TABLE 1.—Background of the subjects

| | | n | % |
|---|---|---|---|
| Subject number | | 62 | |
| | Male | 34 | 54.8 |
| | Female | 28 | 45.2 |
| Age (years) | | 57.6±13.4 | |
| Severity | | | |
| | Step 1 | 9 | 14.5 |
| | Step 2 | 26 | 41.9 |
| | Step 3 | 2 | 3.2 |
| | Step 4 | 18 | 29.1 |
| | Step 5 | 7 | 11.3 |
| Asthma control level | | | |
| | Controlled | 36 | 58.1 |
| | Partly Controlled | 26 | 41.9 |
| | Uncontrolled | 0 | 0 |
| Drugs used | | | |
| | Inhaled steroid | 50 | 80.6 |
| | Oral steroid (regular use) | 7 | 11.3 |
| | Oral steroid (as-needed use) | 6 | 9.68 |
| | Long-term β2 stimulant (adhesive and inhaled) | 24 | 38.7 |
| | Short-term β2 stimulant (inhaled) | 19 | 30.6 |
| | β2 stimulant (internal use) | 7 | 11.3 |
| | Theophylline (internal use) | 40 | 64.5 |
| | Anticholinergic drug (inhaled) | 3 | 4.83 |

mean ± SD

TABLE 2.—Respective mean values of CgA, PEF, VAS, and SF-36.

| | | Mean value |
|---|---|---|
| CgA | pmol/mL | 0.8 ± 0.9 |
| %PEF | % | 87.1 ± 17.4 |
| VAS | Point | 80.8 ± 16.4 |
| SF-36* | | |
| PF | Point | 85.2 ± 13.6 |
| RP | Point | 84.8 ± 21.0 |
| BP | Point | 69.8 ± 24.9 |
| GH | Point | 52.6 ± 15.7 |
| VT | Point | 58.9 ± 22.0 |
| SF | Point | 81.3 ± 21.6 |
| RE | Point | 84.1 ± 23.3 |
| MH | Point | 67.7 ± 19.5 |
| SF-36** | | |
| PCS | Point | 48.9 ± 8.90 |
| MCS | Point | 47.1 ± 9.98 |

Mean ± SD

*Raw score
**Summary score
CgA: ChromograninA
PEF: Peak Expiratory Flow
%PEF: peak flow measured value/peak flow standard value (predicted)
VAS: Visual Analog Score
SF-36: MOS Short-Form 36-Item Health Survey
PF: physical functioning
BP: bodily pain
VT: vitality
MH: mental health
RP: role physical
GH: general health perception
SF: social functioning
RE: role emotional
PCS: physical component summary
MCS: mental component summary

In addition, the subjects were asked to indicate the score for that day, with the best condition of asthma as 100 points, and the symptoms of the subjects on the day of the test were evaluated in the range of 0 to 100 points using a 100-mm VAS to obtain a subjective symptom VAS score.

These measurements were made in an outpatient examination room, and all examinations and measurements were completed in the morning.

For analyzing the data, the Kruskal-Wallis rank test was used for comparison among multiple groups, unpaired $t$ test for comparison between two groups and Spearman's correlation coefficiency by rank for correlations. We used nonparametric statistical procedures with the Kruskal-Wallis test (Table 3) and Spearman's correlation by rank (Table 4) to analyze the data in our study because we had an uneven distribution in the number of subjects in terms of the asthma severity (from step 1 to step 5) and the data were not normally distributed.

In all cases, a value of $p < 0.05$ was considered to be significant.

## RESULTS

As for the average value for all patients measured, %PEF was 87.1 ± 17.4, and the VAS score was 80.8 ± 16.4. The average value of the CgA level in saliva was 0.81 ± 0.90 pmol/mL (Table 2).

The CgA level in saliva was 0.74 ± 0.84 pmol/mL in the controlled group and 0.96 ± 1.05 pmol/mL in the partly controlled group, and there was no significant difference between the two groups ($p = 0.369$) (Table 3).

In the categories based on the therapeutic steps according to the asthmatic severity, the CgA level in saliva was 0.45 ± 0.37 pmol/mL at step 1, 0.82 ± 0.91 pmol/mL at step 2, 0.58 ± 0.27 pmol/mL at step 3, 0.81 ± 1.06 pmol/mL at step 4, and 1.51 ± 1.10 pmol/mL at step 5, with no significant difference among the respective steps ($p = 0.217$) (Table 3).

Concerning gender difference, the CgA level was 0.86 ± 0.99 pmol/mL for males and 0.76 ± 0.78 pmol/mL for females, and therefore no significant difference between the two groups was observed ($p = 0.662$) (Table 3).

Regarding the scoring based on the average value of the summary score for SF-36, PCS indicated that physical QOL was 48.9 ± 8.90, and MCS indicated that psychological QOL was 47.1 ± 9.98 (Table 2).

Among the 8 items of the SF-36, the CgA level showed a significant negative correlation with the RP score ($r = -0.298$, $p < 0.05$) and the RE score ($r = -0.294$, $p < 0.05$), but no significant correlation was observed with the other items (Table 4).

In addition, the CgA level in saliva showed a significant negative correlation with PCS ($r = -0.310$, $p < 0.05$), but no significant correlation was observed with MCS ($p = 0.36$) (Table 4).

