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The Correlation Between Nasal Symptom and Mucociliary Clearance in Allergic Rhinitis

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Objective/Hypothesis: The Allergic Rhinitis and Its Impact on Asthma (ARIA) classification of allergic rhinitis (AR) is based on the severity and duration of nasal symptoms. Whether the nasal symptoms actually represent underlying nasal inflammation is unclear. The aim of this study was to evaluate the correlation between nasal symptoms and nasal inflammation using mucociliary clearance time (MCCT) in AR.

Study Design: A prospective cross-sectional study.

Methods: 73 AR patients were classified according to ARIA class: mild or moderate-severe intermittent AR (MIAR or MSIAR) and mild or moderate-severe persistent AR (MPAR or MSPAR). Each nasal symptom was scored as 1 to 3 on a severity scale (mild-moderate-severe). The sum of the individual nasal symptom scores gave the total symptoms score (TSS). MCCT was determined with the charcoal-saccharin method. MCCTs between ARIA classes were compared and correlations between TSS or days with symptoms per week (DSW) and MCCT were analyzed.

Results: Of the patients, 67.1% were moderate-severe degree. MSPAR had the worst MCCT, followed by MSIAR, MPAR, and MIAR (mean MCCTs of 14.32, 13.87, 11.94, and 10.28 minutes, respectively). TSS was well correlated with MCCT ($P = .538$, $P < .001$). DSW was also correlated with MCCT, but did not reach statistical significance ($r = 0.217$, $P = .065$). The mean MCCT of overall nasal symptoms increased along with each score step and a significant difference was noted between scores 2 and 3 ($P < .001$).

Conclusions: A high percentage of moderate-severe disease and a significant correlation of the severity and MCCTs suggest an important heterogeneity in this disease severity group. Discriminating between moderate and severe rhinitis should help to obtain homogeneous populations and develop improved disease management strategies.

Key Words: Allergic rhinitis, duration, mucociliary clearance, nasal symptom, severity.

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INTRODUCTION

Allergic rhinitis (AR) is classically considered to result from an IgE-mediated allergy associated with a nasal inflammation of variable intensity. Cells, mediators, cytokines, chemokines, neuropeptides, as well as adhesion molecules and cells all cooperate in a complex network causing mucosal inflammation and provoking nasal symptoms such as nasal obstruction, sneezing, itching, and watery discharge.[1]

Filtration of inspired air is one of the major functions of the nose. Mucociliary clearance of the nasal extracellular fluid that contains filtered particles and gases is fundamental to the function of the nose. Disturbances in nasal mucociliary clearance function are clearly a common cause of long-term respiratory disease, nasal infection, sinusitis, and otitis media, and are probably the cause of the high associations between AR and these comorbidities. Changes in ciliary structure occur in patients with long-standing AR. Damage to nasal cilia includes absence of dynein arms, radial spokes, ciliary membrane injury, and disorientation of central tubules.[2,3] Measurement of mucociliary clearance provides an overall integrated measurement of cilial function and allows assessment of the net effect of disease processes associated with underlying allergic inflammation. Disease states of AR lead to a significant decline in mucociliary function by adversely affecting the mucous layer or slowing the nasal ciliary beat frequency or both.[4,5]

The Allergic Rhinitis and its Impact on Asthma (ARIA) World Health Organization (WHO) workshop[1] proposed a classification system for AR based on

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duration and severity of symptoms, subdivided into intermittent or persistent disease and mild or moderate/severe degree. A stepwise therapeutic approach has been recommended based on this classification. This management guideline assumes that patients' nasal symptoms are well correlated with underlying allergic mucosal inflammation. This new classification is based on expert consensus and requires further validation. It is likely that nasal inflammation persists longer in patients with persistent AR than in those with intermittent AR, and should be more severe in moderate/severe than mild degree symptoms; however, these assumptions have never been confirmed. In rhinosinusitis, several studies have found no correlation between symptoms, quality of life, and objective findings.[6,7] If there was no or poor correlation between severity of nasal symptom and nasal mucosal inflammation in AR, the guideline could cause under/overtreatment in a number of cases. To clarify this situation, this study was undertaken, in which mucociliary clearance was used as objective data in relation to underlying mucosal inflammation and evaluated together with duration or severity of nasal symptoms to better understand the correlations.

