

# Clinical features of asthmatic patients with increased urinary leukotriene E4 excretion (hyperleukotrienuria): Involvement of chronic hyperplastic rhinosinusitis with nasal polyposis

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**Background:** The urinary leukotriene E4 (U-LTE4) concentration is significantly increased in patients with aspirin-intolerant asthma (AIA). However, the relationship between the clinico-pathogenetic factors of asthma and the U-LTE4 concentration remains undetermined.

**Objective:** We sought to examine the clinical features of asthmatic patients with increased excretion levels of U-LTE4 (hyperleukotrienuria).

**Methods:** We measured the U-LTE4 concentrations in 137 asthmatic patients (including 64 patients with AIA) who were in clinically stable condition. A U-LTE4 concentration of 150 pg/mg creatinine or greater (mean U-LTE4 + 3 SDs of normal healthy control subjects) was indicative of hyperleukotrienuria.

**Results:** The basal concentration of U-LTE4 was significantly higher in the patients with AIA than in those with aspirin-tolerant asthma (ATA; median, 227.2 vs 90.3 pg/mg creatinine;  $P < .01$ ). Compared with normal leukotrienuria in the patients with AIA, hyperleukotrienuria in the patients with AIA was associated with older age and decrease in pulmonary function. On the other hand, compared with normal leukotrienuria in the patients with ATA, hyperleukotrienuria in the patients with ATA was associated with severe asthma and chronic hyperplastic rhinosinusitis with nasal polyposis (CHRS/NP), which are well-known symptoms of the aspirin triad, as well as hypereosinophilia and anosmia. The patients with ATA with CHRS/NP excreted U-LTE4 at significantly high concentrations. There were significant decreases in the U-LTE4 concentrations before and after the sinus surgery in both the AIA and ATA groups ( $P < .05$ ).

**Conclusion:** Cysteinyl leukotrienes are not strictly associated with aspirin intolerance itself but rather with clinical features, such as CHRS/NP, that are similar to those seen in AIA.

CHRS/NP might be involved in cysteinyl leukotriene overproduction in asthmatic patients. (*J Allergy Clin Immunol* 2004;113:277-83.)

**Key words:** Aspirin-intolerant asthma, urinary leukotriene E4, chronic hyperplastic rhinosinusitis with nasal polyposis

Cysteinyl leukotrienes (cys-LTs), namely leukotriene C4 (LTC4), LTD4, and LTE4, play an extremely important role in the pathophysiology of asthma.<sup>1</sup> Cys-LTs cause potent bronchoconstriction, mucosal edema, and increased mucus secretion within the airways of asthmatic patients.<sup>2,3</sup> LTE4 has been identified as a major metabolite of LTC4,<sup>4,5</sup> and urinary LTE4 (U-LTE4) is now considered as the most reliable analytic parameter for monitoring the endogenous synthesis of cysLTs.<sup>6,7</sup> Previous studies have shown that the U-LTE4 concentration is useful in demonstrating cys-LT release in vivo during allergen challenge<sup>8,9</sup> and acute exacerbation of asthma.<sup>10,11</sup> Moreover, even in clinically stable conditions, basal urinary excretion levels of LTE4 in patients with aspirin-intolerant asthma (AIA) are significantly higher than those in patients with aspirin-tolerant asthma (ATA).<sup>12,13</sup> The cellular source of cys-LTs is as yet unknown, but it possibly includes eosinophils and mast cells.<sup>14,15</sup> It also remains unclear which step in the pathway is responsible for cys-LT overproduction in patients with AIA. Cowburn et al<sup>16</sup> reported that the number of cells expressing LTC4 synthase (LTC4S) is higher in the bronchial mucosa of patients with AIA than in that of patients with ATA and that the amount of cys-LTs in bronchoalveolar lavage fluid is strongly correlated with the number of LTC4S-positive cells. In addition, Sanak et al<sup>17,18</sup> found that the polymorphism (ie, A to C transversion at 444 nucleotides upstream of the ATG translation start site) in the promoter region of the *LTC4S* gene is associated with the development of AIA in a Polish population. However, this polymorphism of the *LTC4S* gene might not be the probable mechanism underlying cys-LT overproduction in patients with AIA. Van Sambeek et al<sup>19</sup> reported that the C allele in the *LTC4S* gene is not correlated with the phenotype of AIA in the United States and that this polymorphism does not affect the transcriptional activity of the *LTC4S* gene. More recently, Kawagishi et al<sup>20</sup> also reported similar findings that there is no clear association between this polymorphism of the *LTC4S* gene and the aspirin intolerance or the enzymatic activity of the *LTC4S* gene in eosinophils. There has been no

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Received for publication January 21, 2003; revised September 2, 2003; accepted for publication October 27, 2003.

