Independent factors contributing to the daytime and nighttime asthmatic cough refractory to inhaled corticosteroids

Brief running title: Daytime and nighttime asthmatic cough

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Abstract

Background: Cough is a common feature of asthma, which is often resistant to inhaled corticosteroids (ICS). The pathophysiology involved in such refractoriness may be different between the daytime and nighttime asthmatic cough. We sought to identify factors contributing to the daytime and nighttime asthmatic cough refractory to ICS treatment.

Methods: Sixty-seven patients with asthma solely or predominantly presenting with chronic cough were prospectively enrolled from April 2012 to December 2014. At baseline and 12 weeks after ICS treatment, capsaicin cough threshold (C2, C5) and methacholine airway sensitivity and reactivity were examined. Cough visual analogue scales (VAS) and numeric scores were used to evaluate daytime and nighttime cough symptoms separately. The Japanese version of Leicester Cough Questionnaire was also completed. When either cough VAS or numeric scores showed an improvement of ≥50% or ≥2 points, patients were considered responders to ICS treatment.

Results: Fifty-five patients were eligible for evaluation. Subjective cough indices significantly improved at 12 weeks after ICS treatment ($p < 0.001$). Multivariate analysis revealed that lower C2 significantly contributed to the residual daytime cough ($p = 0.04$). Meanwhile, methacholine hyperreactivity and lower IgE levels were predictors of the nighttime residual cough ($p = 0.002$, and $p = 0.03$, respectively).

Conclusions: Heightened cough sensitivity is an independent factor of the daytime asthmatic cough refractory to ICS. In contrast, airway reactivity and less-allergic nature contribute to the nighttime cough refractory to ICS.

Keywords: Asthmatic cough. Cough sensitivity. Airway reactivity. IgE. Inhaled corticosteroids.

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Resumen

Antecedentes: La tos es una característica común del asma, que a menudo es resistente a los corticosteroides inhalados (ICS). La fisiopatología involucrada en dicha refractariedad al tratamiento esteroideo puede ser diferente entre la tos asmática diurna y nocturna. El objetivo del estudio es intentar identificar los factores que contribuyen a esta insensibilidad al tratamiento en la tos asmática diurna y nocturna.

Métodos: Sesenta y siete pacientes, con asma solo o con tos crónica, se inscribieron prospectivamente desde abril de 2012 a diciembre de 2014. Al inicio del estudio y 12 semanas después del tratamiento con ICS, se examinaron el umbral de tos frente a capsaicina (C2, C5) y la sensibilidad y reactividad de las vías respiratorias a la metacolina. Se usaron escalas analógicas visuales (VAS) y puntajes numéricos para evaluar los síntomas de tos diurna y nocturna de forma separada. La versión japonesa del Leicester Cough Questionnaire también se completó. Cuando las VAS o los puntajes numéricos mostraron una mejoría de ≥50% o ≥2 puntos, los pacientes se consideraron respondedores al tratamiento con ICS.

Resultados: Cincuenta y cinco pacientes completaron adecuadamente toda la evaluación. Los índices subjetivos de tos mejoraron significativamente a las 12 semanas después del tratamiento con ICS ($p < 0{,}001$). El análisis multivariante reveló que una C2 más baja contribuía significativamente a la tos diurna residual ($p = 0{,}04$). Por otra parte, la hiperreactividad a la metacolina y los niveles más bajos de IgE fueron predictores de la tos residual nocturna ($p = 0.002$ y $p = 0.03$, respectivamente).

Conclusiones: La sensibilidad aumentada a la tos es un factor independiente de la tos asmática diurna refractaria a los corticoides. Por el contrario, la hiperreactividad de las vías respiratorias y la ausencia de atopia contribuyen a la tos nocturna refractaria a los ICS.

Palabras clave: Tos asmática. Sensibilidad a la tos. Reactividad de las vías respiratorias. IgE, corticosteroides inhalados

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Introduction

Cough is the most common symptom for which patients seek medical care worldwide. Many patients with chronic cough lasting for 8 weeks or longer are referred to cough specialists. According to an epidemiological study in the United Kingdom, 12% of general population complained of cough once a week or more often[1]. Classical asthma and cough variant asthma (CVA) are major causes of chronic cough lasting for 8 weeks or longer, together with rhinosinusitis and gastroesophageal reflux disease (GERD)[2]. "Asthmatic cough", is generally alleviated by inhaled corticosteroids (ICS)[3]. However, a subset of patients are refractory to this mainstay treatment and cough is associated with poor asthma control in such patients, independent of airway obstruction[4].

