

## Original article

# Nasal blockage and urinary leukotriene E4 concentration in patients with seasonal allergic rhinitis

**Background:** Cysteinyl-leukotrienes have been reported to have a primary role in the induction of nasal blockage of allergic rhinitis. However, there has been little experimental evidence that substantiates the relationship between nasal blockage severity and urinary leukotriene E4 (U-LTE4) concentration in patients with seasonal allergic rhinitis (SAR).

**Methods:** The concentrations of urinary mediators in 20 SAR patients were measured using an enzyme immunoassay to determine the relationship between nasal blockage severity and U-LTE4 concentration in patients with SAR.

**Results:** The basal U-LTE4 concentration was significantly higher in SAR patients with severe nasal blockage than in those with mild nasal blockage and in healthy control subjects. Although U-LTE4 concentration was significantly higher in patients with both asthma and SAR than in SAR patients with mild nasal blockage, no significant difference in the U-LTE4 concentration between patients with both asthma and SAR and SAR patients with severe nasal blockage was found. There was a significant correlation between U-LTE4 and urinary  $9\alpha11\beta$ -prostaglandin F<sub>2</sub> ( $9\alpha11\beta$ PGF<sub>2</sub>) concentrations ( $r_s = 0.51$ ,  $P = 0.02$ ) in SAR patients.

**Conclusions:** Although specific sites and cells of cysteinyl-leukotriene biosynthesis could not be determined in this study, severe nasal blockage is associated with the increased excretion level of U-LTE4.

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Key words: cysteinyl-leukotriene; nasal blockage;  $9\alpha11\beta$ -prostaglandin F<sub>2</sub>; seasonal allergic rhinitis.

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As the recently published Allergic Rhinitis and its Impact on Asthma (ARIA) guideline (1), which was established in collaboration with the World Health Organization (WHO), draws on the epidemiologic and pathophysiologic evidence supporting the 'one airway' disease concept, there are strong and consistent associations between asthma and allergic rhinitis (2). There are many pathophysiologic similarities between asthma and allergic rhinitis. The same inflammatory mediators, that is, histamine (3, 4) and cysteinyl-leukotrienes (cys-LTs) (5–7), are found in both the upper and lower airways, and play an extremely important role in the pathophysiologies of asthma and allergic rhinitis. However, the effect of intranasal administration of histamine and cys-LTs on allergic rhinitis symptoms is quite characteristic. Histamine is primarily involved in the induction of

sneezing, rhinorrhea, and nasal itchiness, but it has an obstructive effect only at relatively high concentrations (8). On the other hand, intranasal administration of cys-LTs mainly causes nasal blockage, with very limited effects on the three other characteristic symptoms of allergic rhinitis (5, 6, 9). In addition, some clinical studies also provided objective evidence that a leukotriene synthesis inhibitor, zileuton (10), and leukotriene receptor antagonists (LTRAs) (11, 12) are effective for the treatment of allergic rhinitis. Recently, the effectiveness of montelukast and cetirizine cotherapy in improving symptom scores for nasal blockage as demonstrated by Wilson et al. (13) and Meltzer et al. (14), compared with the lack of effectiveness of antihistamines against nasal blockage observed in previous studies (15), confirms the particular involvement of cys-LTs in inducing nasal blockage in seasonal allergic rhinitis (SAR). As opposed to these findings, Nayak et al. (16) demonstrated that monotherapy with loratadine 10 mg alone provided the clinical effectiveness against nasal blockage as observed in the monotherapy with montelukast 10 mg alone.

Previous studies have shown that the urinary leukotriene E4 (U-LTE4) concentration is useful in demonstrating cys-LTs release *in vivo* during allergen challenge

**Abbreviations:** CAP-RAST, capsulated hydrophobic carrier polymer-radioallergosorbent; Cys-LTs, cysteinyl-leukotrienes; EDN, eosinophil-derived neurotoxin; EIA, enzyme immunoassay; HPLC, high-performance liquid chromatography; JCP, Japanese cedar pollinosis; LTRA, leukotriene receptor antagonist;  $9\alpha11\beta$  PGF<sub>2</sub>,  $9\alpha11\beta$ -prostaglandin F<sub>2</sub>; SAR, seasonal allergic rhinitis; U-LTE4, urinary leukotriene E4.