Between the CgA level in the saliva and VAS score, a relatively strong negative correlation was observed ($r = -0.435$, $p < 0.01$). In addition, the VAS score showed a significant correlation with all variables, except for the SF of SF-36 ($p = 0.09$) (Table 4).

The CgA level in saliva showed no significant correlation with %PEF ($p = 0.98$), which had a relatively strong positive correlation with the VAS score ($r = 0.400$, $p < 0.01$) (Table 4).

## DISCUSSION

In the present study the CgA level in the saliva of the patients with bronchial asthma showed no correlation with the%PEF, but a correlation was observed with the VAS score

TABLE 3.—Comparison of the concentration of chromogranin A in the saliva between sexes, the asthma severity, and the asthma control level

| Sex | | | Asthma severity | | | | | | Asthma control level | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Male | Female | p value | Step 1 | Step 2 | Step 3 | Step 4 | Step 5 | p value | Controlled | Partly Controlled | p value |
| (n = 34) | (n = 28) | | (n = 9) | (n = 26) | (n = 2) | (n = 18) | (n = 7) | | (n = 36) | (n = 26) | |
| 0.86 ± 0.99* | 0.76 ± 0.78* | p = 0.662** | 0.45 ± 0.37* | 0.82 ± 0.91* | 0.58 ± 0.27* | 0.81 ± 1.06* | 1.51 ± 1.10* | p = 0.217** | 0.74 ± 0.84* | 0.96 ± 1.05* | p = 0.369** |

mean ± SD
- *:Unit of concentration of chromogranin A in saliva: pmol/ml
- **: $p < 0.05$ is considered significant
- We reviewed the significant differences between 'males' and 'females' and between the 'controlled patients' and 'partly controlled patients' regarding the asthma control level with the t test, and significant differences at the five intervals from step1 to step5 of asthma severity were then examined by the Kruskal-Wallis test.

(subjective symptoms) as well as the RP score, the RE score, and the PCS score.

Osman et al. reported (8) similar scores in the eight items of SF36 in patients with asthma whose mean %FEV1.0 was 87.6 ± 18.0%. Since the patients described in the present study were 91.5 ± 25.5%, the present SF36 scores were consistent with theirs.

The subjective symptom score by VAS in asthmatics was 80.8 ± 16.4 in our study, but 74.6 in the report by Hazell et al. (9), although the severity of asthma was not described in their study. The relationship between the VAS score of asthmatic symptoms and asthma severity needs to be studied more precisely.

The average value of the CgA level in saliva for the subjects in our study was 0.81 ± 0.90 pmol/mL, which was higher than that for the healthy subjects reported by Suzuki et al. (0.32 ± 0.28 pmol/mL) (10). CgA, used as a psychological stress marker, is a soluble protein found in adrenal chromaffin cells and is thought to be associated with the storage and secretion of catecholamine because it is secreted together with catecholamine into the blood *via* sympathetic stimulation. Recently, CgA was detected also in saliva and was proven to be secreted in saliva owing to psychological stress, from the submaxillary gland duct *via* the autonomic nerve system in a study by Kanno et al. (11).Nakane et al. reported a significant increase of CgA in the saliva due to psychological stress experienced when speaking in front of an audience or driving a car, while no significant increase in CgA was observed during physical exercise on a bicycle ergometer. Therefore, it can be used as a less invasive method to measure acute psychological stress in healthy adult subjects (4).

Although there are few reports on the correlation between chronic stress and the CgA level in saliva, Toda et al. investigated the relationship between the lifestyle score and CgA level in saliva in healthy subjects and found that the CgA level in saliva was affected by changes in the comprehensive lifestyle (12). In addition, Suzuki et al. reported that the CgA levels in the saliva of patients with depression, panic disorder, or white coat hypertension at rest were significantly higher than those of healthy subjects (1.02 ± 0.93 pmol/mL, 1.56 ± 1.78 pmol/mL, and 8.97 ± 6.50 pmol/mL, respectively) (10). These results suggested that the CgA level in saliva may reflect not only acute stress but also chronic stress.

The effects of steroid on the concentration of CgA in saliva have never been reported. In this study, there was no significant difference between the patients with and those without inhaled corticosteroid. We think that the effects of steroid on the concentration of CgA in saliva need to be evaluated further.

Significant negative correlations were observed between the CgA level and RP and between the CgA level and RE indicating that the CgA level in saliva was increased in subjects when they had been experiencing limitations in both ordinary work and daily life over the previous month. In addition, a significant negative correlation was also observed between the CgA level and PCS indicating that the CgA level in saliva was increased in subjects with decreased QOL in the physical QOL. The present evidence suggests that the effects of asthma on daily life and work result from both the decreased physical QOL and from psychological stress (4).

The CgA level in saliva and the subjective symptoms score of VAS showed a weak but significant negative correlation indicating that the patients with greater symptoms of dyspnea showed higher CgA levels in the saliva suggesting a stronger degree of psychological stress.

When the CgA level in the saliva of asthma patients shows a high value, it may be important to consider a psychosocial approach, such as addressing the stress that patients may experience at home and work. Furthermore, it is important that people around the asthmatics understand the psychological effects of this disease and provide appropriate support.