As was clearly demonstrated by surveys conducted in Europe[5] and Canada[6], nocturnal cough is a common feature of asthma. Meanwhile, asthmatic cough may persist even when other symptoms such as wheezes and dyspnea are stabilized, and this may occur more frequently in the daytime than in the nighttime[7]. Indeed, in patients with stable asthma, the objective cough count is predominantly higher in the daytime than in the nighttime[7, 8]. Marsden et al. showed a significant correlation between the cough frequency of daytime, but not that of nighttime, and cough hypersensitivity to inhaled citric acid in patients with asthma[8]. However, little is known about the pathophysiology of the daytime and nighttime asthmatic cough refractory to ICS.

We hypothesised that different or independent factors are involved in the pathophysiology of the daytime and nighttime asthmatic cough refractory to ICS treatment. We conducted this study to identify such factors with a use of subjective cough measures, such as visual analogue scales (VAS), cough numeric scores, and the Japanese version of Leicester cough questionnaire (J-LCQ) before and after the treatment with ICS, with or without long acting β_2 agonists (LABA).

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Methods

Patients

We prospectively recruited consecutive patients with asthmatic cough lasting for ≥8 weeks, who newly visited our asthma and chronic cough clinic between April 2012 and September 2014. Patients were eligible for this study if they had not received ICS or leukotriene receptor antagonists for ≥4 weeks before their first visit. All were treated with ICS whose doses were 500 μg or higher (fluticasone propionate equivalent) for 12 weeks after the initial diagnosis. The use of LABA in combination with ICS as an initial therapy is considered by cough specialists (Y. K., H. M, T. O, and I. I.) according to the latest version of the national guideline for the management of cough by Japanese Respiratory Society (in Japanese, unpublished in English) as follows; (1) Patients are afflicted with frequent coughing on every day, and (2) Their daily life and sleeping are interfered by cough once a week or more. We refrained from using leukotriene receptor antagonists and histamine H1 receptor antagonists, as they may attenuate cough by improving cough sensitivity to inhaled capsaicin[9, 10].The use of proton pump inhibitors (PPI) for esophageal symptoms of GERD was permitted only if patients has received it for ≥4 weeks before their first visit, while its use for cough was not permitted. Current smokers, ex-smokers of >10 pack-years or those who quitted smoking in the past 6 months, or patients with other pulmonary diseases were excluded.

According to the original version of the Japanese Respiratory Society guidelines for management of cough [11], the definition of cough predominant asthma and cough variant asthma as follows. Clinical features of cough variant asthma included chronic cough without wheezing or dyspnea. Patients show almost normal pulmonary function but increased airway responsiveness. In the diagnosis of cough predominant asthma, cough is the commonest symptom but involves mild wheezing. The only difference

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between cough predominant asthma and cough variant asthma is the presence or absence of wheezing. Cough was improved by the inhalation of short acting β_2 agonists, which is the most specific characteristic finding of cough predominant asthma and cough variant asthma[12]. As clinical manifestations, pathophysiology, and treatments are similar between cough predominant asthma and cough variant asthma, they are considered as "asthmatic cough".

This study was approved by the ethics committee of Kyoto University and was registered in the UMIN Clinical Trials Registry (Registry ID UMIN 000007495). Written informed consent was obtained from all participants.

Measurements of functional and inflammatory markers

All participants underwent meticulous work-up between 09:00 and 13:00, including blood tests, measurement of fractional nitric oxide (FeNO), impulse oscillometry, spirometry, AHR to inhaled methacoline, and cough sensitivity to inhaled capsaicin, before and after 12 weeks ICS treatment. Detailed methods for obtaining each measurement were described previously[9, 13-15].

FeNO levels at an expiratory flow rate of 50 mL/s were measured with a chemiluminescence analyser (NOA^{TM} 280; Sievers, Boulder, CO, USA)[13]. Respiratory impedance [resistance at 5 Hz (R5) and 20 Hz (R20) and reactance at 5 Hz (X5)] was determined with a Jaeger MasterScreen impulse oscillometry system (MasterScreen IOS^{TM}, Fukuda denshi Corp, Tokyo, Japan)[14]. Spirometry was performed using a ChestGraph HI-801 spirometer (Chest MI Corp, Tokyo, Japan). AHR and cough sensitivity were measured using an Astograph (Chest MI Corp). AHR was measured by continuous inhalation of 10 doubling concentrations of methacholine[15, 16] (49 to 25,000 μg/mL) for 1 min for each concentration, following physiological saline inhalation to determine baseline respiratory resistance (Rrs). The total cumulative dose of