(17, 18) and acute exacerbation of asthma (19). In contrast, there is only one study showing that there is no significant difference in the U-LTE4 concentration between symptomatic patients with allergic rhinitis and healthy control subjects (20). Furthermore, there is no experimental evidence that substantiates the relationship between nasal symptom severity and urinary eicosanoid concentration in patients with SAR. Therefore, we hypothesized that the basal U-LTE4 concentration is significantly higher in SAR patients with severe nasal blockage than in healthy control subjects. We attempted to measure the U-LTE4 concentration in patients with SAR and to determine its relationship with nasal blockage severity. Here, we demonstrated for the first time that there is a significant relationship between nasal blockage severity and U-LTE4 concentration. Although specific sites and cells of cys-LT biosynthesis could not be determined in this study, this result suggests that severe nasal blockage is associated with the increased excretion level of U-LTE4.

## Materials and methods

### Subjects

Twenty nonsmoking patients with SAR (mean age, 38.9 years; five males and 15 females; Table 1) participated in this study. The diagnosis of allergic rhinitis was based on the currently used criteria (21). All the patients were selected on the basis of a well-documented history of seasonal attack of sneezing, rhinorrhea and nasal blockage during the season of Japanese cedar pollinosis (JCP) (from the first week of February to the end of April; in-season), no clinical history of asthma, and clinical examination by anterior rhinoscopy and allergy tests, including the intradermal test, nasal provocation test and *in vitro* specific IgE test (capsulated hydrophobic carrier polymer-radioallergosorbent or CAP-RAST) test. All the patients had normal lung function and normal airway hyperresponsiveness. None of the patients were taking medications such as intranasal corticosteroids, oral antihistamines, and leukotriene receptor

Table 1. Clinical characteristics of patients who participated in the study

|                                              | SAR              | SAR + BA        | P value |
|----------------------------------------------|------------------|-----------------|---------|
| Number of patients                           | 20               | 20              |         |
| Male                                         | 5                | 11              | NS      |
| Age (years)*                                 | 38.9 (13–61)     | 43.4 (25–66)    | NS      |
| Age at onset (years)*                        | 30.7 (7–55)      | 28.0† (9–51)    | NS      |
| Blood eosinophil ( $\times 10^9$ per liter)* | 0.38 (0.10–0.70) | 0.64 (0.2–1.42) | <0.005  |
| IgE (IU/ml)‡                                 | 93 (18.1–1225)   | 316.5 (20–430)  | <0.05   |
| IgE RAST against                             |                  |                 | NS      |
| Japanese cedar, score                        |                  |                 |         |
| Score 2 (number)                             | 3                | 4               |         |
| Score 3 (number)                             | 7                | 6               |         |
| Score 4 (number)                             | 10               | 8               |         |
| Score 5 (number)                             | 0                | 2               |         |

Definition of abbreviations: NS, not significant; SAR, seasonal allergic rhinitis; BA, bronchial asthma.

\* Arithmetic mean with range in parentheses.

† Age at onset of SAR.

‡ Median, with range in parentheses.

antagonists at the time prior to this study. None of the patients had an upper respiratory tract infection or had taken antibiotics in the 6 weeks preceding the study. In addition, a total of 20 patients with both allergic rhinitis and asthma (mean age 38.9 years; 11 males and nine females) were also enrolled in this study as disease control subjects. The diagnosis of asthma was based on the American Thoracic Society criteria (22). The patients were classified into moderately or severely persistent asthmatics according to the Global Initiative for Asthma guideline (23). Patients who had a respiratory tract infection or exacerbation of asthma during the 6 weeks preceding the study were excluded from the study. Thirty-five healthy volunteers without subjective symptoms or objective findings of diseases including asthma and allergic rhinitis were also enrolled in this study as healthy control subjects (mean age 38.9 years; 23 males and 12 females).

Permission to conduct this study was obtained from the Ethics Committee of the National Sagami Hospital and all the patients who participated in the study gave their informed consent.