In this study, 13 subjects had histories of taking oral glucocorticosteroid. Seven of them were taking 5 to 10 mg

TABLE 4.—Correlation coefficient between the respective variables.

| | CgA | %PEF | VASs | PF | RP | BP | GH | VT | SF | RE | MH | PCS | MCS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CgA | | −0.169 | −0.435** | −0.038 | −0.298* | −0.246 | −0.123 | −0.128 | −0.217 | −0.294* | −0.146 | −0.310* | −0.119 |
| %PEF | −0.169 | | 0.400** | 0.210 | 0.040 | 0.180 | 0.102 | 0.236 | 0.056 | 0.042 | 0.130 | 0.065 | 0.192 |
| VASs | −0.435** | 0.400** | | 0.303* | 0.344** | 0.246* | 0.487** | 0.395** | 0.219 | 0.438** | 0.256* | 0.310* | 0.229* |

- $p < 0.05$ is considered significant, * $p < 0.05$, ** $p < 0.01$
- We examined the correlation between each variable interval with Spearman's correlation coefficient by rank.
- CgA: ChromograninA level in saliva; %PEF: Percent Peak Expiratory Flow (peak flow measured value/peak flow standard value (predicted)); VASs: Visual Analog Scale score; PF: physical functioning; RP: role physical; BP: bodily pain; GH: general healthperception; VT: vitality; SF: social functioning; RE: role emotional; MH: mental health; PCS: physical component summary; MCS: mental component summary

predonisolone every day. Because of asthma severity and because their symptoms were stable for several months, their control levels of asthma in the last week were, therefore, classified as "controlled" according to the criteria in GINA 2006. Conversely, the remaining 6 subjects were administered oral predonisolone (10–20 mg) for a couple of days a month when they experienced exacerbations. However, their symptoms were almost stable during the last week. Their control levels were therefore classified as "controlled" or "partly controlled" according to the criteria in GINA 2006. In this regard, no subjects administered oral glucocorticosteroids in this study were classified as "uncontrolled" (Table 1).

In the present study, it was not clear whether the psychological stress evaluated by CgA came from only asthma or other factors besides asthma. The control level of asthma was determined based on the symptoms in the last one week. Quality of Life in SF36 was estimated for the last one month, and VAS by subjective symptoms and PEF was determined on the day tested. The collection of the saliva for CgA was performed also on the day VAS was tested.

As described earlier, the current study was a cross-sectional study and evaluating the relationships between the concentration of CgA in saliva and each variable made it difficult to judge whether the psychological stress came from only asthma or other factors besides asthma. To address this problem, it will be necessary to perform a longitudinal study to evaluate the relationship between the changes of the concentration of CgA and the variables including QOL, VAS, and PEF.

In conclusion, the CgA level in the saliva in bronchial asthma patients had no significant correlation with %PEF that would reflect airflow obstruction in asthmatics, a temporal physical abnormality, while there was a significant correlation with RP, RE, and PCS of SF-36 in the previous month as well as with the subjective symptoms VAS score. This suggests that the CgA level may therefore be a useful indicator that reflects the decreased QOL in daily life and work due to the psychological stress associated with asthma. Furthermore, CgA also reflected the subjective dyspnea symptoms in such patients rather than the objective impairment.

## Acknowledgment

The authors thank Professor Kei Takahashi for valuable help in performing the statistical analysis. They are indebted to Mr. Brent Bell for reading this manuscript.

## References

1. Vig RS, Forsythe P, Vliagoftis H. The role of stress in asthma: insight from studies on the effect of acute and chronic stressors in models of airway inflammation. Ann NY Acad Sci 2006; 1088:65–77.
2. Nishimura K, Hajiro T, Oga T, Tsukino M, Ikeda A. Health-related quality of life in stable asthma: what are remaining quality of life problems in patients with well-controlled asthma? J Asthma 2004; 41:57–65.
3. Bousquet J, Knani J, Dhivert H, Richard A, Chicoye A, Ware JE Jr, Michel FB. Quality of life in asthma. I. Internal consistency and validity of the SF-36 questionnaire. Am J Respir Crit Care Med 1994; 149 :371–375.
4. Nakane H, Asami O, Yamada Y, et al. Salivary chromogranin A as an index of psychosomatic stress response. Biomed Res 1998; 19:401–406.
5. Fukuhawa S, Suzukamo Y. Manual of SF-36v2 Japanese version. Kyoto Institute for Health Outcomes & Process Evaluation Research, 2004. [in Japanese]
6. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention Revised 2006. NHLBI/WHO Workshop Report. National Institutes of Health Publication, 2006.
7. Nagasawa S, Nishikawa Y, Jun L, et al. Simple enzyme immunoassay for the measurement of immunoreactive chromogranin A in human plasma, urine, and saliva. Biom Res 1998; 19:407–410.
8. Osman LM, Calder C, Robertson R, Friend JA, Legge JS, Douglas JG. Symptoms, quality of life, and health service contact among young adults with mild asthma. Am J Respir Crit Care Med 2000; 161:498–503.
9. Hazell M, Frank T, Frank P. Health-related quality of life in individuals with asthma related symptoms. Respir Med 2003; 97:1211–1218.
10. Suzuki J, Hoshino K, Inoue H. Study of the relationship between stress-related disease and salivary chromogranin A levels. J Iwate Med Assoc 2004; 56:361–366. [in Japanese]
11. Kanno T, Asada N, Yanase H, et al. Salivary secretion of highly concentrated chromogranin A in response to noradrenaline and acetylcholine in isolated and perfused rat submandibular glands. Exp Physiol 1999; 84:1073–1083.
12. Toda M, Den R, Nagasawa S, Kitamura K, Morimoto K. Relationship between lifestyle scores and salivary stress markers cortisol and chromogranin A. Arch Environ Occup Health 2005; 60:266–269.

