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Letter to the Editor

Characteristics of Japanese cypress pollen-induced allergic rhinitis by environmental challenge chamber

Dear Editor,

Japanese cedar (*Cryptomeria japonica*) pollen (JCP) and Japanese cypress (*Chamaecyparis obtusa*) pollen (JCyP) are most prevalent pollen allergen in Japan.^{1,2} Dispersal of JCP generally precedes that of JCyP, but the pattern of each is typically arch-shaped over time. JCP dispersal commences in early February and peaks between late February and early March, whereas dispersal of JCyP peaks between late March and early April, with some variation due to yearly climatic changes. In and around Tokyo, the pollen dispersal season is in excess of 10 weeks.²

Many patients with JCP-induced AR also have known sensitivity to JCyP, given their shared allergenicity.³ AR triggered by JCyP alone is thus a rarity. Because dispersal periods of the two pollen species do overlap, AR due exclusively to JCyP has been difficult to characterize. Through its antecedent or concurrent dispersal, JCP may well impact the symptoms and severity of JCyP-induced AR.

Environmental challenge chamber (ECC) enables selective introduction of various pollen types at constant levels and under identical conditions, allowing highly reproducible clinical evaluations.^{4,5} Qualifying patients with JCP-induced AR by participated in two pollen exposure studies conducted at the Chiba University ECC. JCP-induced AR was defined as rhinitis for at least two consecutive seasons of JCP dispersal and serum JCP-specific IgE ≥ 70 UA/ml (class 2) by ImmunoCAP test (Phadia Co [Thermo Fisher Scientific], Uppsala, Sweden).

The first involved a total of 59 subjects (21 males, age 19–66) exposed to uniform concentrations (8000 grains/m³) of JCP or JCyP. During a second experiment, 35 subjects (14 males, aged 27–57) underwent similar exposures at differing concentrations (JCP: 8000 grains/m³, JCyP: 12,000 grains/m³). Both studies fell outside natural JCP and JCyP dispersal periods, starting in July 2009. Each exposure was 3 h long, recording symptoms thereafter. Between JCP and JCyP exposures, there were washout periods of >2 weeks to avoid JCP carry-over effects.⁴ To avoid repeated pollen exposures of questionable ethics, first and second study enrollees were not the same individuals.

This investigation (clinical registration number: UMIN000001449, UMIN000015667) complied with Ethical Guidelines for Clinical Studies and the Declaration of Helsinki (2008 and 2013 revision). The Ethics Committee of Chiba University approved the study protocol. All enrollees received detailed explanations of planned procedures and possible adverse effects, granting written informed consent prior to participation.

A previous study of ours,⁴ there was no significant difference in symptom severity at JCP exposure levels of 8000 or 12,000 grains/m³, but symptoms did worsen significantly during consecutive 2-day exposures. During the present study, many participants (each sensitive to JCP) showed significant symptomatology after specified JCyP exposures (83% in the first study and 97% in the second study). However, nasal symptoms induced by JCyP at the same concentration (8000 grains/m³) proved significantly milder (Fig. 1A). To achieve almost equivalent symptom severity, a JCyP concentration of 12,000 grains/m³ was needed (Fig. 1B). Although the reasons for milder nasal symptoms to JCyP are not clear, the annual JCyP dispersal amount is usually lower than that of JCP in the residential area of the participants (Chiba prefecture). The lower JCyP exposure in natural pollen dispersal season may influence the milder symptoms observed in this study using the environmental challenge chamber. In addition, the difference of the amount of major causal allergens between JCP and JCyP might reflect the different severities of the symptoms to these pollen exposures.

On the other hand, nasal, ocular, or laryngeal symptoms related to JCyP seemed to resemble those of JCP exposure and were not distinctive (Fig. 1). There have been some reports, which are not aligned with our data, that laryngeal symptoms are more likely to result during natural periods of JCyP (vs JCP) dispersal.⁶ Sustained oral breathing (due to nasal obstruction) after cumulative JCP and JCyP exposures may conceivably accentuate laryngeal symptoms by default.⁷ Ocular symptoms were mild during pollen exposure to both JCP and JCyP.

JCP has several known allergens, Cry j 1 and Cry j 2 being the two major proteins. They show strong amino acid sequence homology with major JCyP allergens, Cha o 1 and Cha o 2, respectively.^{8,9} Cha o 3 is another recently discovered major JCyP allergen demonstrating strong homology with amino acid sequencing of the Cry j 4 protein, a low-level JCP allergen.^{10,11} Unfortunately, the impact of these major JCyP allergens on clinical symptoms remains unclear. Thinking of a very rare incidence of JCyP AR patients who do not have allergic reaction to JCP in the real life data, the role of JCyP allergens must be addressed in careful clinical studies. Herein, the severity of nasal symptoms induced by JCP and JCyP correlated well, suggesting that homology of major allergens (as above) is an important factor in this regard (Fig. 2A). The symptoms were not detected by JCyP in 10 participants in the first study ($n = 59$, JCyP 8000 grains/m³) and one participant in the second study ($n = 35$, JCyP 12,000 grains/m³), respectively. The TNSS engendered by JCP in these 10 participants in the first study were significantly lower