### Measurements

Urine samples were collected between 9 : 00 AM and 11 : 00 AM.

**Leukotriene E4.** The U-LTE4 concentration was measured as previously described (24, 25). Briefly, after extraction with an Empore C18 cartridge (3M, St. Paul, MN), the extract was purified by high-performance liquid chromatography (HPLC). The column effluents whose retention times corresponded to that of authentic LTE4 were collected. The concentrations of cys-LTs were measured using an enzyme immunoassay (EIA; Cayman, Ann Arbor, MI). The antiserum showed a slightly lower affinity for LTE4 (70% cross-reactivity); thus, the LTE4 concentration was calculated from a standard curve constructed using authentic LTE4.

**Prostanoids.** The concentration of urinary  $9\alpha 11\beta$  prostaglandin F2 ( $9\alpha 11\beta$ PGF2) in the 20 SAR patients, the corresponding urinary metabolite of PGD2, was measured using EIA (Cayman) after extraction with an Empore C18 cartridge, according to the methods of O'Sullivan et al. (26). The percentage of  $9\alpha 11\beta$ PGF2 recovered after purification was approximately 60–70%.

**Eosinophil-derived neurotoxin (EDN).** The urinary EDN concentration in the 20 SAR patients was measured using a commercially available EIA kit (MBL, Nagoya, Japan) after diluting the urine 50 times in phosphate buffer (27).

The urinary concentrations of eicosanoids and EDN were expressed as picograms per milligram (pg/mg) of creatinine.

### Nasal blockage score in SAR

At the first visit at our hospital, the 20 patients with SAR were instructed to keep a record of their nasal and eye symptoms and of the degree to which these symptoms interfered with their everyday life in accordance with the manual that was prepared in advance with regard to recording these symptoms. For allergic rhinitis symptoms, scores of 0–4 indicated no, mild, moderate, severe, and very severe symptoms, respectively (28). In this study, we focused on the relationship between nasal blockage severity and U-LTE4 concentration. Therefore, the degree of nasal blockage due to allergic rhinitis and the degree of disturbance in daily life were scored on a scale of 0–4 points as reported previously (29). Briefly, the following scoring system was used for nasal blockage: 0, breathing through the nose freely and easily; 1, slight difficulty in breathing through the nose;

2, moderate difficulty in breathing through the nose; 3, severe difficulty in breathing through the nose; and 4, breathing through the nose is extremely difficult or impossible.

We compared the U-LTE4 concentration between patients with severe nasal blockage (3, 4 points) and those with negative or mild nasal blockage (0–2 points).

### Statistical analyses

Clinical characteristics are expressed as means with the minimum to maximum range. Comparison of IgE concentrations between patients with SAR and those with both SAR and asthma was performed using Wilcoxon–Mann–Whitney's *U*-test. Comparisons of other clinical characteristics were performed using the unpaired *t*-test or the chi-squared test and Fisher's test. Comparisons of U-LTE4 concentrations among all the groups were first carried out using the Kruskal–Wallis test. When a significant difference was found, the Student–Newman–Keuls test for comparison between groups was performed. Analyses of relationships were carried out using Spearman's rank correlation test. *P* values of less than 0.05 were regarded as statistically significant.