*Allergology International*. 2009;58:55-61
DOI: 10.2332/allergolint.08-OA-0004

ORIGINAL ARTICLE

# Analysis of the Comorbidity of Bronchial Asthma and Allergic Rhinitis by Questionnaire in 10,009 Patients

Kohei Yamauchi[1], Gen Tamura[2], Toru Akasaka[3], Toshihiko Chiba[4], Kohei Honda[5], Motoji Kishi[6], Hitoshi Kobayashi[1], Tadayuki Kuronuma[7], Atsushi Matsubara[8], Toshio Morikawa[9], Hiroshi Ogawa[10], Nobuo Ohta[11], Masahiko Okada[12], Masahiro Sasaki[13], Junpei Saito[14], Kunio Sano[15], Morito Satoh[16], Yoko Shibata[17], Yoshihiro Takahashi[18], Shingo Takanashi[19] and Hiroshi Inoue[1]

## ABSTRACT

**Background:** Bronchial asthma (BA) and allergic rhinitis (AR) are thought to share a common pathogenesis. However, reports concerning the comorbidity of the two diseases in a large-scaled population are rare in Japan. In the present study, we performed an analysis on the two diseases using questionnaires that addressed the diagnosis, symptoms and period of occurrence in more than 10,000 patients with BA or AR.

**Methods:** Patients with BA (adult: $n$ = 2,781, childhood: $n$ = 3,283) and AR ($n$ = 3,945) were enrolled in the present study during the 3 months from August 1, 2006 to October 31, 2006.

**Results:** Sixty one percent of the patients with adult BA showed symptoms of AR. Among them, 68% of the patients were diagnosed with AR. Among the patients with childhood BA, 68% showed AR symptoms and 60% were diagnosed with AR. On the other hand, 49% of AR patients showed BA symptoms and 35% of them were diagnosed with BA. The symptoms of both BA and AR in the BA and AR patients were frequent in two seasons, March and April, and September and October. In addition, BA and AR symptoms often co-occurred in the patients with BA and AR.

**Conclusions:** Comorbidity of BA and AR was high in both populations of BA and AR. The symptoms of both BA and AR co-occurred on both a daily and seasonal basis. These results suggested that BA and AR share a common immuno-pathogenesis in the airway and need to be treated as a single airway disease.

## KEY WORDS

allergen, allergic rhinitis, asthma, exacerbation, pollen

## *INTRODUCTION*

The high comorbidity of bronchial asthma (BA) and allergic rhinitis (AR) has been reported.[1-5] Since Th2 lymphocytes, mast cells and eosinophils are known to infiltrate the mucosal layer of the upper and lower air-

[1]Third Department of Internal Medicine, Iwate Medical University School of Medicine, [2]Department of Pediatrics, Medical Support Center for Children and Families, [16]Satoh ENT Clinic, Iwate, [3]Airway Institute in Sendai, [4]Otolaryngology Department, Sendai City Hospital, [9]Morikawa Paediatrics & Allergy Clinic, [15]Facilities Sano Clinic, Miyagi, [5]Department of Sensory Medicine, Division of Otorhinolaryngology Head and Neck Surgery, [13]Department of Internal Medicine, Division of Cardiovascular and Respiratory Medicine, Akita University School of Medicine, Akita, [6]Department of Pediatrics, Fujita General Hospital, [10]Otorhinolaryngology, [14]Pulmonary Medicine, Fukushima Medical University, Fukushima, [7]Department of Pediatrics, National Hospital Organization Aomori Hospital, [8]Department of Otorhinolaryngology, [18]Respiratory Medicine, Hirosaki University Graduate School of Medicine, [19]Department of Pediatrics & Pediatrics Allergy, Odate Municipal Hospital, Aomori, [11]Department of Otolaryngology, [17]Department of Cardiology, Pulmonology and Nephrology, Yamagata University School of Medicine and [12]Yonezawa City Hospital, Yamagata, Japan.
Correspondence: Kohei Yamauchi, MD, Associate Professor, The Third Department of Internal Medicine, Iwate Medical University School of Medicine, 19-1 Uchimaru Morioka, 020-8505, Japan.
Email: kyamauch@iwate-med.ac.jp
Received 16 April 2008. Accepted for publication 1 July 2008.

**Table 1** The ratio of the subjects with AR symptoms in BA patients and BA symptoms in AR patients

| | Number of cases | With syms | Without complications | Not answered |
|---|---|---|---|---|
| Adult asthma | 2,781 | 1,693 (60.8%)* | 1,044 (37.5%) | 44 (1.6%) |
| Childhood asthma | 3,283 | 2,238 (68.2%)** | 1,035 (31.5%) | 10 (0.3%) |
| Allergic rhinitis | 3,945 | 1,935 (49.0%) | 2,010 (51.0%) | — |

The following questions to the patients with adult BA, childhood BA and AR;

1) Question to BA patients: Have you had an experience in which symptoms such as sneezing, runny nose and stuffy nose developed repeatedly when you did not have a cold?

2) Question to AR: Have you had an experience in which asthma-like symptoms such as a wheezing sound, cough, sputum, and exercise-induced breathing difficulty developed repeatedly when you did not have a cold?

#; The complications mean AR symptoms in BA patients and BA symptoms in AR patients.

