Asthma in Patients With Japanese Cedar Pollinosis

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Abstract: Japanese cedar pollen is the most common causative allergen for seasonal allergic rhinitis (AR) in Japan. More commonly known as Japanese cedar pollinosis, it occurs in spring causing the typical symptoms of seasonal AR, such as sneezing, rhinorrhea, nasal obstruction, nasal itching, and itching of the eyes. Previous reports indicate that the prevalence of Japanese cedar pollinosis among Japanese was 26.5%. According to a more recent questionnaire-based survey, the prevalence of Japanese cedar pollinosis in patients with adult asthma might be up to 30% to 50%, suggesting higher rates than that previously reported. Moreover, 30% to 60% of adult asthmatic patients with concomitant pollinosis have exacerbations of their asthma symptoms during the Japanese cedar pollen season. These findings suggest that concomitant Japanese cedar pollinosis may be an aggravating factor in patients with asthma. As with other pollens, such as grass and birch, Japanese cedar pollen was shown to be a trigger factor for worsening asthma. In clinical practice, a number of Japanese patients with asthma are mono-sensitized to Japanese cedar pollen but not to other antigens. Further studies are needed to elucidate the mechanisms of Japanese cedar pollen in inducing and in exacerbating asthma. The presence of concomitant AR is often associated with the difficulty in asthma control. However, there has been a controversy whether treating concomitant AR by intranasal corticosteroid would produce better asthma-related outcomes in patients with asthma and AR. The effect of treating concomitant cedar pollinosis by intranasal corticosteroids on asthma control in patients with asthma and cedar pollinosis also remains unknown. Certain systemic treatments, such as leukotriene receptor antagonist and anti-IgE monoclonal antibody, are supposed to reduce the symptoms of both asthma and AR in patients with asthma and concomitant AR. In conclusion, Japanese cedar pollinosis is often associated with exacerbations of asthma. Further investigations are expected to elucidate the precise impact and mechanisms of Japanese cedar pollinosis in asthma.

Key Words: Japanese cedar pollinosis, asthma, allergic rhinitis

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were enrolled in the study (137 males and 196 females). The prevalence of Japanese cedar pollinosis was 34.8% (116 patients). Patients’ characteristics are shown in Table 1. Distribution of the population classified by severity was similar between the groups with and without cedar pollinosis (Table 1). Asthmatic patients with Japanese cedar pollinosis were found across all age groups (Fig. 1). Among 116 asthmatic patients with Japanese cedar pollinosis, 41 (35.3%) patients reported that their asthmatic control was aggravated during Japanese cedar pollen season. Among 41 patients whose asthma was well controlled, but was aggravated during the Japanese cedar pollen season, 13 patients showed a decrease in morning peak expiratory flow more than 10% compared with the baseline values (Fig. 2). However, it should be taken into account that the effect of virus infection, the most potent inducer of

### TABLE 1. Patient Characteristics

|                          | Total   | Cedar Pollinosis (-) | Cedar Pollinosis (+) |
|--------------------------|---------|----------------------|----------------------|
| No. patients             | 333     | 217                  | 116                  |
| Age, yr                  | 48.3 ± 1.0 | 48.7 ± 1.3           | 47.5 ± 1.6           |
| Sex, n (%)               |         |                      |                      |
| Male                     | 137 (41.1) | 91 (41.9)           | 46 (39.7)           |
| Female                   | 196 (58.9) | 126 (58.1)          | 70 (60.3)           |
| Type Atopic, n (%)       | 211 (63.4) | 129 (59.5)          | 82 (70.7)           |
| Nonatopic                | 122 (36.6) | 88 (40.5)          | 34 (29.3)           |
| Duration of asthma, yr   | 15.3 ± 0.8 | 15.0 ± 1.0          | 15.8 ± 1.3          |
| IgE RIST (U/mL)          | 565.8 ± 51.6 | 580.6 ± 72.9       | 538.9 ± 60.3        |
| Cedar RAST (UA/mL)       | 10.9 ± 1.4 | 4.2 ± 1.2          | 23.4 ± 2.8          |
| Histamine-PC₂₀ (µg/mL)   | 1424 ± 194 (n = 125) | 1550 ± 262 (n = 81) | 1193 ± 267 (n = 44) |
| Severity of asthma, n (%)|         |                      |                      |
| Mild                     | 81 (24.3) | 54 (24.9)           | 27 (23.3)           |
| Moderate                 | 177 (53.2) | 116 (53.5)         | 61 (52.6)           |
| Severe                   | 75 (22.5) | 47 (21.6)           | 28 (24.1)           |
| Therapy, n (%)           |         |                      |                      |
| BDP                      | 275 (82.6) | 182 (83.9)         | 93 (80.2)           |
| Slow-release theophylline| 259 (77.8) | 165 (76.0)         | 94 (81.0)           |
| Oral β₂-agonists         | 126 (37.8) | 77 (35.5)         | 49 (42.2)           |
| Anti-allergic agents, n (%)| 57 (17.1) | 37 (17.1)         | 20 (17.2)           |
| Oral steroids, n (%)     | 20 (6.0) | 13 (6.0)           | 7 (6.0)             |