### Results

Table 1 shows the clinical characteristics of the patients with SAR. The groups were age- and sex-matched. The subjects of this study comprised 14 SAR patients who had no or mild nasal blockage (mean age 37.6 years; four males and 12 females), and six SAR patients who had severe nasal blockage (mean age 41.8 years; one male and five females). Figure 1 shows the U-LTE4 concentrations in each group. The basal U-LTE4 concentration was significantly higher in patients with severe nasal blockage than in healthy control subjects (mean, 98.2 vs 55.8 pg/mg of creatinine;  $P < 0.05$ ) and in those with mild or no nasal blockage (mean, 98.2 vs 43.5 pg/mg of creatinine;  $P < 0.01$ ). In addition, the basal U-LTE4 concentration was significantly higher in patients with both asthma and SAR than in healthy control subjects (mean, 109.4 vs 55.8 pg/mg of creatinine;  $P < 0.01$ ) and in those with mild or no nasal blockage (mean, 109.4 vs 43.5 pg/mg of creatinine;  $P < 0.01$ ). However, no significant difference in the U-LTE4 concentration between patients with both asthma and SAR and SAR patients with severe nasal blockage (mean, 109.4 vs 98.2 pg/mg of creatinine; NS) was found. In contrast, there was no significant difference in the U-LTE4 concentration between all the 20 patients with SAR and healthy control subjects in-season (mean, 59.9 vs 55.8 pg/mg of creatinine, NS). There were no significant differences in the urinary concentrations of EDN and in those of  $9\alpha11\beta$ PGF2 between the patients with severe nasal blockage and those with mild or no nasal blockage (mean urinary EDN, 324.0 vs 201.5 ng/mg of creatinine; median urinary  $9\alpha11\beta$ PGF2, 41.9 vs 18.7 pg/mg of creatinine). There was a significant correlation between the concentration of U-LTE4 and that of urinary  $9\alpha11\beta$ PGF2 ( $r_s = 0.51$ ,  $P = 0.02$ , Fig. 2). However, no correlation between U-LTE4 and urinary EDN

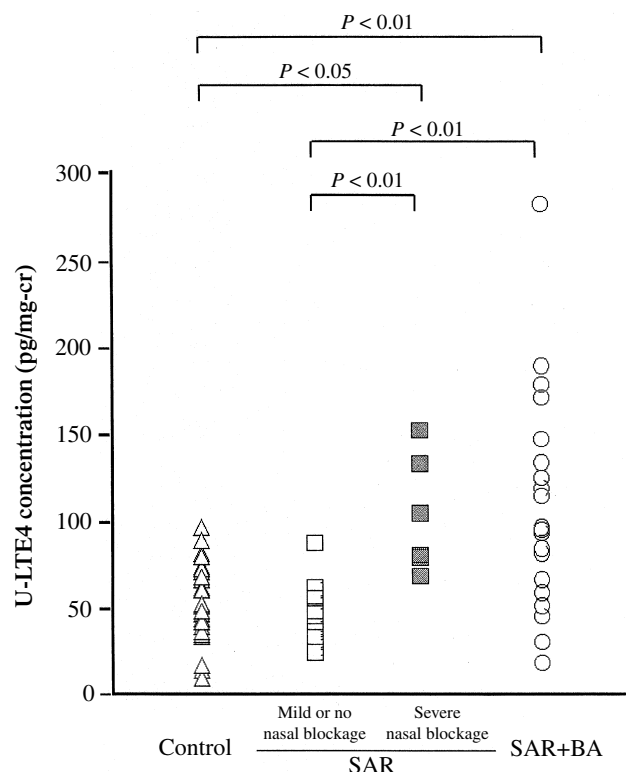


Figure 1. Urinary leukotriene E4 concentration (pg/mg of creatinine) in each group. Healthy control subjects, seasonal allergic rhinitis patients with mild or no nasal blockage, seasonal allergic rhinitis patients with severe nasal blockage, and patients with both seasonal allergic rhinitis and asthma, are designated by open triangles, open squares, solid squares, and open circles, respectively.

concentrations was observed (data not shown). There was no significant correlation between any other measured urinary biological parameters and nasal blockage severity in patients with SAR.

### Discussion

Cys-LTs have been reported to have a primary role in the induction of nasal blockage of allergic rhinitis, with limited effect on other rhinitis symptoms (5–7, 9). However, there has been little experimental evidence that substantiates the relationship between nasal blockage severity and U-LTE4 concentration in patients with SAR. Thus, we were particularly interested in the relationship between nasal blockage severity and U-LTE4 concentration in patients with SAR, and therefore the scale used for recording blockage symptoms was more specific than that used for other symptoms. In this study, we demonstrated for the first time that the basal U-LTE4 concentration was significantly higher in SAR patients with severe nasal blockage than in those with mild or no nasal blockage and in healthy control subjects. In accordance with a previous