MATERIALS AND METHODS

A prospective cross-sectional study was conducted on 73 AR patients at the Allergy and Rhinology Clinic, Department of Otolaryngology, Faculty of Medicine, Songklanagarind Hospital, Prince of Songkla University, Songkhla, Thailand, between January 1, 2007 and July 30, 2008. The protocol was approved by the ethics committee of the faculty of medicine at Prince of Songkla University. All volunteers gave their signed, informed consent before being recruited into the study. All subjects had rhinitis symptoms, were above 15 years or age, and had a positive puncture skin test to a panel of common local inhalant allergens (*Dermatophagoides pteronyssinus*, *D. farinae*, American cockroach, cat pelt, dog epithelium, mixed feathers, kapok, Bermuda, Johnson, Acacia, Careless weed, *Alternaria* sp, Aspergillus mix, *Candida albicans*, Penicillium mix, Fusarium, and *Cladosporium sphaerospermum*). Patients were excluded if they had current rhinorrhea symptoms or positive nasal endoscopic findings or sinus radiography (Caldwell and Waters' view) suggestive of concomitant sinusitis, nasal polyposis or severe septal deviation. Patients who had used intranasal, inhaled or systemic steroids within 2 months, an antihistamine within 2 to 7 days, a decongestant within 2 days, or were current smokers were also excluded from the study.

The medical history, including age, sex, nasal symptoms, concomitant diseases, and medications, was recorded. Asthma was noted if patient had a history of recurrent wheezing, dyspnea, chest tightness or cough (particularly at night), and a normal chest x-ray.

Clinical Assessment

AR patients were classified according to the ARIA guideline. Duration of symptoms was divided into intermittent (<4 days/week or <4 weeks/year) and persistent (>4 days/week and >4 weeks/year). The severity was moderate-severe in those patients who had one or more of the following: abnormal sleep, impairment of daily work or school performance, impairment of leisure activities, or presence of troublesome symptoms, and was classified as mild in those patients who had none of these items. According to the above criteria, the patients were divided into four groups: mild intermittent AR (MIAR), moderate/severe intermittent AR (MSIAR), mild persistent AR (MPAR), and moderate/severe persistent AR (MSPAR).

The evaluation of nasal symptoms was performed by each patient based on a compilation score of blocked nose, rhinorrhea, sneezing, nasal itching, and postnasal drip, scored as follows: score 0 = no symptoms, score 1 = mild symptoms (present but not troublesome), score 2 = moderate symptoms (troublesome symptoms but not sufficient to interfere with sleep, daily activities/sport, and/or work/school), and score 3 = severe symptoms (symptoms interfered with at least one of the following items: sleep, daily activities/sport, and/or work/school). The sum of the individual scores for nasal blockage, rhinorrhea, sneezing, nasal itching, and postnasal drip gave the total symptoms score (TSS).

Bilateral nasal mucociliary clearance times (MCCTs) were determined using a mixture of charcoal and saccharin powder. The method of the charcoal-saccharin test used was that described by Rutland and Cole, which is a modification of Andersen's original description of the test.[8] Approximately 1 to 2 mm on average of charcoal-saccharin powder in diameter was placed on the anterior end of the inferior turbinate behind the area of slow anterior clearance, 1 cm below the top of the concha. The subject was asked to sit quietly with head forward, and not to sniff, sneeze, eat, or drink. The first sensation of a sweet taste was reported by the subjects, and the pharyngeal wall was examined for the appearance of charcoal. Repeated inspections were made at 15-second intervals until charcoal was observed to confirm MCCT. The test was repeated on the other side, and the average of the two scores was taken as the nasal MCCT. This was done to exclude the effect of nasal cycle on MCCT. The charcoal-saccharin tests were performed between 1 PM and 3 PM to eliminate the influence of circadian and nasal rhythms.

Statistical Analysis

The nasal symptom, TSS, and MCCT were analyzed as mean ± standard deviation (SD). In comparisons of MCCTs between ARIA classes of AR and between nasal symptom scores, the normality assumption of MCCT was checked using the Komolgorov-Smirnov one-sample test. When the normality and homogeneity assumptions were satisfied, one-way analysis of variance was used first to ascertain whether or not significant variance existed among the groups. If a significant difference was apparent, post hoc multiple comparisons using the Tukey test were then used to test the significance of the differences between the groups. Correlation analyses between TSS or days with symptoms per week (DSW) and MCCT were analyzed by Spearman rank correlation coefficients and Pearson correlation coefficients, respectively. In all tests of significance, two-tailed alternatives were used. A P value of less than .05 was considered statistically significant.

