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RESEARCH ARTICLE

## Evaluation of aspirin hypersensitivity in patients with chronic rhinosinusitis

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### ABSTRACT

**Conclusion** The recurrence rates of chronic rhinosinusitis (CRS) were higher in the aspirin nasal provocation test (ANPT)-positive group, regardless of the presence of nasal polyps. Thus, a careful endoscopic examination is required during follow-up in ANPT-positive patients with CRS. **Objectives** The aim of this study was to evaluate the clinical features and prognosis after surgical treatment in patients with CRS and aspirin hypersensitivity. **Methods** In a prospective study, 100 patients were analyzed with CRS who underwent endoscopic sinus surgery at the hospital from October 2012 to March 2013. This study measured changes in nasal volume and symptoms before and after the ANPT and examined patient's asthma history, allergy, Lund-Mackay score (LMS), total immunoglobulin E, percentage of peripheral eosinophils, and objectively measured relapse at 6 months. **Results** Patients with CRS and nasal polyps (CRSwNP) were more likely to have a positive ANPT test result compared to those without nasal polyps (CRSsNP) (21.4% vs 5.5%). The ANPT-positive group had a higher LMS and required more revision endoscopic sinus surgery than those in the ANPT-negative group. The results were that similar results were observed in CRSwNP and CRSsNP.

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Aspirin nasal provocation test; chronic rhinosinusitis

### Introduction

Aspirin-exacerbated respiratory disease (AERD) is a clinical tetrad of related conditions, including nasal polyps (NPs), chronic hypertrophic eosinophilic sinusitis, asthma, and sensitivity to any medication that inhibits cyclooxygenase-1, such as aspirin and other non-steroidal anti-inflammatory drugs [1]. Asthma is associated with sinusitis, and nasal and sinus symptoms are very common in patients with asthma.

The aspirin challenge test is the gold standard for diagnosing AERD [2,3], and oral, bronchial inhalation, nasal inhalation, and intravenous are the four routes for the provocation challenge. Several hypotheses have been proposed to explain the links between the upper and lower airways [4,5]. The bronchial inhalation challenge test has been used to diagnosis AERD and to evaluate clinical features of chronic rhinosinusitis (CRS) and asthma. However, if a subject has lower airway hypersensitivity, particularly when it is due to asthma or chronic bronchitis, this challenge mode can be dangerous. Some studies have indicated that the aspirin nasal provocation test (ANPT) is as effective as the bronchial challenge test [6]. Because aspirin is administered directly into the nasal mucosa during the ANPT, absorption into the bloodstream occurs at a slower rate, and the risk of serious reaction is much lower than with oral or bronchial provocation tests [6,7].

Most studies have only investigated the efficacy of ANPT in patients with CRS and nasal polyps (CRSwNP) [8,9], and little information is available about the diagnostic potential of ANPT in patients with CRS without nasal polyps (CRSsNP).

The aim of this study was to evaluate the clinical features and prognosis after surgical treatment in patients with CRS, regardless of NP, who have aspirin hypersensitivity.

### Materials and methods

#### Subjects and study design

We identified 100 patients with CRS with or without NPs who underwent endoscopic sinus surgery (ESS) between October 2012 and March 2013. The patients were divided into two groups according to Hadley's scoring of polyps [10]. We examined all four of the subjective CRS symptoms, including nasal obstruction, rhinorrhea, sneezing, and an itching sensation. Each patient was assigned a total nasal symptom score (TNSS) ranging from 0–3 according to severity.

We performed endoscopic examination at the 6 month post-operative follow-up, and defined patients with CRS as 'recurrence cases' if they presented with a relapse of NPs or polypoid epithelium. We obtained institutional review board (IRB) approval before starting the study (No. Kyung Hee Medical Center IRB 1523-08).

