome [27], which is strongly associated with the nervous system, the Arnold nerve reflex is associated with protracted cough in adults; however, its effect is not seen in children [28]. Thus, the mechanism of cough onset may differ between adults and children as well as between younger and older children [29]. We therefore intend to increase the number of cases and perform a stratified analysis by age in a future study.

In the present study, using a cough monitor, the characteristics of cough during acute exacerbation of children with atopic asthma and allergic rhinitis with PND were compared with those without PND. It was found that the total number of coughs was significantly higher in the subjects with PND, while the overnight cough pattern was not markedly different between those with and without PND.

In the subjects with PND, the possibility was suggested that the presence of upper airway secretions and allergic inflammation in the airway mucosa may give rise to frequent coughing and specific patterns. An objective evaluation of cough using a cough monitor will continue to be useful for the phenotypic classification of chronic cough and determination of therapeutic effect.

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CONFLICT OF INTEREST

none.

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