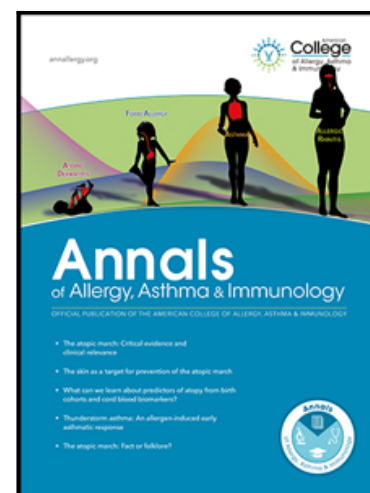


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Olfactory dysfunction out of season in seasonal allergic rhinitis

Short Title: Olfactory dysfunction out of season

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Keywords Olfactory dysfunction; Seasonal allergic rhinitis; Olfactory test

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Motohiko Suzuki and Makoto Yokota wrote the manuscript. Makoto Yokota and Shinya
Ozaki contributed to data collection. Shinya Ozaki and Yoshihisa Nakamura performed the
statistical analysis and interpretation of the results. All authors read and approved the final
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Olfactory dysfunction (OD) is one of the major symptoms caused by seasonal allergic rhinitis (AR).¹ It has been reported that in allergic rhinitis, inflammatory cells infiltrate the olfactory mucosa.² Moll et al.³ showed that the extra-seasonal score in the 1-butanol threshold test of patients with grass pollen allergy was lower than that of control subjects. It was also reported that all patients had normal olfactory function (OF) prior to the season.¹ It is therefore unclear whether OD persists out of pollen season in patients with seasonal AR, especially in patients who do not complain of OD. We investigated extra-seasonal OF in patients with severe AR caused by Japanese cedar pollen (the allergen that causes the largest number of problems in Japan) and who did not complain of OD out of season.

This study was a prospective trial. Fifty control subjects (27 women and 23 men, mean age 43.0 ± 1.6 years, range 22–55 years), 50 patients with Japanese cedar AR for 2–9 years after onset (patients <10 years, 22 women and 28 men, mean age 41.2 ± 1.5 years, range 21–54 years), and 50 patients with Japanese cedar AR for 10 or more years after onset (patients ≥ 10 years, 24 women and 26 men, mean age 42.2 ± 1.2 years, range 26–54 years) were included in this study. There were no significant differences in age or sex among the three groups. The inclusion criteria for the patients were as follows: mono-sensitized patients with specific serum IgE to Japanese cedar pollen $\geq$ class III by the CAP system (Pharmacia & Upjohn, Uppsala, Sweden), a history of seasonal symptoms requiring treatment for at least 2 years, and unawareness of OD out of season. Exclusion criteria included the existence of any nasal disease such as sinusitis, nasal tumor, and nasal polyp; specific immunotherapy; age under 20 or over 55 years; pregnancy; any other diseases except Japanese cedar pollinosis;

the presence of asthma; or refusal of consent. The presence of a nasal polyp and rhinosinusitis was ruled out by examination with nasal endoscopy and CT. Japanese cedar season runs from February until April, and olfactory tests were performed in August. This study was approved by the ethical committee in Nagoya City University, and informed consent was obtained from each subject.

Odor identification was evaluated using the Open Essence test (OE, Wako Pure Chemical Industries, Saitama, Japan) which includes 12 odors.⁴ The OE score is defined as the number of correct answers. An olfactory threshold test was also performed using the T&T Olfactometry test (T&T, Daiichi Yakuhin Sangyo, Tokyo, Japan),^{5,6} which is the standard method in Japan. The mean detection thresholds (DT, the minimum concentration at which an odorant is detected) and recognition thresholds (RT, the minimum concentration at which an odorant is recognized) for five odors were treated as the results. Data are expressed as mean $\pm$ SEM. Statistical comparison of results between groups was performed using the chi-squared test or Mann-Whitney test.