#### Objective measurements

ANPTs were performed using aspirin-soaked paper discs rather than nasal spray. We defined nasal volume change percentage (NVCP) as: (constant nasal volume before ANPT – nasal volume after ANPT)/nasal volume before ANPT × 100. A decrease in nasal volume of at least 25% and

an increase in the TNSS were the criteria for a positive ANPT result. If a patient did not have increased volume but had a substantial TNSS, they were considered negative on the ANPT.

Nasal volume was measured using acoustic rhinometry by one otolaryngologist specializing in rhinology. We observed four symptoms, such as nasal obstruction, rhinorrhea, itching, and sneezing. This procedure was repeated using paper discs (5 mm × 5 mm size) soaked in aspirin lysine (50 mg/ml) [11,12]. This paper was bilaterally attached to the fronts of the inferior turbinates. We waited 30 min after placing the discs before measuring nasal volume by acoustic rhinometry. To exclude any non-specific hypersensitivity, a placebo paper disc soaked with normal saline was used.

Patients were evaluated for asthma using the allergic skin test and the multiple allergen simultaneous test. Total serum immunoglobulin E (IgE) level and the percentage of serum eosinophils were evaluated in each patient.

The Lund–Mackay score (LMS) was used to rank the objective appearances of the nasal and para-nasal sinus structures on a computed tomography scan. The range of possible scores for each side was 0–12; we averaged the score for the two sides to determine each patient's final score.

## Results

Twenty-eight subjects (21 males and seven females) were included in the CRSwNP and 72 subjects (46 males and 26 females) were included in the CRSsNP group. No differences were observed among allergy, asthma, total IgE, eosinophils, or the TNSS. However, the LMS and recurrence rates were significantly higher in the CRSwNP than in those in the CRSsNP group ( $p < 0.001$  and  $0.008$ , respectively) (Table 1).

The incidence of positive ANPT results was significantly higher in the CRSwNP group than that in the CRSsNP group (21.4% vs 5.5%,  $p = 0.017$ ; Table 2).

Table 3 shows the characteristics in the ANPT (+) and ANPT (–) groups. Significantly more of the ANPT(+) group had a history of asthma than those who were ANPT(–) ( $p = 0.049$ ). The LMS and recurrence rates were significantly higher in the ANPT(+) than those in the ANPT(–) group ( $p = 0.038$  and  $0.016$ , respectively). NVCP was significantly higher in ANPT(+) than that in the ANPT(–) group (25.71% vs –4.71%,  $p = 0.00$ ).

Finally, we compared four groups separately; CRSwNP with ANPT(+), CRSwNP with ANPT(–), CRSsNP with ANPT(+), and CRSsNP with ANPT(–), and found a higher LMS in the CRSwNP than that in the CRSsNP, regardless of the ANPT result ( $p < 0.001$ ). We found a higher recurrence rate in the ANPT(+) group than that in the ANPT(–) group, regardless of NP ( $p = 0.037$ ) (Table 4).

## Discussion

When patients with CRS have a NP, chronic sinusitis becomes resistant to antibiotic treatment and frequently requires surgical intervention, such as ESS. Because ESS is an invasive procedure, testing must be conducted before surgery. In particular, the ANPT is carried out for patients with NPs, and

**Table 1.** The clinical characteristics of CRSwNP and CRSsNP.

|                    | CRSwNP (n = 28) | CRSsNP (n = 72) | p value |
|--------------------|-----------------|-----------------|---------|
| Sex (Male: Female) | 21:7            | 46:26           | 0.349   |
| Age (years)        | 45.42 ± 19.96   | 42.00 ± 18.22   | 0.413   |
| Allergy            | 5 (17.9%)       | 27 (37.5%)      | 0.093   |
| Asthma             | 7 (25.0%)       | 9 (12.5%)       | 0.139   |
| Total IgE (IU/ml)  | 222.02 ± 322.29 | 327.06 ± 516.24 | 0.319   |
| Eosinophil (%)     | 3.80 ± 2.98     | 3.72 ± 3.15     | 0.916   |
| TNSS               | 2.25 ± 3.43     | 2.54 ± 3.30     | 0.696   |
| LMS                | 8.25 ± 2.96     | 3.69 ± 2.21     | <0.001* |
| Recurrence         | 10 (35.7%)      | 8 (11.1%)       | 0.008*  |

CRSwNP, chronic rhinosinusitis with nasal polyps; CRSsNP, chronic rhinosinusitis without nasal polyps; TNSS, total nasal symptom score; LMS, Lund–Mackay score.