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methacholine at the end of inhaling the highest concentration was 50 units. Subjects inhaled methacholine until maximum methacholine concentrations or Rrs reached 2 folds of that of baseline values, followed by salbutamol inhalation for 2 min. Dmin, the cumulative dose of inhaled methacholine at the inflection point at which Rrs began to increase, was used as an index for airway sensitivity[15]. Astograph can automatically calculate the reciprocal of Rrs, airway conductance (Grs). A slope of methacholine-Grs dose-response curve (SGrs) is considered an index for airway reactivity[16]. Higher value indicates heightened airway reactivity. AHR was considered positive if Dmin was ≤12.5 units[15]. Cough sensitivity was measured by inhalation of 10 doubling concentrations of capsaicin (0.61 to 312.5 μM) for 15 sec for each concentration at 1-min intervals, following physiological saline inhalation for 1 min[9]. The concentrations required to induce at least two (C2) or five (C5) coughs were determined as cough thresholds[9]. The cough sensitivity test was conducted at least 15 min after the end of the AHR test.

Serum total and 7 antigen-specific IgE levels [house dust mite, cat or dog dander, Japanese cedar, mixed gramineae pollens (orchard grass, sweet vernal grass, bermuda grass, timothy, reeds), mixed weed pollens (ragweed, mugwort, goldenrod, dandelion, oxeye daisy), and mixed moulds (*Penicillium*, *Cladosprium*, *Aspergillus*, *Candida*, *Alternaria*)] (ImmunoCAP® total IgE and ImmunoCAP® specific IgE, Phadia K.K., Tokyo, Japan) were analysed at enrolment to determine atopic status. Patients were considered atopic when one or more specific IgE antibodies were positive at ≥0.35 IU/mL[17]. The number of sensitised aeroallergens was counted.

Subjective measures of cough

Three subjective cough measures were completed by all participants for the evaluation of cough frequency, cough severity, and cough-specific QoL.

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Numeric cough scores ranging from 0 to 5 reflected cough frequency and severity for both the daytime and nighttime (i.e. 0 = no cough during the day or night, 5 = cannot perform usual daytime activities or sleep at all because of severe symptoms) [7].

Daytime and nighttime cough VAS were also measured everyday. The cough VAS is a 100 mm-line scale, where its length represents cough severity (i.e. 0 mm = no cough, 100 mm = worst cough imaginable).[8, 17, 18]

Daytime was defined as between 06:00 and 22:00, according to the environmental quality standards for noise from the Basic Environment Law in Japan (https://www.env.go.jp/en/air/noise/noise.html). Average of daily numeric scores and VAS for the 7 days immediately before the commencement of ICS and the final evaluation at 12 week were calculated both in the daytime and nighttime. When either cough VAS or numeric scores showed an improvement of ≥50% or ≥2 points, patients were arbitrarily considered responders to ICS treatment.

Cough-specific QoL was evaluated using the J-LCQ[17, 19]. It consists of 19 questions with a 7 point Likert response scale covering three subdomains (physical, social, and psychological). The total scores range from 3 to 21. High scores indicate better QoL[17, 19-21]. J-LCQ was translated from the original version[19], and its validity and reliability were confirmed in a previous study.[17]

Statistical analysis

To determine cough frequency and severity by subjective measures, the sample size of the study subjects was set according to a previous study on the correlation between subjective and objective cough measures.[8] By aiming to test approximately 60 patients, subjective cough measures can be considered reliable for the evaluation of the severity and frequency of cough with a power of 0.8.[8]

Data obtained from patients were analysed using JMP 9.0 software (SAS Institute

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Inc., Tokyo, Japan). Data were presented as means (SD) or median (range) as appropriate. Gender was treated as dichotomous variables. When data were not normally distributed, they were log-transformed. Paired t-tests or unpaired t-tests were performed for the comparison of data. Multivariate regression analysis was applied to determine factors contributing the daytime and nighttime asthmatic cough refractory to ICS treatment. Variables with $p < 0.10$ by the univariate analysis among pre-treatment indices and their changes indices with ICS were included in the multivariate analysis, where variables with a $p \leq 0.05$ were considered statistically significant.