When scores from the CAP-system were compared between patients with disease duration <10 years and ≥ 10 years, there was no significant difference. Symptoms of sneezing, rhinorrhea, and nasal obstruction, examined on March, were classified into five severity levels according to Japanese Guidelines, and scored 0-4.⁷ There were no significant differences in sneezing, rhinorrhea, or nasal obstruction between the two groups. An

identification test using the OE showed the scores of patients ≥ 10 years were significantly lower than those of the control subjects and patients < 10 years (Figure 1A). OS scores of 8 or higher were judged as normal.⁴ In the present study, OE score < 8 was seen in six control subjects, 12 patients < 10 years, and 31 patients ≥ 10 years. DT and RT assessed using T&T also showed that DT and RT of patients ≥ 10 years were significantly higher than those of control subjects and patients < 10 years (Figure 1B and C). RT of 1.1 to 5.8 was defined as OD, and RT of -2 to 1.0 was defined as normal.^{5,6} In this study, RT ≥ 1.1 was seen in two normal subjects, six patients < 10 years, and 38 patients ≥ 10 years. Not only OE but also T&T showed that OD existed in more than half of the patients ≥ 10 years, and that the mean score of patients ≥ 10 years was outside of the normal range, although the mean was within normal limits in control subjects and patients < 10 years. A deterioration in the T&T RT score by 1.0 or more is considered exacerbation.⁸ Difference between the mean scores of control subjects and patients ≥ 10 years was 1.39 in this study, indicating exacerbation. These findings suggest that OF was impaired extra-seasonally in patients ≥ 10 years. However, it is possible that OD was induced by other causes such as nutraceuticals and medicines,⁸ but not allergic rhinitis. Further experiments are needed to resolve these questions.

Correlations between OF and disease duration were also estimated using the Pearson's product moment correlation coefficient, and two-tailed P-values were calculated. Although there were significant correlations between OD and disease duration for patients

<10 years ($p < 0.0001$ for OE, DT, and RT) as well as for patients ≥ 10 years ($p < 0.01$ for OE and DT, $p < 0.001$ for RT), the correlations were stronger, in either the positive or negative direction, for patients <10 years ($r = -0.64$ for OE, 0.828 for DT, 0.834 for RT) than for patients ≥ 10 years ($r = -0.43$ for OE, 0.37 for DT, 0.47 for RT).

Lack of awareness of olfactory loss is common.⁹ It is possible for patients who are initially unaware of OD to notice it later.¹⁰ This study demonstrated that OD tends to develop over time in patients with AR, and that AR may be a cause of OD even in patients who visit clinics out of season. Our results also show that physicians should enlighten patients without olfactory complaints that OD in setting of long-term AR may exist. If OD is discovered, then proper safety measures, such as smoke alarms, should be implemented.

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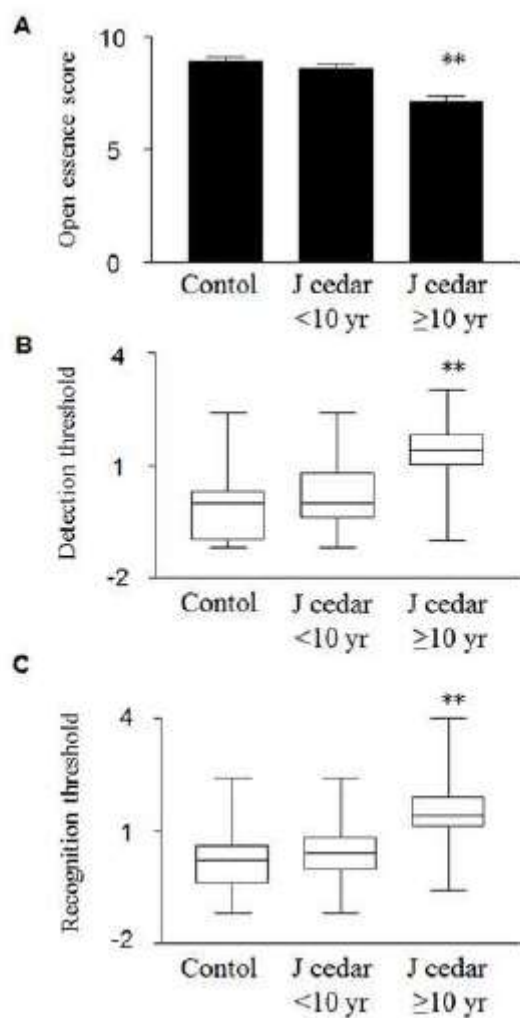


Figure 1. Olfactory function test

(A) Open Essence test was performed in normal subjects (Control), patients with J. cedar AR for less than 10 years (J. cedar < 10 yr), and patients with AR for 10 or more years (J. cedar ≥ 10 yr). (B) Detection threshold test using T&T olfactometry. (C) Recognition threshold test.

**P < 0.001 versus control and J. cedar allergy <10 yr.