

Analysis of the Comorbidity of Bronchial Asthma and Allergic Rhinitis by Questionnaire in 10,019 Patients

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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

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Received 16 April 2008. Accepted for publication 1 July 2008.
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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 χ^2 analysis.

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 airways 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 an-

swer 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 χ^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 ($n =$

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 χ^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 χ^2 analysis.

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 significantly 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

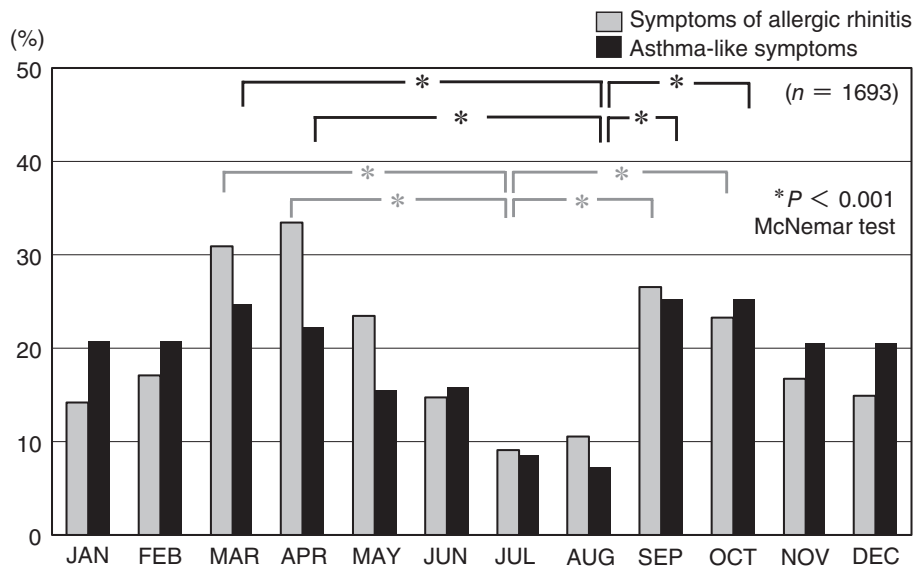


Fig. 1 Frequency of BA and AR symptoms in adult BA patients. The following questions were given to the adult BA patients who repeatedly developed symptoms of sneezing, runny nose or stuffy nose without having a cold: 1) In which months do you have symptoms such as sneezing, runny nose and stuffy nose?;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

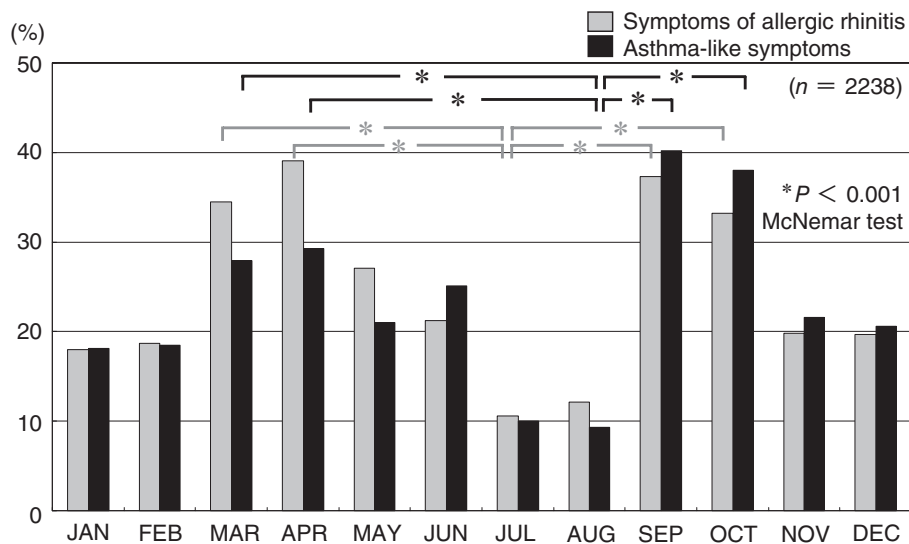


Fig. 2 Frequency of BA and AR symptoms in childhood BA patients. The following questions were given to the childhood BA patients who repeatedly developed symptoms of sneezing, runny nose or stuffy nose without having a cold: 1) In which months do you have symptoms such as sneezing, runny nose and stuffy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

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 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

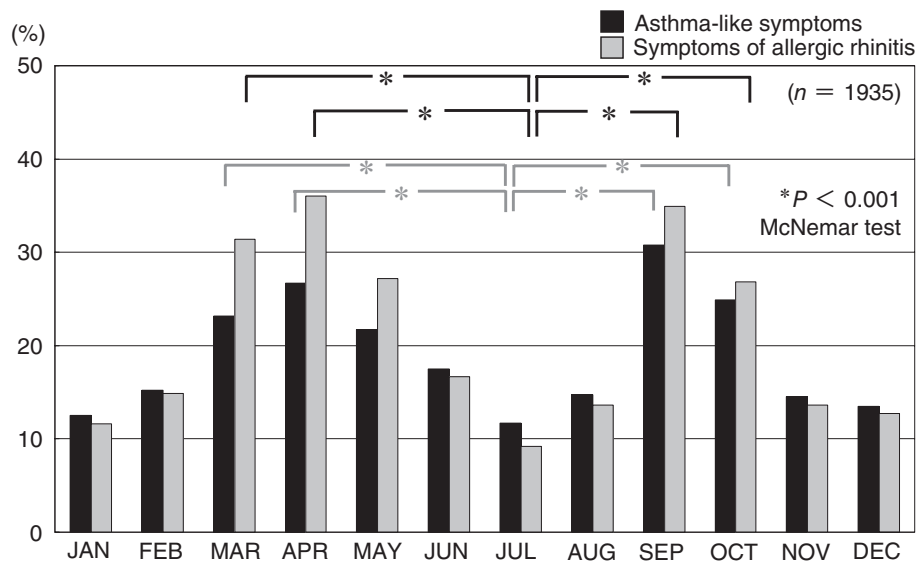


Fig. 3 Frequency of BA and AR symptoms in AR patients. The following questions were given to patients with AR who repeatedly developed asthma-like symptoms without having a cold: 1) Do you have aggravated symptoms of allergic rhinitis in specific months?; 2) In which months do you develop asthma-like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

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 ($n = 546$) 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.² 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 confirmed 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.

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