\* $p < 0.05$ .

**Table 2.** Incidence of ANPT positivity in CRSwNP and CRSsNP.

|         | CRSwNP (n = 28) | CRSsNP (n = 72) | p value |
|---------|-----------------|-----------------|---------|
| ANPT(+) | 6 (21.4%)       | 4 (5.5%)        | 0.017*  |
| ANPT(–) | 22 (78.6%)      | 68 (94.5%)      |         |

CRSwNP, chronic rhinosinusitis with nasal polyps; CRSsNP, chronic rhinosinusitis without nasal polyps; ANPT, aspirin nasal provocation test.

\* $p < 0.05$ .

**Table 3.** Clinical characteristics of the ANPT(+) and ANPT(–) groups.

|                    | ANPT(+) (n = 10) | ANPT(–) (n = 90) | p value |
|--------------------|------------------|------------------|---------|
| Sex (Male: Female) | 6:4              | 61:29            | 0.726   |
| Age (years)        | 43.90 ± 20.23    | 42.85 ± 18.63    | 0.868   |
| Allergy            | 3 (30.0%)        | 29 (32.2%)       | 1.000   |
| Asthma             | 4 (40.0%)        | 12 (13.3%)       | 0.049*  |
| Total IgE (IU/ml)  | 177.20 ± 200.68  | 311.03 ± 490.64  | 0.397   |
| Eosinophil (%)     | 3.39 ± 2.61      | 3.78 ± 3.15      | 0.703   |
| TNSS               | 1.80 ± 2.74      | 2.53 ± 3.39      | 0.512   |
| LMS                | 6.95 ± 3.05      | 4.75 ± 3.13      | 0.038*  |
| Recurrence         | 5 (50.0%)        | 13 (14.4%)       | 0.016*  |
| NVCP (%)           | 35.71 ± 10.10    | –4.81 ± 29.80    | 0.000*  |

ANPT: aspirin nasal provocation test; TNSS: total nasal symptom score; LMS: Lund–Mackay score; NVCP: nasal volume change percentage: (constant nasal volume before ANPT – nasal volume after ANPT)/nasal volume before ANPT × 100.

\* $p < 0.05$ .

some investigators have reported that the ANPT is particularly helpful for treatment planning and assessment of a patient's condition [13–15].

However, many patients with CRS do not have NPs. In this study, all participants had CRS, and the majority did not have NPs. Prior to this study, no study had reported on the difference in ANPT efficacy between patients with CRS with and without NPs. Thus, we administered the ANPT to patients with CRS, regardless of the presence of NPs, to study the clinical features and treatment options. Other factors, such as sex, age, allergies, asthma history, and LMS, were analyzed, but no differences were observed between the CRSwNP and CRSsNP groups except the LMS and ANPT. Thus, we conclude that LMS and ANPT are significant factors when assessing patients with CRS, regardless of whether the patient has NPs.