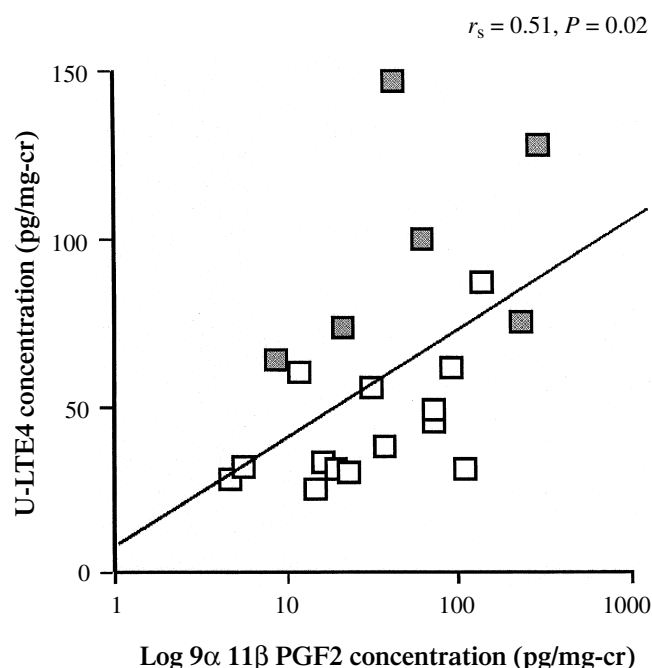


Figure 2. Correlation between urinary  $9\alpha11\beta$ PGF<sub>2</sub> concentration and urinary leukotriene E4 concentration in patients with seasonal allergic rhinitis. Seasonal allergic rhinitis patients with severe nasal blockage, and those with mild or no nasal blockage are designated by solid squares and open squares, respectively.

study by Taylor et al. (20), we also confirmed that there was no significant increase in the U-LTE4 concentration in all the patients with SAR compared with that in healthy control subjects. However, all the six patients with severe nasal blockage excreted U-LTE4 at increased concentrations. More interestingly, there was no significant difference in the U-LTE4 concentration between the patients with both SAR and asthma and SAR patients with severe nasal blockage. Taken together, these results indicate that nasal blockage may be induced by overproduction of cys-LTs in the nasal cavity of SAR patients.

The U-LTE4 concentration has been regarded as an index of systemic cys-LT biosynthesis. Since measure-

ment using urine samples may not be as sensitive as that using nasal lavage samples for detecting minor differences in the concentration of cys-LTs in the nasal cavity, it is important to measure cys-LT concentration in nasal lavage. However, our finding that rhinitis patients with severe nasal blockage exhibit an increase in their urinary excretion of LTE4, which is reported for the first time in this study, suggests the possibility of a further increase in U-LTE4 concentration in asthmatic patients with rhinitis having a severe rhinitis-induced nasal blockage. In the future, it is necessary to carry out further prospective investigations using a large number of patients, and determine whether or not the decrease in the U-LTE4 concentration is associated with the attenuation of the severity of the nasal blockage by manometry in SAR patients or in patients with both asthma and SAR. Volovitz et al. (30) demonstrated that the concentration of cys-LTs in nasal washes of children with asthma decreased during the therapy with montelukast.

Next, the main source of U-LTE4 in patients with SAR remains unknown. We assessed the relationship between the concentration of U-LTE4 and that of urinary  $9\alpha11\beta$ PGF<sub>2</sub>, another metabolite presumably related to mast cell activation (26). Our study demonstrated that there is a significant correlation between U-LTE4 and  $9\alpha11\beta$ PGF<sub>2</sub> concentrations. On the other hand, in this study, we found that there is no significant correlation between U-LTE4 and EDN concentrations. Taking these data together, the major source of U-LTE4 in patients with SAR is considered to be cys-LTs generated by mast cells rather than by eosinophils. In support of this notion, Yamasaki et al. (31) have demonstrated in an experimental guinea pig allergic rhinitis model that eosinophils are not required for the development of nasal symptoms and nasal hyperresponsiveness in allergic rhinitis.

In conclusion, cys-LTs in the nasal cavity are involved in the pathophysiology of nasal blockage in SAR patients. Although specific sites and cells of cys-LTs biosynthesis still remain to be clarified, we demonstrated for the first time that there is a significant relationship between nasal blockage severity and U-LTE4 concentration.

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