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0091-6749/\$30.00

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doi:10.1016/j.jaci.2003.10.068

*Abbreviations used*

|          |                                                          |
|----------|----------------------------------------------------------|
| AIA:     | Aspirin-intolerant asthma                                |
| ATA:     | Aspirin-tolerant asthma                                  |
| CHRS/NP: | Chronic hyperplastic rhinosinusitis with nasal polyposis |
| cys-LT:  | Cysteinyl leukotriene                                    |
| LTC4S:   | Leukotriene C4 synthase                                  |
| LTE4:    | Leukotriene E4                                           |
| U-LTE4:  | Urinary leukotriene E4                                   |

report demonstrating that the basal concentration of U-LTE4 differs between wild-type A homozygotes and variant C allelic carriers in patients with AIA<sup>18,20</sup> or in patients with ATA.<sup>20</sup> The clinicopathogenetic factors associated with the increased excretion levels of U-LTE4 in asthmatic patients have not been determined. In our study we evaluated the clinicopathogenetic factors that might be associated with the increased excretion level of U-LTE4 in asthmatic patients and demonstrated that the cys-LT overproduction is associated with some clinical features also observed in AIA, such as chronic hyperplastic rhinosinusitis with nasal polyposis (CHRS/NP).

## METHODS

### Subjects

The hospital-based case-control study was conducted from June 1998 through March 2002. The subjects of this study were 64 non-smoking asthmatic outpatients with AIA (age range, 21-79 years; mean age, 53.3 years; 23 male and 41 female patients) and 73 control asthmatic outpatients who tolerated aspirin well (ATA; age range, 21-80 years; mean age, 51.2 years; 38 male and 35 female patients; Table 1). The diagnosis of asthma was based on the American Thoracic Society criteria.<sup>21</sup> Asthma severity was classified on the basis of daily medication regimen and response to treatment according to the Global Initiative for Asthma guidelines.<sup>22</sup> All the patients with AIA have been proved to have histories of severe bronchoconstriction and nasal symptoms after ingestion of at least 2 different nonsteroidal anti-inflammatory drugs or have had a positive reaction to aspirin systemic challenge.<sup>20</sup> All the patients with ATA have had a negative reaction to the aspirin challenge. All the patients were in clinically stable condition. None of the patients had complications of cystic fibrosis, immotile cilia syndrome, or autoimmune diseases, and none of them had an upper respiratory tract infection in the 6 weeks preceeding 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 (age range, 25-81 years; mean age, 50.1 years; 23 male and 12 female subjects). Permission to conduct the study was obtained from the Ethics Committee of the National Sagamihara Hospital, and all the patients who participated in the study provided informed consent.

### Study design

On entry into this study, the patients were documented according to a detailed structured questionnaire. The age at onset of asthma was determined as accurately as possible. In case of uncertainty, the earliest respiratory symptoms, including cough, wheezing, and episodic dyspnea, were taken into account. Nasal symptoms were also assessed. Self-assessment of olfactory disturbance was performed by the patients using an analog scale for rating symptoms from 0 (none)

to 4 points (anosmia) by evaluating the degree at which the disturbance interfered with their everyday life. When a 4-point (anosmia) score was obtained, we reconfirmed the presence of anosmia by using cards or smell bottles containing cigarettes, coffee, deodorants, and cloves, as previously described but with some modifications.<sup>23</sup> Subjective assessment of olfactory disturbance in asthmatic patients with seasonal allergic rhinitis was performed during the off season of pollen allergens. The diagnosis of CHRS/NP<sup>24-26</sup> was assessed by an independent observer on the basis of clinical histories, rhinoscopic findings, and sinus radiographic or computed tomographic scans. In this article CHRS/NP is determined by evaluating the clinical symptoms of chronic rhinosinusitis with evidence of bilateral sinus mucosal thickening on radiographic studies in conjunction with nasal polyposis.<sup>27-30</sup> In contrast, infectious chronic rhinosinusitis,<sup>31</sup> as determined by means of clinical definition, such as the presence of facial pain, purulent drainage, or an extensive air fluid level on sinus radiographs, was an exclusion criterion.