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Results

Patients' characteristics

A total of 67 patients with asthmatic cough (29 with cough predominant asthma and 38 with CVA) were enrolled. Eight of the 67 patients were lost during the 12-week follow-up, and 4 were additionally given PPI, as they were considered to have comorbid GERD potentially associated with cough. Thus, 55 patients were suitable for evaluation (Table 1). Of these, 31 patients (56%) received LABA in combination with ICS (ICS/LABA) during the 12-week follow-up. Thirteen patients had a smoking history with the average of 3.8 (3.6) packs-years. Fifteen patients were diagnosed to have allergic rhinitis (AR) prior to the first visit to our hospital, two of which had been treated with nasal corticosteroids for more than 8 weeks. At enrolment, eight patients had already been taking PPI for esophageal symptoms of GERD, but not for cough. These patients continued on the same treatment during the follow-up period.

The impact of ICS on cough severity and clinical indices

The impact of ICS on subjective cough measures is presented in Figure 1. At enrolment, 7 patients showed no nighttime cough. Of these, 6 remained without nighttime cough during follow-up. Cough was more frequent and severe in the daytime than in the nighttime both before and after ICS treatment. Cough severity, frequency and cough-specific QoL were significantly abated by ICS treatment. With respect to response to ICS, cough numeric scores of the daytime showed significant improvement as compared to that of the nighttime ($p = 0.001$, Figure 2). On the other hand, improvement of cough VAS was similar between daytime and nighttiime (Figure 2).

We have also evaluated the impact of ICS on subjective measures of cough stratified according to gender as females generally show higher prevalence of asthma and

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chronic cough than males. When patients were stratified according to gender, there was no difference of subjective cough indices before the initiation of ICS between males and females. All of subjective cough measures after ICS treatment except for nighttime cough numeric scores were significantly more marked in females than in males (Figure 3), while changes of subjective cough measures with ICS treatment according to gender were not significant (data not shown).

FeNO levels, airway reactivity, and R5 declined significantly with ICS treatment, but spirometry and cough sensitivity were unchanged (Table 1).

Factors independently associated with the daytime and nighttime asthmatic cough refractory to ICS

To determine factors contributing to the daytime and nighttime asthmatic cough refractory to ICS treatment, patients were stratified according to response to ICS treatment. Among the 55 patients, 16 (29%) and 8 (15%) showed a poor response of the daytime and nighttime cough respectively, at 12 weeks after ICS treatment. Of these, 6 complained of both the daytime and nighttime cough refractory ICS treatment.

Next, clinical factors associated with the daytime and nighttime cough refractory to ICS treatment were investigated. For the daytime cough refractory to ICS, lower levels of C2 before ICS treatment and female gender were marginal but no significant factors ($0.05 < p < 0.10$) (Table 2). Meanwhile, the use of LABA, lower serum total IgE levels, and lower number of sensitized aeroallergens were significantly related to the refractory nighttime cough after ICS treatment (Table 3). Female gender and airway hyperreactivity evaluated by SGrs were marginally associated with the refractory nighttime cough. Comorbidities such as GERD and AR were unrelated to both the daytime and nighttime cough (Table 2, 3). For changes of each index with ICS treatment, no relationships were

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also observed with either the daytime or nighttime cough (data not shown). Multivariate analysis of factors with $p < 0.10$ in the univariate analysis revealed that cough hypersensitivity as indicated by lower levels of C2 before ICS treatment solely contributed to the residual daytime cough after ICS treatment (Table 2). Female gender tended to associate with the daytime cough refractory to ICS. Meanwhile, airway highperreactivity and lower serum total IgE levels at enrolment were predictors of the residual nighttime cough (Table 3). Receiver operating characteristic analyses performed using significant indices on multivariate analysis revealed that serum IgE of <50 U/mL was significant markers to predict refractoriness to ICS for the nighttime cough with high AUC of 0.84 ($p = 0.001$, sensitivity 0.875, 1-specificity 0.298, Figure 4A). Indeed, patients who showed good response of the nighttime cough were higher serum IgE levels than those with the residual nighttime cough (284 IU/mL *vs* 27 IU/mL, $p = 0.005$, Figure 4B). However, values of C2 and SGrs were not significant for the detection of refractoriness to ICS for the daytime or nighttime cough (data not shown).