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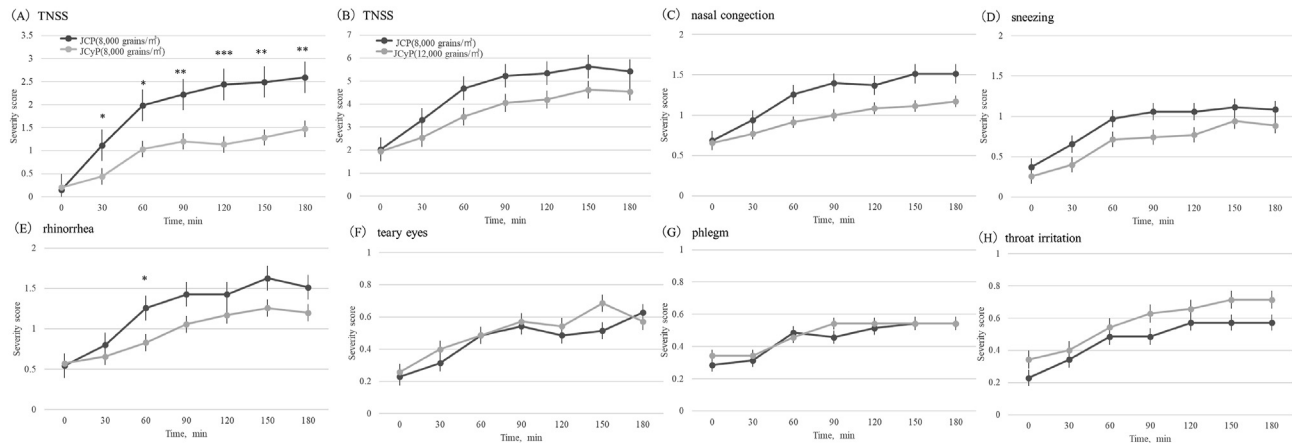


Fig. 1. (A) Comparison of the change of TNSS in the ECC between JCP and JCyP exposure at the same concentration of 8000 grains/m³. Data represent the mean with standard error of mean (SEM) in day 2. * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$. (B)–(H) Comparison of the change of symptoms in the ECC between JCP at a concentration of 8000 grains/m³ and JCyP exposure at a concentration of 12,000 grains/m³. Data represent the mean with standard error of mean (SEM) in day 2. * $P < 0.05$. The response to each pollen in individual subjects was compared using paired-samples t-test. The statistical analyses were performed at a two-sided significance level of 5%. IBM SPSS statistics 23® software was used for the analyses.

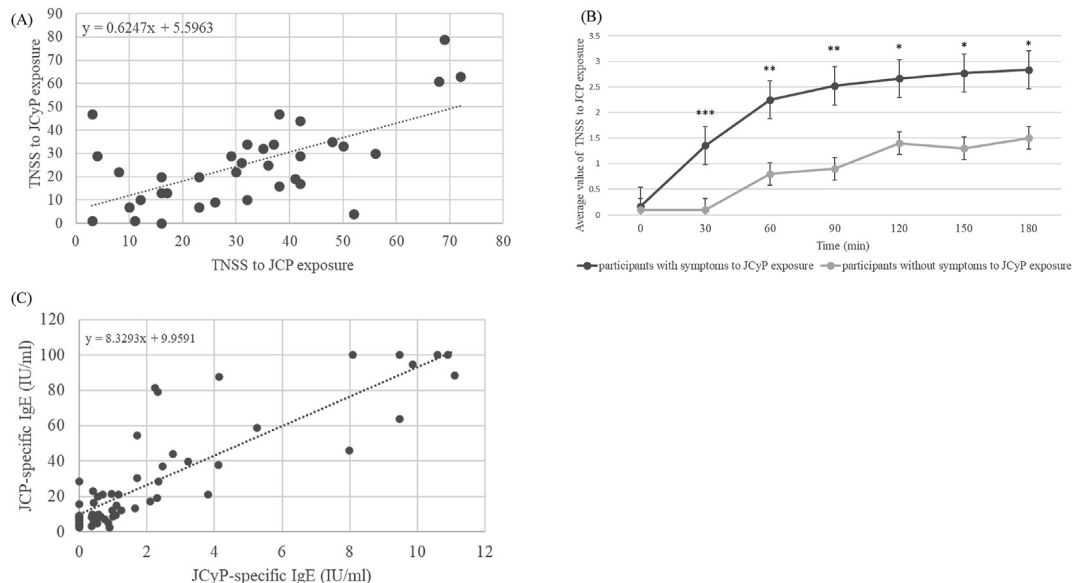


Fig. 2. (A) Relationship between TNSS by JCyP and that by JCP. The data from the second study showed that JCyP (12,000 grains/m³) and JCP (8000 grains/m³) in day 2 were used. (B) Comparison of the TNSS to JCP exposure between the participants with symptoms ($n = 49$) and without symptoms ($n = 10$) to JCyP exposure. The data from the first study showed that JCP and JCyP were exposed at the concentration of 8000 grains/m³. Data represent the means with SEM in day. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. (C) Correlation between JCP-specific IgE and JCyP-specific IgE. The data from the first study showed that JCyP (8000 grains/m³) and JCP (8000 grains/m³) were used. Student t-test were used to analyze (B) and Pearson correlation coefficients were used to (A) and (C). The statistical analyses were performed at a two-sided significance level of 5%. IBM SPSS statistics 23® software was used for the analyses.

than those in the participants who had symptoms to JCyP (Fig. 2B). Although the correlation between JCyP-specific IgE, and JCP-specific IgE was seen (Fig. 2C), there was no significant difference in JCyP-specific IgE, or JCP-specific IgE between the group with and without symptoms. This indicates that specific IgE is not related to the intensity of symptoms.

In conclusion, the current investigation has shown that at a concentration (8000 grains/m³) identical to that of JCP, selective JCyP exposure induced milder but significantly correlated AR symptoms. Distinctive symptoms by JCyP were not observed.

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Conflict of interest

Yoka serves in an advisory role for Torii Pharmaceutical. Yoka and DS have received honoraria from Torii Pharmaceutical. The rest of the authors have no conflict of interest.

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