We collected blood and urine samples from the patients, and then pulmonary function tests were performed between 9 and 11 AM. The number of eosinophils in peripheral blood was determined by using a standard automated cell counter. Because treatment with  $\beta_2$ -agonists or with anti-inflammatory drugs, including oral or inhaled corticosteroids, sodium cromoglycate, or oral leukotriene receptor antagonists themselves, does not affect U-LTE4 levels,<sup>32</sup> these medications were not withheld at the time of urine sample collection in this study.

To reconfirm the involvement of CHRS/NP in the increase in the excretion level of U-LTE4, we compared the LTE4 concentration in urine between before and after the elective endoscopic surgery for CHRS/NP (3-4 weeks after the surgical treatment), which is not part of the goal of this study. The subjects in the reconfirmatory study were 7 patients with AIA (age range, 37-68 years; mean age, 52.9 years; 2 male and 5 female patients) and 8 patients with ATA (age range, 22-71 years; mean age, 48.4 years 5 male and 3 female patients). Before and after the endoscopic surgery for CHRS/NP (sinus surgery), all these patients were in clinically stable condition, with no changes in asthma symptoms or the kind and dose of medication. Treatments included only inhaled steroids, leukotriene receptor antagonists, and single use of short-acting  $\beta_2$ -agonists but not systemic corticosteroid administration.

### Measurements

We measured the LTE4 concentration in spot urine by using a method previously described.<sup>20,33-35</sup> The U-LTE4 concentration is expressed as picograms per milligram of creatinine.

### Analysis of data

Demographic characteristics are expressed as means  $\pm$  SD. The U-LTE4 concentration is shown as the median and the range. U-LTE4 concentrations in the AIA, ATA, and healthy control groups were first compared by using the Kruskal-Wallis test. When a significant difference was found, the Mann-Whitney *U* test with the Bonferroni correction for comparison between groups was performed. U-LTE4 concentrations in the patients with different clinical asthma severity levels were compared by using the same statistical analyses described above. U-LTE4 concentrations in patients with CHRS/NP and those with normal sinuses were compared with the Mann-Whitney *U* test. Similarly, U-LTE4 concentrations in patients with AIA and ATA were compared with the Mann-Whitney *U* test. U-LTE4 concentrations before and after the sinus surgery were compared by using the Wilcoxon *t* test.

In this study the U-LTE4 concentration was the basis for classifying the patients into those showing either increased excretion levels of U-LTE4 (hyperleukotrienuria) or nonincreased excretion levels of U-LTE4 (normal leukotrienuria). A U-LTE4 concentration of

**TABLE I.** Demographic characteristics of the patients with AIA and those with ATA

|                                                              | AIA                 | ATA               | P value |
|--------------------------------------------------------------|---------------------|-------------------|---------|
| No.                                                          | 64                  | 73                |         |
| Male/female sex                                              | 23/41               | 38/35             | NS      |
| Age (y), mean (SD)                                           | 53.3 (13.5)         | 51.2 (15.2)       | NS      |
| Onset age (y), mean (SD)                                     | 38.1 (14.0)         | 37.3 (17.7)       | NS      |
| Atopic status, n (%)                                         | 32 (50.0)           | 51 (69.9)         | <.05    |
| Blood eosinophil ( $\times 10^6/\text{mL}$ ), median (range) | 585 (5-3520)        | 430 (20-4160)     | NS      |
| Serum IgE-RIST (IU/mL), median (range)                       | 114 (14-1390)       | 233 (15-2290)     | <.05    |
| U-LTE4 (pg/mg creatinine), median (range)                    | 227.2 (30.9-1465.7) | 90.3 (16.5-915.8) | <.01    |
| Pulmonary function tests                                     |                     |                   |         |
| FEV <sub>1</sub> (mL), mean (SD)                             | 2043 (757)          | 2100 (796)        | NS      |
| FEV <sub>1</sub> (% predicted), mean (SD)                    | 77.3 (19.8)         | 80.7 (21.5)       | NS      |
| Clinical features                                            |                     |                   |         |
| Severity                                                     |                     |                   | NS      |
| Intermittent, n (%)                                          | 5 (7.8)             | 10 (13.7)         |         |
| Mild persistent, n (%)                                       | 12 (18.8)           | 23 (31.5)         |         |
| Moderate persistent, n (%)                                   | 17 (26.6)           | 17 (23.3)         |         |
| Severe persistent, n (%)                                     | 30 (46.9)           | 23 (31.5)         |         |
| CHRS/NP, n (%)                                               | 43* (71.7)          | 27† (40.3)        | <.001   |
| Anosmia, n (%)                                               | 41‡ (67.2)          | 16§ (24.2)        | <.001   |
| Treatment                                                    |                     |                   |         |
| Oral systemic CS, n (%)                                      | 22 (34.4)           | 11 (15.1)         | <.05    |
| LTRAs, n (%)                                                 | 11 (17.2)           | 18 (24.7)         | NS      |
| Dose of inhaled CS (mg/d), median                            | 800                 | 800               | NS      |

NS, Not significant; RIST, radioimmunosorbent test; CS, corticosteroids.