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Discussion

To date, ICS have been the mainstay treatment for asthmatic symptoms including cough. In the present study, we confirmed that subjective asthmatic cough occurred more frequently and severely in the daytime than in the nighttime both before and after ICS treatment. ICS significantly abated cough numeric scores of the daytime as compared to that of the nighttime, while response of cough VAS to ICS was similar between the daytime and nighttime. Cough hypersensitivity contributed to the residual daytime cough after ICS treatment; meanwhile, airway hyperreactivity and lower serum total IgE levels were predictors of the refractory nighttime cough. Thus, independent factors contribute to the refractoriness of daytime and nighttime asthmatic cough to ICS treatment.

Although asthmatic cough is alleviated by ICS irrespective of the time of day, cough hypersensitivity as indicated by lower C2 before ICS was significantly associated with the daytime cough refractory to ICS treatment. In studies of the difference in cough frequency between daytime and nighttime using objective cough measures, asthmatic cough occurred more frequently in the daytime than in the nighttime when patients were stable[7, 8]. Regarding the association between gender and cough frequency in patients with chronic cough, including asthma, females coughed more often than males, and heightened cough sensitivity was associated with the increased objective cough count[18]. In normal adults, cough threshold is lower during the daytime than the nighttime during sleep[22]. Recently, patients with asthma, especially females and non-atopic patients, showed significantly heightened capsaicin cough sensitivity than healthy subjects[23]. Besides cough hypersensitivity, female gender tended to associate with the refractoriness of the daytime cough in the current study. Cough hypersensitivity could be involved in the pathophysiology of the daytime asthmatic cough persisting after ICS treatment.

Our study also demonstrated that airway hyperreactivity and less-allergic nature as

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demonstrated by lower serum IgE levels were associated with the refractoriness of the nighttime cough refractory to ICS. Because of the nocturnal fall in circulating epinephrine and cortisol, nocturnal worsening cough, wheezing and airflow limitation are common in patients with asthma irrespective of their atopic status[24]. It is known that less atopic patients with asthma show poorer response to ICS treatment. In a study on the association between treatment response to ICS and lung function decline, long-term ICS treatment significantly supressed a decline in FEV_1 of patients who showed elevated serum total IgE levels of ≥100 kU/mL[25]. In contrast, such effect of ICS on pulmonary function was not observed in counterpart population[25]. Meanwhile, another study demonstrated that patients who showed no atopic predisposition or lower serum total IgE levels showed more exaggerated cough response to inhaled capsaicin than atopic patients[23]. In the present study, we did not find the association between less allergic nature and capsaicin cough sensitivity in the pathophysiology of the daytime or nighttime cough.

There are several limitations involved in this study. First, the number of subjects in this study was 55 patients without control subject. Furthermore, comorbidities such as GERD and rhinitis may have influenced the residual daytime and nighttime cough even if the condition of such comorbidities was stable. In addition, we should consider the onset or worsening seasons of cough, as well as patient's conditions such as concomitant rhinitis and atopic predisposition, since there factors may relate to the treatment response to ICS. When patients were stratified according to the seasons during which patients entered the study, the prevalence of rhinitis and atopic predisposition were similar irrespective of the seasons. The seasons and the atopic predisposition were also unrelated to the treatment response to ICS for either the daytime or nighttime cough (data not shown). Therefore, the influence of seasonal bias and allergic condition on cough could

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be negligible in this study. However, we should have included control groups to exclude the effect of comorbid rhinitis, atopy, and season variation. Second, we did not evaluate cough frequency using objective measures. This is because no validated method to record cough sounds is available in Japan. To address this weakness, we determined the number of subjects required to assess cough severity and frequency using subjective cough measures according to a previous study[8]. Nonetheless, we cannot preclude the possibility of measurement and recall bias. Third, the use of LABA in 56% of the patients may also have complicated the interpretation of the results. ICS/LABA is often prescribed in patients with asthma for the initial treatment in clinical practice. We confirmed no associations of the residual daytime and nighttime cough with the use of LABA by multivariate analysis. Lastly, symptom of the nighttime cough might be under-evaluated because nighttime was defined as from 22:00 p.m. to 6:00 a.m. of the next day according to the Basic Environment Law in Japan. Meanwhile, previous study defined the day and night as 5:00 to 23:00 and 23:00 to 5:00 the next morning, respectively[7].

In conclusion, cough sensitivity and airway reactivity are independently involved in the refractory daytime and nighttime asthmatic cough after ICS treatment. Less allergic nature also may contribute to such pathophysiology. To effectively treat persistent daytime and nighttime cough after ICS treatment, further detailed investigations on the roles of cough sensitivity, airway reactivity, and less atopic nature in asthmatic cough are needed.

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