*Adult asthma *vs* Allergic rhinitis, $p < 0.001$, **Childhood asthma *vs* Allergic rhinitis, $p < 0.001$ by $\chi^2$ analysis.

ways of these two diseases, they have been thought to share a common pathogenesis.[6,7] Inhalant allergens common to BA and AR have been also evaluated.[5]

Recently, BA and AR have come to be considered as "one airway disease" and therapeutic strategies have been considered consistent with this concept.[8]

To date, epidemiological studies on the comorbidity of BA and AR have been reported globally. Greisner, *et al.* reported that among college students in the US, 85.7% of patients with BA had a history of AR. On the other hand, the frequency of asthma was 16.2% among individuals with rhinitis in a European population.[5] There have been few reports on the comorbidity of BA and AR in a large Japanese population. The present study examined more than 10,000 patients, including patients with adult BA, child BA and AR, in the same period in the Tohoku district of Japan.

## METHODS

*Subjects*: The subjects enrolled in the present study were patients who visited private medical offices, public hospitals and university hospitals during the 3 month period from August 1, 2006 to October 31, 2006, in the Tohoku district of Japan. The patients with BA ($n$ = 2,781) were diagnosed by internal medicine physicians according to ATS guidelines. The patients with childhood BA ($n$ = 3,283) who were less than the age of 16 years were diagnosed by pediatricians according to the Japanese Pediatric Guideline for the Treatment and Management of Asthma 2005.[9] The patients with AR ($n$ = 3,945) who included both children and adults were diagnosed by otolaryngologists according to Practical Guideline for the Management of Allergic Rhinitis in Japan.[10]

*Questionnaire*: The patients were requested to answer a questionnaire based on the following questions: for patients with adult BA and child BA, patients were asked "Have you had an experience in which symptoms such as sneezing, runny nose and stuffy nose developed repeatedly when you did not have a cold?"; "Have you been diagnosed with perennial allergic rhinitis or seasonal allergic rhinitis?"; "Do you have symptoms such as sneezing, runny nose and stuffy nose when asthma is aggravated?"; "In which months do you have symptoms such as sneezing, runny nose and stuffy nose?"; and "In which months do you have aggravated symptoms of asthma?". In these questionnaires, the patients could answer "all year" when they had the symptoms perennially. For patients with AR, patients were asked: "Have you had an experience in which asthma-like symptoms such as a wheezing sound, cough, sputum, and exercise-induced breathing difficulty developed repeatedly when you did not have a cold?"; "Have you been diagnosed with asthma?"; "Do you have asthma-like symptoms when allergic rhinitis is aggravated?"; "In which months do you have symptoms such as sneezing, runny nose and stuffy nose?"; and "In which months do you develop asthma-like symptoms?". In the patients with childhood BA, the mothers or adult attendants answered the questions if the patients seemed unable to understand the questionnaire.

*Statistics*: Data in the present study were analyzed by McNemar Analysis and $\chi 2$ analysis.

## RESULTS

### COMORBIDITY OF BA AND AR

Among the patients with adult BA ($n$ = 2,781), 60.8% answered that they had had symptoms of AR (Table 1). Among the adult BA patients with AR symptoms ($n$ = 1,693), 68.2% were diagnosed with AR (Table 2).

Among patients with childhood BA ($n$ = 3,283), 68.2% answered that they had had symptoms of AR (Table 1). Among the childhood BA patients with the AR symptoms ($n$ = 1,335), 59.7% were diagnosed with AR (Table 2).

On the other hand, among patients with AR (n = 3,945), 49% answered that they had ever had symptoms of BA (Table 1). Among AR patients with BA symptoms ($n$ = 1,935), 34.8% had been diagnosed with BA (Table 2).

The ratios of subjects with AR symptoms among both adult and childhood BA patients were signifi-

**Table 2** The ratio of the subjects diagnosed as AR in BA patients with AR symptoms and BA in AR patients with BA symptoms

| | Number of cases | Diagnosed | Not diagnosed | Not answered |
|---|---|---|---|---|
| Adult asthma | 1,693 | 1,155 (68.2%)* | 509 (30.1%) | 29 (1.7%) |
| Childhood asthma | 2,238 | 1,335 (59.7%)** | 873 (39.0%) | 30 (1.3%) |
| Allergic rhinitis | 1,935 | 674 (34.8%) | 1,219 (63.0%) | 42 (2.2%) |

The following questions to the patients with adult BA, childhood BA and AR;

1) Question to asthma patients: Have you been diagnosed with perennial allergic rhinitis or seasonal allergic rhinitis?

2) Question to patients with allergic rhinitis: Have you been diagnosed with asthma?

*Adult asthma *vs* Allergic rhinitis, $p<0.001$, **Childhood asthma *vs* Allergic rhinitis, $p<0.001$ by $\chi 2$ analysis.

**Table 3** The ratio of the subjects who aggravated both AR and BA symptoms in BA patients with AR symptoms and AR patients with BA symptoms

| | Number of cases | Aggravated | Not aggravated | Not answered |
|---|---|---|---|---|
| Adult asthma | 1,693 | 886 (52.3%)* | 769 (45.4%) | 38 (2.2%) |
| Childhood asthma | 2,238 | 1,391 (62.2%)** | 810 (36.2%) | 37 (1.7%) |
| Allergic rhinitis | 1,935 | 1,449 (74.9%) | 402 (20.8%) | 84 (4.3%) |

The following questions to the patients with adult BA, childhood BA and AR;

1) Question to asthma patients: Do you have symptoms such as sneezing, runny nose and stuffy nose when asthma is aggravated?