Adapted from Ueno et al (2002) with permission from Arerugi. RIST, Radio ImmunoSorbent Test; RAST, Radio AllergoSorbent Test.

FIGURE 1. Distribution of the age of patients with asthma with or without complication with Japanese cedar pollinosis. Number of the patients was demonstrated. Adapted from Ueno et al (2002) with permission from Arerugi.

FIGURE 2. Number of patients whose morning peak expiratory flow decreased more or less than 10% compared with the baseline values was demonstrated. Adapted from Ueno et al (2002) with permission from Arerugi.
asthma exacerbation, was not ruled out in this study. Next, we compared the patients’ characteristics between the group that had and the group that did not have exacerbation of their asthma symptoms during Japanese cedar pollen season (Table 2). Among 116 asthmatic patients with Japanese cedar pollinosis, airway hyperresponsiveness was determined in 44 patients before the season of Japanese cedar pollen. Although the level of histamine-PC<sub>20</sub> in the group in which asthmatic symptoms were exacerbated was lower than that in the group in which asthmatic symptoms were not exacerbated, they did not show statistical significance. Total IgE levels and specific IgE levels to Japanese cedar pollen showed no significant difference between the 2 groups.

According to the article reported by Fukushi et al, the prevalence of Japanese cedar pollinosis in 151 patients with asthma was 47.0%, and 54.9% of the asthmatic patients with concomitant Japanese cedar pollinosis was associated with aggravation of asthma symptoms and reduced asthma control during Japanese cedar pollen season. These researchers also showed that the asthmatic patients with concomitant Japanese cedar pollinosis had lower levels of peak expiratory flow during the Japanese cedar pollen season.

These reports including ours suggest that the prevalence of Japanese cedar pollinosis in patients with adult asthma might be 30% to 50%, and 30% to 60% of adult asthmatic patients with concomitant pollinosis might be associated with exacerbation of asthma during Japanese cedar pollen season. However, it is noteworthy that the diagnosis of Japanese cedar pollinosis is sometimes difficult, and the prevalence of Japanese cedar pollinosis has been changed decade by decade and by the area.

### TABLE 2. Patient Characteristics on Exacerbation During Japanese Cedar Pollen Season

| Exacerbation (+) | Exacerbation (-) |
|------------------|------------------|
| No. patients     | 41               | 75               |
| Age, yr          | 49.5 ± 2.9       | 46.5 ± 1.9       |
| Sex, n (%)       |                  |                  |
| Male             | 16 (39.0)        | 30 (40.0)        |
| Female           | 25 (61.0)        | 45 (60.0)        |
| Type Atopic, n (%)| 31 (75.6)        | 51 (68.0)        |
| Nonatopic        | 10 (24.4)        | 24 (32.0)        |
| Duration of asthma, yr | 16.8 ± 2.2     | 15.2 ± 1.6       |
| IgE RIST (U/mL)  | 532.2 ± 101.1    | 542.7 ± 75.7     |
| Cedar RAST (UA/mL) | 25.1 ± 5.5    | 22.4 ± 8.1       |
| Histamine-PC<sub>20</sub> (µg/mL) | 841 ± 288 (n = 15) | 1375 ± 886 (n = 29) |
| Severity of asthma, n (%) |                  |                  |
| Mild             | 6 (14.6)         | 21 (28.0)        |
| Moderate         | 22 (53.7)        | 39 (52.0)        |
| Severe           | 13 (31.7)        | 15 (20.0)        |
| Therapy, n (%)   |                  |                  |
| BDP             | 34 (82.9)        | 59 (78.7)        |
| Slow-release theophylline | 37 (90.2) | 57 (76.0)        |
| Oral β2-agonists | 21 (51.2)        | 28 (37.3)        |
| Anti-allergic agents, n (%) | 5 (12.2)     | 14 (18.7)        |
| Oral steroids, n (%) | 2 (4.9)        | 4 (5.3)          |

Adapted from Ueno et al (2002) with permission from Arerugi.<sup>6</sup>
increased in lower airways of patients with seasonal AR, 24 hours after nasal allergen challenge. Moreover, eosinophilic inflammation was enhanced by the segmental endobronchial allergen challenge with grass pollen in the nasal lamina propria and nasal epithelium of atopic subjects. These findings suggest a cross talk between allergic nasal inflammation and allergic lower airway inflammation, and the presence of more AR patients who have the potential of developing asthma and more asthmatic patients who have the potential of developing AR.