\*n = 60 and ‡n = 61, patients with AIA.

†n = 67 and §n = 66, patients with ATA.

||Dose of inhaled corticosteroids is the median daily dose in beclomethasone equivalent units. Beclomethasone is assumed to be equipotent with budesonide and has a potency half that of fluticasone.

greater than 150 pg/mg creatinine, which corresponds to the mean U-LTE4 plus 3 SDs of the healthy control subjects, indicated hyperleukotrienuria, and a U-LTE4 concentration of less than 100 pg/mg creatinine (mean U-LTE4 + 1 SD of the healthy control subjects) indicated normal leukotrienuria. We compared the clinical features between asthmatic patients with hyperleukotrienuria and those with normal leukotrienuria. The differences in demographic characteristics between these 2 groups were analyzed by using the unpaired Student *t* test and the  $\chi^2$  test. Relationships were analyzed by using the Spearman rank correlation test. *P* values of less than .05 were regarded as statistically significant.

## RESULTS

Table I shows the clinical characteristics of the patients with AIA and those with ATA. These 2 groups were well matched for age, sex, severity of asthma, respiratory function, and doses of both inhaled steroids and leukotriene receptor antagonists. In the ATA group, however, both the frequency of atopic asthmatic patients (69.9% vs 50.0%, *P* < .05) and the level of serum IgE on radioimmunosorbent testing (median, 233 vs 114 IU/mL; *P* < .05) were significantly higher than those in the AIA group. The frequency of the complication of CHRS/NP was higher in the patients with AIA than in the patients

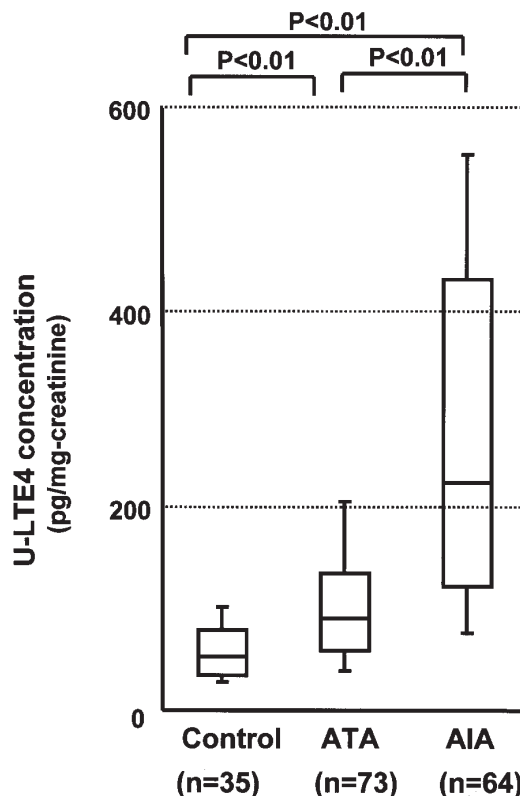


**FIG 1.** U-LTE4 concentration (in picograms per milligram of creatinine) in patients with AIA, patients with ATA, and healthy control subjects. U-LTE4 concentration in each group is expressed as median plus percentile (10%, 25%, 75%, and 90%).

with ATA (71.7% vs 40.3%, *P* < .001). In addition, the frequency of anosmia was higher in the patients with AIA (frequency, 67.2% vs 24.2%; *P* < .001).

The basal excretion level of U-LTE4 was significantly higher in patients with AIA than in those with ATA (median, 227.2 vs 90.3 pg/mg creatinine; *P* < .01; Fig 1 and Table I). There was no significant difference in the U-LTE4 concentration between the sexes for these 2 groups (data not shown). When U-LTE4 concentrations between these 2 groups with different clinical asthma severity levels were compared, the U-LTE4 concentrations in patients with AIA with moderate or severe persistent asthma were significantly higher than those in patients with ATA with the same severity of asthma (*P* < .01 and *P* < .05, respectively; Fig 2). Table II shows the clinical characteristics of patients with hyperleukotrienuria and those with normal leukotrienuria in each group. The frequency of the patients with AIA with hyperleukotrienuria was 67.2%. Compared with the patients with AIA with normal leukotrienuria, the patients with AIA with hyperleukotrienuria were significantly older (mean, 56.1 vs 44.8 years, *P* < .05) and had a lower pulmonary function (mean FEV<sub>1</sub>, 1907 vs 2401 mL; *P* < .05). In contrast, the frequency of patients with ATA with hyperleukotrienuria was 21.9%, and patients with ATA with hyperleukotrienuria had more severe asthma (*P* < .05) and a higher frequency of anosmia (frequency, 50.0% vs 13.9%; *P* < .05). In addition, 81.3% of the