RESULTS

Seventy-three patients were enrolled in this study. The baseline characteristics of the four ARIA classes of patients with AR, including nasal symptom scores and MCCTs, are presented in Table I.

Comparisons of MCCT Between Each ARIA Class of Patients With AR

MCCTs were evaluated in the four ARIA classes of AR (Fig. 1). MSPAR had the worst MCCT, followed by

TABLE I.
Baseline Characteristics of the Four ARIA Classes of Patients With AR (N = 73).

Characteristics	All Patients (n = 73)	Mild Intermittent Allergic Rhinitis (n = 10)	Moderate-Severe Intermittent Allergic Rhinitis (n = 12)	Mild Persistent Allergic Rhinitis (n = 14)	Moderate-Severe Persistent Allergic rhinitis (n = 37)
Age, y					
Mean	32.0	32.0	37.0	29.6	31.3
Range	15–62	15–44	17–62	17–46	18–62
Sex ratio, M/F	26/47	4/6	1/11	5/9	16/21
Duration of symptoms, y					
Mean	7.36	7.0	6.5	6.7	7.9
Range	1–29	1–20	1–16	1–20	1–29
History of asthma, No.	12	2	3	1	6
Nasal symptom score, mean±SD					
Blocked nose	2.05 ± 0.78	1.3 ± 0.48	1.83 ± 1.03	1.86 ± 0.36	2.41 ± 0.69
Rhinorrhea	2.01 ± 0.96	0.9 ± 0.88	2 ± 1.28	1.79 ± 0.43	2.41 ± 0.76
Sneezing	2.01 ± 0.92	1.4 ± 0.52	2.42 ± 0.90	1.43 ± 0.51	2.27 ± 0.96
Nasal itching	1.69 ± 0.97	0.8 ± 0.63	1.92 ± 0.99	1.36 ± 0.49	2.00 ± 1.00
Postnasal drip	1.33 ± 0.97	0.9 ± 0.74	1.75 ± 1.29	1.14 ± 0.66	1.38 ± 1.01
Total symptoms score	9.11 ± 2.95	5.3 ± 2.06	9.92 ± 3.63	7.57 ± 1.65	10.46 ± 2.06
Mucociliary clearance time	13.25 ± 3.94	10.28 ± 3.49	13.87 ± 3.94	11.94 ± 2.91	14.34 ± 3.97

ARIA = Allergic Rhinitis and Its Impact on Asthma; AR = allergic rhinitis; M = male; F = female; SD = standard deviation.

MSIAR, MPAR, and MIAR, respectively (mean MCCTs were 14.32, 13.87, 11.94, and 10.28 minutes, respectively). The moderate-severe degree of persistent AR had a significantly longer MCCT than the mild degrees of both intermittent and persistent AR ($P = .005$ and $P = .046$), but not the moderate-severe degree of intermittent AR ($P = .736$). The moderate-severe degree of intermittent AR had a significantly longer MCCT than the mild degree of intermittent AR ($P = .0364$), and tended to have a longer MCCT than the mild degree of persistent AR. There were no differences of MCCT between the mild degrees of intermittent and persistent AR, and also between the moderate-severe degrees of intermittent and persistent AR ($P = .216$ and $P = .736$).

The Correlation Between MCCT and TSS, and DSW

Figure 2A shows a positive correlation between TSS and MCCT ($P = .538$, $P < .001$). DSW and MCCT also show a positive correlation, but fail to achieve statistical significance ($r = 0.217$, $P = .065$) (Fig. 2B). As can be seen, TSS shows more of a correlation with MCCT than DSW.

The Relationships Between MCCTs and Nasal Symptom Scores

The MCCTs showed a tendency to increase in step with a higher nasal symptom scores. MCCTs between scores 0 and 3 were statistically significantly different in all nasal symptoms except for postnasal drip. Blocked nose had the largest MCCT difference between scores 0 and 3 (Fig. 3). The mean MCCT of overall nasal symptoms increased along with each score step, and a significant difference was presented between scores 2 and 3 ($P < .001$).