2) Question to patients with allergic rhinitis: Do you have asthma-like symptoms when allergic rhinitis is aggravated?

*Adult asthma *vs* Allergic rhinitis, $p < 0.001$, **Childhood asthma *vs* Allergic rhinitis, $p < 0.001$ by $\chi 2$ analysis.

cantly higher than that of subjects with BA symptoms among AR patients. In addition, the ratios of subjects diagnosed with AR among both adult and childhood BA patients were significantly higher than that of subjects diagnosed with BA among AR patients. In the current study, the complications of AR in adult and child BA patients, and BA in AR patients were diagnosed according to the questionnaire.

### CO-OCCURRENCE OF THE SYMPTOMS OF BA AND AR

Among patients with adult BA ($n$ = 1,693), 52.3% showed AR symptoms when their BA symptoms were aggravated. Sixty two percent of the patients with childhood BA ($n$ = 2,238) also showed AR symptoms when their BA symptoms were aggravated.

On the other hand, among patients with AR ($n$ = 1,935), 74.9% showed BA symptoms when their AR symptoms were aggravated.

The ratios of subjects with both aggravated AR and BA symptoms among both adult and childhood BA patients were significantly lower than that of those among AR patients (Table 3).

### FREQUENCY OF SYMPTOMS OF BA AND AR

Among patients with adult BA, symptoms of BA occurred frequently in spring (March and April) and autumn (September and October). These two peaks in the frequency of symptoms were statistically significant compared with the month with the lowest frequency. Among those patients, the symptoms of AR occurred frequently in two seasons such as March and April, and September and October, the same as with the BA symptoms (Fig. 1). The two peaks of AR symptoms among the adult BA patients were also significant. The ratio of the adult BA patients with perennial symptoms of BA was 13.6% and 33.7% of these showed perennial symptoms of AR.

Among the patients with childhood BA ($n$ = 2,238), the symptoms of BA also occurred frequently in spring and autumn, similar to those of adult BA (Fig. 2). Among these, the symptoms of AR occurred frequently in two seasons such as March and April, and September and October, similar to that seen in the adult BA patients (Fig. 2). The two peaks of AR symptoms in the childhood BA patients were also seen in two seasons such as March and April, and September and October. Among the child BA patients, 5.9% showed perennial symptoms of BA and 30.2% of these showed perennial symptoms of AR.

On the other hand, in the AR patients, AR symptoms occurred frequently also in spring and autumn, similar to those of adult BA and childhood BA patients. In the same periods, the BA symptoms in the AR patients also occurred frequently, and the two peaks of frequency were significantly high (Fig. 3). Thirty five percent of the AR patients showed perennial symptoms of AR and 23.7% of these showed perennial symptoms of BA.

## *DISCUSSION*

The present study confirmed the high comorbidity of

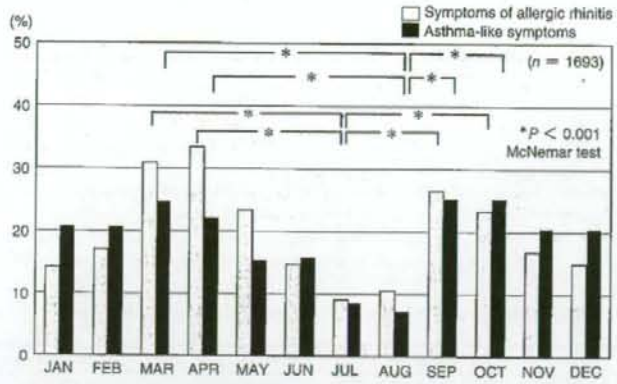


**Fig. 1** Frequency of BA and AR symptoms in adult BA patients. The following questions were given to the adult BA patients who repeatedly developed symptoms of sneezing, runny nose or stuffy nose without having a cold: 1) In which months do you have symptoms such as sneezing, runny nose and stuffy nose?; 2) Do you have aggravated symptoms of asthma in specific months?

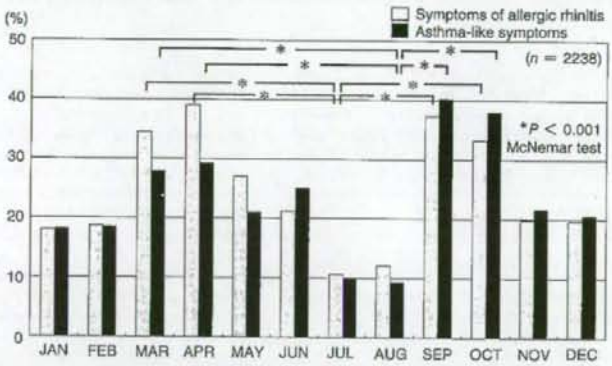


**Fig. 2** Frequency of BA and AR symptoms in childhood BA patients. The following questions were given to the childhood BA patients who repeatedly developed symptoms of sneezing, runny nose or stuffy nose without having a cold: 1) In which months do you have symptoms such as sneezing, runny nose and stuffy nose?; 2) Do you have aggravated symptoms of asthma in specific months?

BA and AR. The symptoms of BA and AR frequently occurred in the same periods such as spring and autumn. The co-occurrence of the symptoms of the two diseases was demonstrated. These results tend to confirm that AR and BA share common pathogenesis in the upper and lower airway.