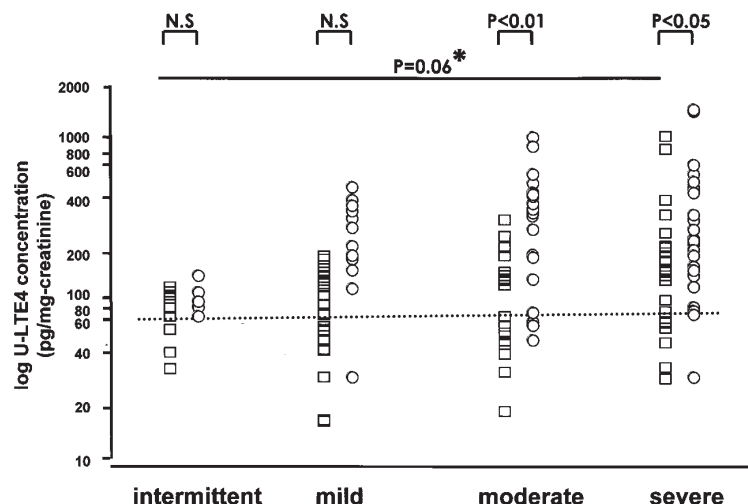


**FIG 2.** U-LTE4 concentration (in picograms per milligram of creatinine) in patients with AIA and patients with ATA classified according to clinical severity of asthma. U-LTE4 concentration is expressed by using the log scale. Patients with ATA and patients with AIA are denoted by an open square and an open circle, respectively. The dotted line indicates the mean level of U-LTE4 in healthy control subjects. \*U-LTE4 concentrations in the patients with ATA with different clinical asthma severity levels were compared by using the Kruskal-Wallis test.

patients with ATA with hyperleukotrienuria appeared to have CHRS/NP compared with 22.9% of the patients with ATA with normal leukotrienuria ( $P < .001$ ). The number of eosinophils in peripheral blood was greater in the patients with ATA with hyperleukotrienuria (median, 860/ $\mu$ L vs 330/ $\mu$ L,  $P < .01$ ). Female patients with ATA with hyperleukotrienuria showed a higher U-LTE4 concentration than male patients with ATA (median, 258.7 vs 184.3 pg/mg creatinine;  $P < .05$ ).

Between the 2 groups with hyperleukotrienuria, the frequency of atopic status was significantly less in the patients with AIA (frequency, 48.8% vs 87.5%;  $P < .05$ ). In contrast, between the 2 groups with normal leukotrienuria, anosmia had a greater frequency in the patients with AIA (frequency, 50.0% vs 13.9%;  $P < .05$ ).

When we examined the correlations between the U-LTE4 concentration and other clinical parameters, a statistically nonsignificant but noteworthy correlation between the U-LTE4 concentration and clinical asthma severity level in the patients with ATA was found ( $P = .06$ , Fig 2). In addition, U-LTE4 concentrations in the patients with ATA with CHRS/NP ( $n = 27$ ) were higher than those in the patients with ATA with normal sinuses ( $n = 30$ ; median, 148.0 vs 81.2 pg/mg creatinine;  $P < .05$ ; Fig 3). In contrast, there were 43 patients with CHRS/NP and only 8 with normal sinuses in the AIA group. No significant correlations between the U-LTE4 concentration and clinical parameters, such as asthma severity or the complication of CHRS/NP, were observed in the AIA group. There was a significant decrease in the U-LTE4 concentration after the sinus surgery in 15 asthmatic patients (median, 221.3 vs 72.3 pg/mg creatinine;  $P < .01$ ). Six of 9 asthmatic patients with hyperleukotrienuria before the sinus surgery were not classified into the hyperleukotrienuria group after the sinus surgery. Fig 4 shows

significant decreases in the U-LTE4 concentrations before and after the sinus surgery in both the AIA and ATA groups (median, 322.7 pg/mg creatinine [before] vs 98.2 pg/mg creatinine [after],  $P < 0.05$ , for the AIA group; 93.4 pg/mg creatinine [before] vs 80.9 pg/mg creatinine [after],  $P < .05$ , for the ATA group). Before the sinus surgery, the U-LTE4 concentrations of both groups were not significantly different. Similarly, the U-LTE4 concentrations of both groups after the sinus surgery showed no significant difference. All the nasal polyp and sinus sections revealed a diffused and marked infiltration of eosinophils, leading to the diagnosis of CHRS/NP.<sup>36-38</sup>