DISCUSSION

Depending on the classification of AR, several algorithm-guided therapeutic schemes, which usually follow a progressive management algorithm, can be used. However, pharmacological treatment based on existing guidelines is not effective in all patients.[9] The ARIA workshop has recommended a stepwise therapeutic approach depending on duration and severity of symptoms.[1] This new classification was based on expert consensus and required quantitative validation. It is questionable whether nasal symptoms actually represent

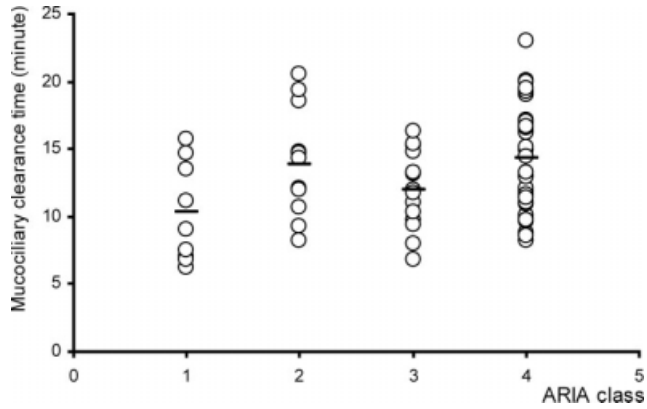

Fig. 1. Mucociliary clearance times (MCCTs) of the four Allergic Rhinitis and Its Impact on Asthma classes of patients with allergic rhinitis. Each symbol represents MCCT for each patient. Bars indicate mean.

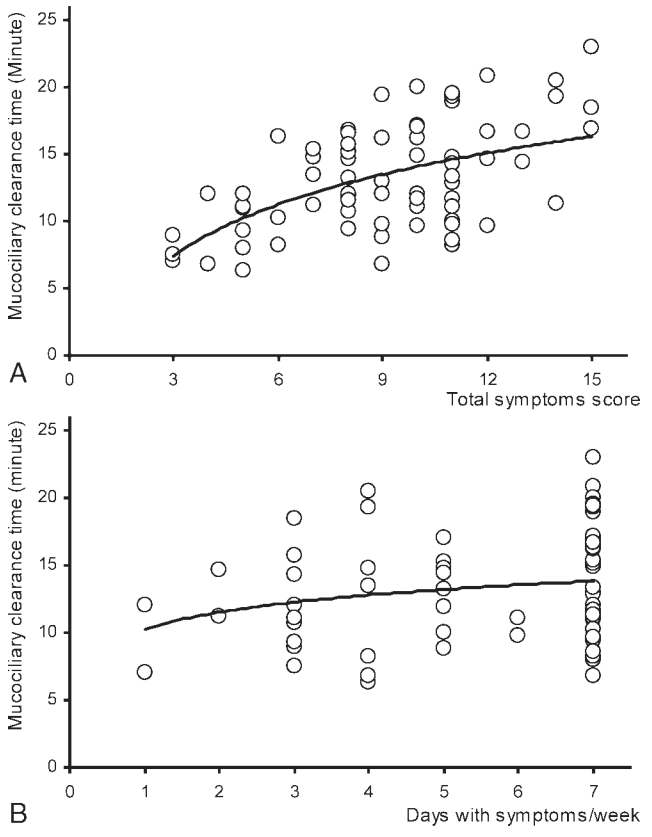

Fig. 2. Correlations between mucociliary clearance time (MCCT) and (A) total symptoms score (TSS), and (B) days with symptoms per week (DSW). Each symbol represents MCCT and TSS, and DSW for each patient.

underlying nasal inflammation. In the present study, MCCT was used to explore, at least in part, the underlying nasal mucosal inflammation, and to study whether duration or severity of nasal symptoms was related to underlying nasal inflammation.