Based on the AR symptoms, the ratio of comorbidity of AR was suggested to be 60.8% among the patients with adult BA and 68.2% among those with childhood BA. Greisner *et al.* reported that 85.7% of patients with BA had a history of AR in the US.[1] Soler *et al.* reported that 63.4% of the patients with asthma

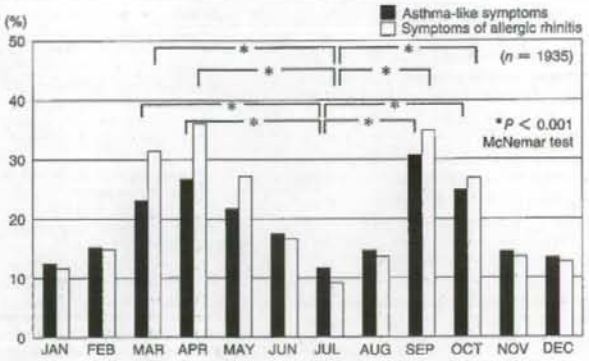


**Fig. 3** Frequency of BA and AR symptoms in AR patients. The following questions were given to patients with AR who repeatedly developed asthma-like symptoms without having a cold: 1) Do you have aggravated symptoms of allergic rhinitis in specific months?; 2) In which months do you develop asthma-like symptoms?

($n$ = 546) had seasonal AR and 77.3% of these had perennial AR.[11] Linneberg *et al.* reported that 89–100% of patients with allergic BA ($n$ = 734) had allergic rhinitis in Denmark.[5] These reported ratios of comorbidity of AR in subjects with BA were higher than those in our study. In the study by Linneberg *et al.*, the ratio of comorbidity of AR was based on pollen-sensitized allergic asthma. In the present study, the adult BA population included both atopic and non-atopic BA. The comorbidity with AR is thought to be less frequent among non-atopic BA subjects compared to those with atopic BA.[4] The ratio of comorbidity of AR among BA subjects may, therefore, depend on the ratio of atopic BA patients in the population. Masuda *et al.* reported that 77.7% of 130 children with asthma (ages 2 through 10) had co-existing AR based on objective findings in a Japanese population.[12] Our data showed a slightly lower ratio of comorbidity of AR (68.2%) in patients with childhood BA. In this case, the difference in the ratio of comorbidity may be caused by the age of the subjects and by the way of diagnosing AR. In the present study, the ratio of comorbidity of BA in AR patients (49.0%) was lower that of AR in BA patients (60.8% in adult BA patients, 68.2% in childhood BA patients). However, we have no data concerning the allergic disposition of the BA patients in the current study. Mullarkey *et al.* reported that 58.8% of patients with AR had histories or findings consistent with asthma.[3] Globally, the population size of AR seemed larger than that of BA. In addition, AR from cedar pollen occupies a dominant position in Japan.[13-15] However, Japanese cedar pollen is not thought to be closely associated with BA compared to other allergens, such as orchard grass, ragweed, or mite.[16] This may account for the fact that the ratio of the comorbidity of BA in AR patients appeared to be lower than that of AR in BA patients. However, we have no data to specify the AR patients with Japanese cedar pollen in the current study. This study was performed based on a questionnaire in a large population. Therefore, the diagnosis of AR in adult and child BA patients, and BA in AR patients may have some limitations. However, we believe that the obtained results including comorbidity of BA and AR have some meaning.

The present study demonstrated that there were two seasonal peaks of frequency of both AR and BA symptoms, in spring and autumn among both the adult and the childhood BA patients. In addition, these two seasonal peaks in the frequency of both AR and BA symptoms in AR patients were also evaluated. We have no clear evidence to answer to the question of why the AR and BA symptoms co-occurred in the same two seasons in the adult BA, childhood BA and AR patients. However, we can speculate that possible causes include seasonal pollen, change of temperature, change of weather, viral infection etc. Among them, seasonal pollen are important allergens that induce AR and BA symptoms in the spring and autumn. Japanese cedar pollen is known to be a major allergen that induces AR symptoms in the spring all over Japan. While Japanese cedar pollen is not closely associated with BA,[16] other seasonal pollen such as ragweed, mugwort, orchard grass, birch etc. are thought

to be common seasonal allergens associated with AR and BA. In this context, the pollen allergens common to AR and BA might play a role in inducing both AR and BA symptoms in spring and autumn.

The present study also revealed that AR and BA symptoms co-occurred both seasonably and perennially among 52.3% of adult BA, 62.0% of childhood BA and 74.9% of AR patients by asking in the questionnaire whether AR symptoms were perennial or seasonal. The common triggers including allergens as described above were the probable causes. Beside these, AR exacerbation has been thought to provoke airway inflammation in the lower respiratory tract or to induce an increase in airway hyperresponsiveness.[17-19] Our results revealed that the ratio of AR patients with BA symptoms when patients experienced aggravated AR was significantly higher than those of adult and childhood BA patients with AR symptoms when they experienced aggravated BA. These findings indicate that more AR patients showed BA symptoms with AR exacerbation as compared with the BA patients with AR symptoms with BA exacerbation. These results support the idea that allergic inflammation in the upper airway influences airway hyperresponsiveness in BA.[18,19] In addition, this result seems to indicate that the upper airway symptoms tended to induce the lower airway symptoms more than the lower airway symptoms influenced the upper airway symptoms.