## DISCUSSION

There is accumulating evidence that supports the central role of cys-LTs as mediators of inflammatory diseases.<sup>1</sup> An increase in the U-LTE4 concentration has been observed not only in asthma but also in autoimmune diseases, including rheumatoid arthritis<sup>39</sup> and systemic lupus erythematosus.<sup>40</sup> However, the relationship between the clinicopathogenetic factors of asthma and U-LTE4 concentration remains undetermined. We have demonstrated for the first time that there are some important clinicopathogenetic factors associated with increased excretion levels of U-LTE4 (ie, hyperleukotrienuria) in asthmatic patients. Hyperleukotrienuria in patients with AIA (67.2% of patients with AIA in this study) was associated with older age and decrease in pulmonary function. On the other hand, hyperleukotrienuria in patients with ATA (21.9% of the patients with ATA in this study) was associated with severe asthma and CHRS/NP, which are well-known symptoms of the aspirin triad,<sup>41</sup> as well as hyper-eosinophilia and anosmia. Conversely, the U-LTE4 concentration in the patients with ATA with CHRS/NP was

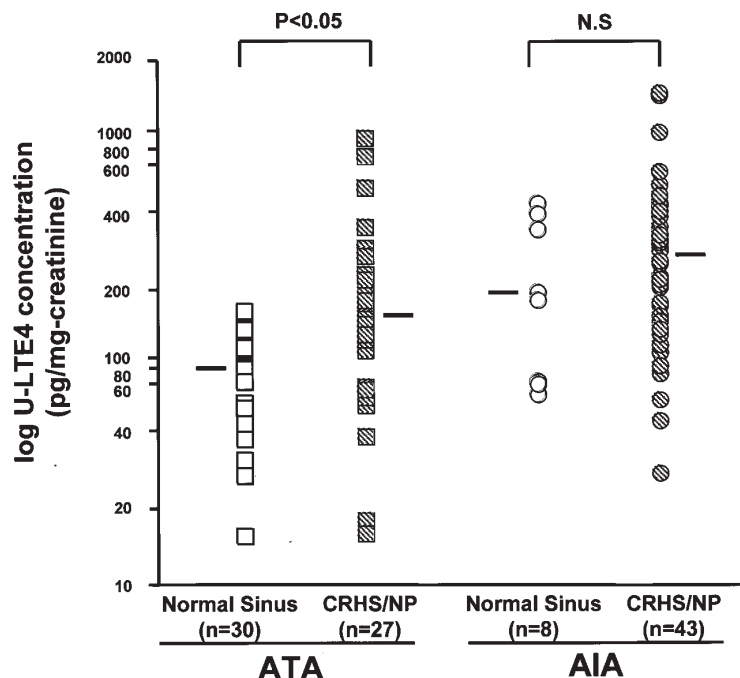


**FIG 3.** U-LTE4 concentration (in picograms per milligram of creatinine) in patients with CHRS/NP and those with normal sinuses. U-LTE4 concentration is expressed by using the log scale. The horizontal bars indicate medians. Patients with ATA and patients with AIA are denoted by an open square and an open circle, respectively.