An early study suggested that a nasobronchial reflex arc would contribute to the linking of AR and asthma. Based on this hypothesis, nasal allergen challenge affects bronchial hyperresponsiveness through a reflex arc that involves trigeminal afferents and vagal efferents.

**TREATMENT STRATEGY OF ASTHMA WITH COMORBID AR OR JAPANESE CEDAR POLLINOSIS**

It is well known that the diagnosis of AR often precedes that of asthma. Rhinitis is an independent risk factor, intriguingly, not only in atopic individuals but also in nonatopic individuals for the subsequent development of asthma. Therefore, early intervention treatment of AR is hopefully considered as a preventive therapy for asthma. In fact, the Preventive Allergy Treatment study demonstrated that continuous pollen-specific immunotherapy for 3 years decreased the occurrence of asthma in patients with AR compared with that in patients with AR not receiving the immunotherapy. However, whether Japanese cedar pollinosis precedes asthma is still unknown.

The presence of concomitant AR is often associated with the difficulty of asthma control. In fact, here, we showed that AR increased the risk of asthma attacks and emergency room visit (Fig. 4). This leads to the question whether treating concomitant AR would produce better asthma-related outcomes in addition to the obvious benefits with regard to nasal symptoms. Studies have produced conflicting results regarding the effects of intranasal corticosteroids on the lower airways of patients with AR. Some of these studies have shown decreased bronchial hyperresponsiveness after treatment with intranasal corticosteroids, whereas other studies failed to show this. One study reported the positive effects of intranasal corticosteroids on the symptoms of asthma but not on bronchial responsiveness. The reason of this controversy has not been elucidated yet. However, at least, the differences of study designs and patient characteristics, including age and the concomitant presence or absence of asthma, are considered to be associated with this controversy. Despite the fact that intranasal steroids are the most effective agents for controlling symptoms of AR, second-generation antihistamines are still regarded as the first-line therapy for especially mild-to-moderate AR. Although antihistamines are not considered an effective treatment for asthma, Grant et al reported that an oral antihistamine given to patients with concomitant AR and asthma could improve persistent asthma symptoms during pollen season.

**FIGURE 3.** Mechanisms of allergic inflammation. Adapted from Holgate (2008) with permission from *Clin Exp Allergy*.11

**FIGURE 4.** Asthma-related resource use and asthma attacks according to the presence of concomitant AR (% patients). □, asthma; ■, asthma with AR. Adapted from Bousquet et al (2005) with permission from *Clin Exp Allergy*.21
Leukotrienes are involved in the mechanisms of both asthma and AR. Therefore, leukotriene receptor antagonist (LTRA) is an effective drug for the patients with asthma and AR. In fact, COMPACT study (Clinical Outcomes with Montelukast as a Partner Agent to Corticosteroid Therapy) showed that LTRA was more effective in patients with asthma and AR than in those with asthma alone.\(^7\) Sagara et al\(^{23}\) demonstrated that a number of the patients with Japanese cedar pollinosis but not with asthma showed an increase in airway hyperresponsiveness during pollen season. They also demonstrated that this increase was inhibited by LTRA. Omalizumab, a humanized monoclonal anti-IgE antibody, is a novel drug for patients with severe asthma. The mechanism of omalizumab is inhibition of the binding of IgE to FcεRI on mast cells and basophils. The effectiveness of omalizumab on AR and Japanese cedar pollinosis was demonstrated as well as on asthma.\(^{29,30}\) These data suggest that certain systemic drugs such asLTRAs and anti-IgE monoclonal antibody would produce better asthma-related outcomes in patients with asthma and concomitant AR.

**CONCLUSIONS**

There is a high prevalence of Japanese cedar pollinosis in patients with asthma. Concomitant Japanese cedar pollinosis is regarded as one of the factors leading to asthma exacerbations in patients with asthma and cedar pollinosis. Therefore, treatment of cedar pollinosis may contribute to better asthma control.

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