We used a modified ANPT because it is less time consuming than the original ANPT or bronchial APT. Previous studies have demonstrated the efficacy of the standard ANPT, but

**Table 4.** Clinical characteristics of patients with CRS according to the presence of nasal polyp and ANPT.

|                    | CRSwNP ANPT(+)<br>(n = 6) | CRSwNP ANPT(–)<br>(n = 22) | CRSsNP ANPT(+)<br>(n = 4) | CRSsNP ANPT(–)<br>(n = 68) | p value |
|--------------------|---------------------------|----------------------------|---------------------------|----------------------------|---------|
| Sex (Male: Female) | 5:1                       | 16:6                       | 1:3                       | 45:23                      | 0.273   |
| Age (years)        | 44.50 ± 21.00             | 45.68 ± 20.17              | 43.00 ± 22.16             | 41.94 ± 18.16              | 0.875   |
| Allergy            | 2 (33.3%)                 | 3 (13.6%)                  | 1 (25.0%)                 | 26 (38.2%)                 | 0.156   |
| Asthma             | 3 (50.0%)                 | 4 (18.2%)                  | 1 (25.0%)                 | 8 (11.8%)                  | 0.073   |
| Total IgE (IU/ml)  | 218.28 ± 250.03           | 223.04 ± 344.47            | 115.57 ± 90.50            | 339.50 ± 528.41            | 0.609   |
| Eosinophil (%)     | 3.81 ± 2.97               | 3.79 ± 3.05                | 2.75 ± 2.19               | 3.78 ± 3.20                | 0.935   |
| TNSS               | 2.00 ± 3.52               | 2.31 ± 3.49                | 1.50 ± 1.29               | 2.60 ± 3.38                | 0.897   |
| LMS                | 8.08 ± 2.53               | 8.29 ± 3.12                | 5.25 ± 3.30               | 3.60 ± 2.13                | <0.001* |
| Recurrence         | 3 (50.0%)                 | 5 (22.7%)                  | 2 (50.0%)                 | 8 (11.7%)                  | 0.037*  |

CRSwNP: chronic rhinosinusitis with nasal polyps; CRSsNP: chronic rhinosinusitis without nasal polyps; ANPT: aspirin nasal provocation test; TNSS: total nasal symptom score; LMS: Lund–Mackay score.

\* $p < 0.05$ .

have not evaluated the modified ANPT. More research is needed to determine whether this modified ANPT can be used in place of the standard ANPT. Additionally, it remains to be seen whether accuracy of the ANPT is similar to that of the bronchial challenge. A high degree of similarity is expected because the upper and lower airways have similar mucosal structures, despite that they have different absorptive capacities for aspirin.

Before administering the modified ANPT, we expected that the TNSS would be higher in the CRSwNP or ANPT(+) groups than in either the CRSsNP or ANPT(–) groups. However, the TNSS for rhinorrhea, nasal obstruction, itching sensation, and sneezing were 0.61, 0.82, 0.25, and 0.54 in the CRSwNP group and 0.79, 1.00, 0.21, and 0.54 in the CRSsNP group, respectively. The same respective TNSS were 0.36, 0.81, 0.09, and 0.36 in the ANPT(+) group and 0.78, 0.96, 0.23, and 0.56 in the ANPT(–) group. These results indicate that subjective symptoms do not always correlate with objective findings. We thought that patients with CRS and NPs would adjust to the chronic symptoms and would understate them.

As discussed in previous studies, LMS was higher in the CRSwNP compared to that in the CRSsNP because NPs block the sinus opening [4,16]. We evaluated each patient's nasal condition based on sinus endoscopy. NPs or polypoid tissues were identified in some cases, although all patients with CRS had an ESS during this period. Thus, these subjects were considered relapse cases. Not surprisingly, the recurrence rate was higher in the CRSwNP than that in the CRSsNP groups. Additionally, the ANPT(+) group experienced more relapses than those in the ANPT(–) group. We conclude that the ANPT(+) patients must be evaluated carefully, even in the absence of structural problems, such as NPs.

## Conclusion

LMS and recurrence rates were higher in the ANPT(+) than those in the ANPT(–) group. In particular, recurrence rates were higher in the ANPT(+) group, regardless of the presence of NPs. Thus, a careful endoscopic examination is required at follow-up in ANPT(+) patients with CRS.

## Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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