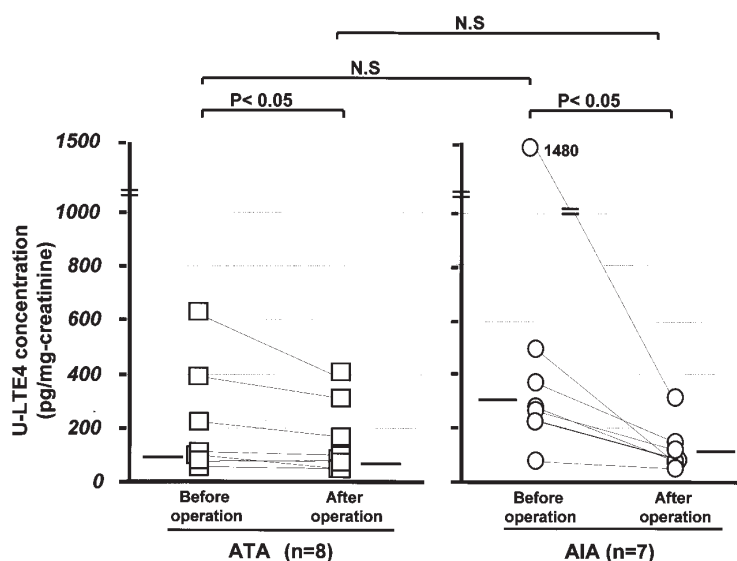


**FIG 4.** A significant decrease in the U-LTE4 concentration between before and after the endoscopic surgery of rhinosinusitis with nasal polyposis. Horizontal bars indicate medians. Patients with ATA and patients with AIA are denoted by squares and circles, respectively.

higher than that in the patients with ATA with normal sinuses. In addition, a statistically nonsignificant but noteworthy correlation between the U-LTE4 concentration and clinical asthma severity in patients with ATA was found. In support of our findings, ten Brinke et al<sup>42</sup> have suggested a direct relationship between hyperplastic rhinosinusitis and lower airway inflammation in severe asthma, and they have suggested that extensive rhinosinusitis

is associated with adult-onset asthma, aspirin intolerance, and nasal polyposis.

Taken together, these findings led us to the following generalizations. First, cys-LT overproduction is not strictly associated with aspirin intolerance itself but is associated with clinical features, such as CHRS/NP, that are similar to those of AIA. Second, CHRS/NP might play an important role in cys-LT overproduction in asthmatic

TABLE II. Demographic characteristics of each group

|                                                             | AIA                      |                          |                                  | ATA                      |                          |                               | PG(h-h) | PG(n-n) |
|-------------------------------------------------------------|--------------------------|--------------------------|----------------------------------|--------------------------|--------------------------|-------------------------------|---------|---------|
|                                                             | Hyperleuko-<br>trienuria | Normal<br>leukotrienuria | <i>P</i> <sub>AIA</sub><br>(h-n) | Hyperleuko-<br>trienuria | Normal<br>leukotrienuria | <i>P</i> <sub>ATA</sub> (h-n) |         |         |
| No.                                                         | 43                       | 12                       |                                  | 16                       | 40                       |                               |         |         |
| Male/female sex                                             | 16/27                    | 3/9                      | NS                               | 6/10                     | 21/19                    | NS                            | NS      | NS      |
| Age (y), mean (SD)                                          | 56.1 (13.0)              | 44.8 (11.4)              | <.05                             | 52.1 (12.2)              | 49.2 (16.1)              | NS                            | NS      | NS      |
| Onset age (y), mean (SD)                                    | 39.2 (14.1)              | 32.3 (15.9)              | NS                               | 39.4 (16.9)              | 33.5 (17.1)              | NS                            | NS      | NS      |
| Atopic status (n)                                           | 21 (48.8)                | 7 (58.3)                 | NS                               | 14 (87.5)                | 23 (57.5)                | NS (.07)                      | <.05    | NS      |
| Blood eosinophil<br>( $\times 10^6$ /mL),<br>median (range) | 535 (12-3520)            | 560 (5-2460)             | NS                               | 860 (200-4163)           | 330 (20-930)             | <.01                          | NS      | NS      |
| Serum IgE-RIST<br>(IU/mL), median (range)                   | 114 (14-1390)            | 119 (15-600)             | NS                               | 314 (44-2290)            | 162 (15-2050)            | NS                            | NS      | NS      |
| Pulmonary function tests                                    |                          |                          |                                  |                          |                          |                               |         |         |
| FEV <sub>1</sub> (mL), mean (SD)                            | 1907 (746)               | 2401 (622)               | <.05                             | 2117 (923)               | 2308 (788)               | NS                            | NS      | NS      |
| FEV <sub>1</sub> (% predicted),<br>mean (SD)                | 73.5 (19.5)              | 91.1 (18.8)              | <.05                             | 81.1 (26.3)              | 84.1 (20.4)              | NS                            | NS      | NS      |
| Clinical features                                           |                          |                          |                                  |                          |                          |                               |         |         |
| Severity                                                    |                          |                          | NS                               |                          |                          | <.05                          | NS      | NS      |
| Intermittent, n (%)                                         | 0 (0)                    | 3 (25.0)                 |                                  | 0 (0)                    | 8 (20.0)                 |                               |         |         |
| Mild persistent, n (%)                                      | 9 (20.9)                 | 1 (8.3)                  |                                  | 2 (12.5)                 | 15 (37.5)                |                               |         |         |
| Moderate persistent,<br>n (%)                               | 12 (27.9)                | 4 (33.3)                 |                                  | 4 (25.0)                 | 8 (20.0)                 |                               |         |         |
| Severe persistent, n (%)                                    | 22 (51.2)                | 4 (33.3)                 |                                  | 10 (62.5)                | 9 (22.5)                 |                               |         |         |
| CHRS/NP, n (%)                                              | 30* (75.0)               | 6 (50.0)                 | NS                               | 13 (81.3)                | 8† (22.9)                | <.001                         | NS      | NS      |
| Anosmia, n (%)                                              | 28* (70.0)               | 6 (50.0)                 | NS                               | 8 (50.0)                 | 5‡ (13.9)                | <.05                          | NS      | <.05    |
| Treatment                                                   |                          |                          |                                  |                          |                          |                               |         |         |
| Oral systemic CS, n (%)                                     | 12 (27.9)                | 4 (33.3)                 | NS                               | 1 (6.3)                  | 6 (15.0)                 | NS                            | NS      | NS      |
| LTRAs, n (%)                                                | 12 (27.9)                | 4 (33.3)                 | NS                               | 3 (18.8)                 | 9 (22.5)                 | NS                            | NS      | NS      |
| Dose of inhaled CS<br>(mg/d), median§                       | 800                      | 950                      | NS                               | 800                      | 800                      | NS                            | NS      | NS      |