MCCTs between the four ARIA classes were compared to examine correlations between both the severity and duration of nasal symptoms and MCCTs. Both severity and duration were correlated with MCCT as MSPAR had the worst MCCT. Because a moderate-severe degree of persistent AR had significantly longer MCCT than a mild degree of both intermittent and persistent AR, and there were no differences of MCCT between mild degrees of intermittent and persistent AR and between moderate-severe degrees of intermittent and persistent AR, the severity probably had more correlation with MCCT than the duration. To study this aspect, TSS, the sum of the individual severity scores for nasal blockage, rhinorrhea, sneezing, nasal itching, and postnasal drip, and DSW were used to represent the severity and duration of nasal symptoms and analyze the correlation with MCCT. The findings showed that TSS was well correlated with MCCT, in contrast to DSW, which was poorly correlated with MCCT. Indirect evidence has indicated that the severity of nasal symptoms might be a better indicator of underlying nasal mucosal inflammation. Studies of cells infiltrating the nasal mucosa during the pollen season have shown an increase in the numbers of various inflammatory cells, which was also correlated with both the severity of symptoms[10–12] and nasal nonspecific hyperreactivity.[13] The severity of rhinitis was found to have more impact on quality of life and sleep, daily activities, and work performance than the duration of rhinitis.[14] For the severity of all individual nasal symptoms except postnasal drip, a linearly increasing MCCT was found from mild to moderate to severe degrees, with blocked nose showing the best correlation. Several studies have reported nasal congestion affects most individuals with AR, and has a notable impact on quality of life, emotional function, productivity, and the ability to perform daily activities.[15] The 3-severity scale nasal symptom scores, particularly for blocked nose, might be a good guide in a stepwise, adjustable management approach.

Epidemiological studies have shown that 69% of patients with rhinitis consulting at otolaryngology and allergy clinics and 90% of those consulting general practitioners,[16–18] and 67% of patients in this study, have had moderate/severe symptoms. Around one-third of these patients with moderate/severe symptoms are uncontrolled despite optimal pharmacological treatment based on existing best-practice guidelines, and some still suffer severe symptoms, particularly conjunctivitis and nasal obstruction.[1] Our findings showed that the severities of nasal symptoms are well correlated with MCCT, with a significant increase of MCCT between each score step. These findings suggest an important heterogeneity in this disease severity group and support the need to discriminate between moderate and severe patients rather than including both in a single moderate/severe group as recommended by the ARIA document.[1] The discrimination between patients with moderate and severe AR using a 3–severity-level scale should help to obtain more homogeneous populations for better clinical research and disease management strategies. Although further clinical studies are required for validation of this proposed classification change, we believe that the discrimination between moderate and severe AR could be important for both research and therapeutic purposes.

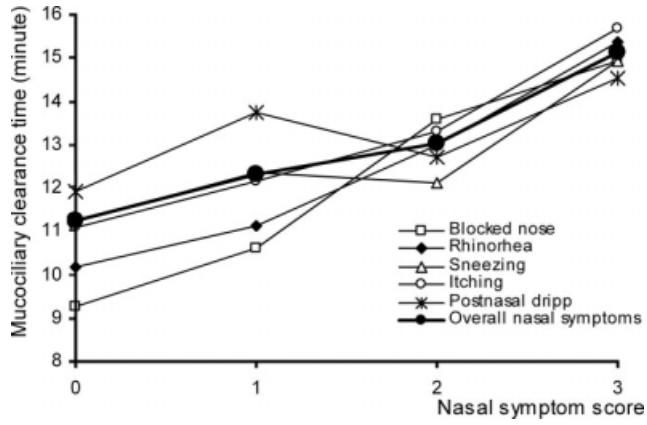

Fig. 3. The relationship between nasal symptom scores and mucociliary clearance times (MCCT)s. Data are shown as mean MCCT.

CONCLUSION

The main findings of the current study were 1) a high percentage of AR patients were moderate-severe degree, 2) a good correlation was found between the severity of nasal symptoms and MCCT, but not duration of nasal symptoms, 3) for the severity of all individual nasal symptoms except postnasal drip, a linearly increasing MCCT was found from mild to moderate to severe degrees, and blocked nose showed the best correlation, and 4) the ARIA severity criteria might be reclassified into three levels: mild (symptoms present but not troublesome), moderate (troublesome symptoms but not sufficient to interfere with sleep, daily activities/sport, and/or work/school), and severe (symptoms interfere with at least one of following: sleep, daily activities/sport, and/or work/school).

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