Our results also revealed that BA aggravation induced AR symptoms and, *vice versa*, AR aggravation induced BA symptoms in BA and AR patients. It is hypothesized that the inflammation in the upper airway in AR and that in the lower airway in BA influence each other *via* the systemic circulation and nervous system.[20-22] This mechanism may contribute, at least in part, to the co-occurrence of AR and BA symptoms both seasonally and perennially among the patients with adult BA, child BA and AR.

In conclusion, the high comorbidity of BA and AR was comfirmed in a large Japanese population. The co-occurrence of the symptoms of the two diseases suggests that AR and BA share a common pathogenesis and should be treated as a single airway disease.

## ACKNOWLEDGEMENTS

The authors appreciate the participation in the current clinical study of the members of Kido Shikkann Taisaku Kaigi (The Airway Disease Task Force in the Tohoku region).

We are indebted to Mr. Brent Bell for reading this manuscript.

## REFERENCES

1. Greisner WA 3rd, Settipane RJ, Settipane GA. Co-existence of asthma and allergic rhinitis: a 23-year follow-up study of college students. *Allergy Asthma Proc* 1998; **19**:185-8.
2. Mullarkey MF, Hill JS, Webb DR. Allergic and nonallergic rhinitis: their characterization with attention to the meaning of nasal eosinophilia. *J Allergy Clin Immunol* 1980;**65**:122-6.
3. Malo JL, Lemiere C, Desjardins A, Cartier A. Prevalence and intensity of rhinoconjunctivitis in subjects with occupational asthma. *Eur Respir J* 1997;**10**:1513-5.
4. Leynaert B, Neukirch C, Kony S *et al.* Association between asthma and rhinitis according to atopic sensitization in a population-based study. *J Allergy Clin Immunol* 2004;**113**:86-93.
5. Linneberg A, Henrik Nielsen N, Frolund L, Madsen F, Dirksen A, Jorgensen T, for the Copenhagen Allergy Study. The link between allergic rhinitis and allergic asthma: a prospective population-based study. *Allergy* 2002;**57**:1048-52.
6. Luskin AT, Scherger JE, Pollart SM. Beyond the nose: the systemic inflammatory effects of allergic rhinitis. *Hosp Physician* 2004:13-22.
7. Gelfand E. Inflammatory mediators in allergic rhinitis. *J Allergy Clin Immunol* 2004;**114**:S135-8.
8. Bousquet J, Van Cauwenberge P, Khaltaev N, for the ARIA Workshop Group and theWorld Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;**108**(5 Suppl):S147-334.
9. Japanese Pediatric Allergological Society. Morikawa A, Nishima S (eds). *[Japanese Pediatric Guideline for the Treatment and Management of Asthma 2005].* Tokyo: Kyowa Kikaku, 2005(in Japanese).
10. Nasal Allergy Therapeutic Guideline Committee. *[Practical Guideline for the Management of Allergic Rhinitis in Japan]*, 5th edn. Tokyo: Life Science, 2005(in Japanese).
11. Solèr M, Matz J, Townley R *et al.* The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001;**18**:254-61. Erratum in: *Eur Respir J* 2001;**18**:739-40.
12. Masuda S, Fujisawa T, Katsumata H, Atsuta J, Iguchi K, Kamiya H. Nasal symptoms in children with bronchial asthma [abstract]. *J Allergy Clin Immunol* 2003;**111**:S138.
13. Sakurai Y, Nakamura K, Teruya K *et al.* Prevalence and risk factors of allergic rhinitis and cedar pollinosis among Japanese men. *Prev Med* 1998;**27**:617-22.
14. Ozasa K, Dejima K, Takenaka H. Prevalence of Japanese cedar pollinosis among schoolchildren in Japan. *Int Arch Allergy Immunol* 2002;**128**:165-7.
15. Okuda M. Epidemiology of Japanese cedar pollinosis throughout Japan. *Ann Allergy Asthma Immunol* 2003;**91**: 288-96.
16. Obase Y, Shimoda T, Mitsuta K, Matsuo N, Matsuse H, Kohno S. Sensitivity to the house dust mite and airway hyperresponsiveness in a young adult population. *Ann Allergy Asthma Immunol* 1999;**83**:305-10.
17. Gibson PG, Manning PJ, O'Byrne PM *et al.* Allergen-induced asthmatic responses. Relationship between increases in airway responsiveness and increases in circulating eosinophils, basophils, and their progenitors. *Am Rev Respir Dis* 1991;**143**:331-5.
18. Okayama M, Iijima H, Shimura S *et al.* Methacholine bronchial hyperresponsiveness in chronic sinusitis. *Respiration* 1998;**65**:450-7.
19. Koh YI, Choi IS. Relationship between nasal and bronchial responsiveness in perennial allergic rhinitic patients with asthma. *Int Arch Allergy Immunol* 2002;**129**:341-7.
20. McCusker CT. Use of mouse models of allergic rhinitis to study the upper and lower airway link. *Curr Opin Allergy Clin Immunol* 2004;**4**:11-6.

21. Fontanari P, Burnet H, Zattara-Hartmann MC, Jammes Y. Changes in airway resistance induced by nasal inhalation of cold dry, dry, or moist air in normal individuals. *J Appl Physiol* 1996;81:1739-43.

22. Undem BJ, McAlexander M, Hunter DD. Neurobiology of the upper and lower airways. *Allergy* 1999;54(Suppl 57):81-93.