\*n = 40, patients with AIA with hyperleukotrienuria.

†n = 35 and ‡n = 36, patients with ATA with normal leukotrienuria.

§Dose of inhaled corticosteroids is the median daily dose in beclomethasone equivalent units. Beclomethasone is assumed to be equipotent with budesonide and has a potency half of that of fluticasone.

*P*(h-n), Significant differences between asthmatic patients with hyperleukotrienuria and those with normal leukotrienuria; *PG*, significant differences between the 2 groups; *PG*(h-h), significant differences between the 2 groups with hyperleukotrienuria; *PG*(n-n), significant differences between the 2 groups with normal leukotrienuria; *NS*, not significant; *RIST*, radioimmunosorbent test; *CS*, corticosteroids.

patients. The precise pathophysiologic mechanism underlying hyperleukotrienuria remains obscure. We attempted to reconfirm the involvement of CHRS/NP in the pathogenesis of hyperleukotrienuria, and thus we compared the U-LTE4 concentrations between before and after the sinus surgery. We demonstrated for the first time that there is a significant decrease in the U-LTE4 concentrations after the sinus surgery, suggesting that sinonasal tissue might be one of the main tissues that produce cys-LTs in asthmatic patients. Surgical resection of both large nasal polyps and extensive hyperplastic sinonasal mucosa contributes to the termination of the vicious cycle in which cys-LTs and chemotactic factors produced in the sinonasal tissue<sup>43</sup> promote the chemotaxis of eosinophils.<sup>44</sup> More recently, it has been reported that cys-LT concentrations were significantly higher in sinus tissues obtained from patients with CHRS/NP than in healthy sinus tissues and noneosinophilic sinus tissues.<sup>45</sup> Thus the complication of severe CHRS/NP might affect the U-LTE4 concentration, and sinonasal tissues might be one of the main tissues that produce cys-LTs in asthmatic

patients. Interestingly, we reconfirmed the decrease in U-LTE4 concentration after surgery for CHRS/NP (72.4 pg/mg creatinine to 32.8 pg/mg creatinine) in only one nonasthmatic patient. Because U-LTE4 has a detection limit to serve as a biomarker of airway inflammation,<sup>32,35</sup> it is necessary to carry out further investigations with a large number of patients. Considering the high recurrence rate of nasal polyposis in patients with AIA,<sup>46</sup> we should examine whether those with CHRS/NP recurrence have significant increases in U-LTE4 levels over time and whether aspirin intolerance will develop in patients with ATA with hyperleukotrienuria exhibiting clinical characteristics similar to those of patients with AIA.

In conclusion, our study showed, for the first time, a close relationship between the U-LTE4 concentration and clinical features of asthmatic patients. We suggest the possibility that cys-LTs are not strictly associated with aspirin intolerance itself but with clinical features such as CHRS/NP that are similar to those of AIA. In particular, our study suggests the involvement of CHRS/NP in cys-LT overproduction in asthmatic patients.

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