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# Oral Allergy Syndrome in Birch Pollen-Sensitized Patients from a Korean University Hospital

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## ABSTRACT

**Background:** Oral allergy syndrome (OAS) is a type of allergic reaction that mainly occurs on oral contact with raw fruit, vegetables, or nuts. The most common type of OAS is birch pollen-related food allergy. Although OAS is a common food allergy in adults, only few epidemiologic studies have been reported in Korea. Here we investigate the prevalence and triggers of birch pollen-related food allergy.

**Methods:** We conducted a retrospective chart review of 1,427 patients who underwent a skin prick test for inhalant allergens at the Asthma and Allergy Clinic in Seoul National University Bundang Hospital from January 2011 to December 2016.

**Results:** Of 1,427 patients, 125 (8.7%) were sensitized to birch pollen. Among them, 20.0% developed OAS, which was the most common food allergy (96.2%). The prevalence of OAS was higher in females, and was 18.2% in birch pollen-sensitized allergic rhinoconjunctivitis patients. Further, 72.0% OAS patients had rhinoconjunctivitis, 20.0% had asthma, and 12.0% had chronic urticaria. Apple (68.0%), peach (56.0%), nuts (36.0%), kiwi (20.0%), persimmon (20.0%), plum (16.0%), and cherry (16.0%) were frequent triggers; however, Chinese yam, kudzu vine, bellflower root, codonopsis, and ginseng were also revealed as triggers. Patients (60.0%) showed OAS with  $\geq 3$  foods at the same time. Only 3 patients showed mono-sensitivity to birch pollen, while others were multi-sensitized to trees, grasses, weed, or house dust mite allergens.

**Conclusion:** OAS was the most common food allergy in birch pollen-sensitized patients. This study revealed the unique triggers of OAS in Korea in addition to well-known triggers.

**Keywords:** Birch Pollen; *Bet v 1*; Oral Allergy Syndrome; Pollen Food Syndrome

## INTRODUCTION

Oral allergy syndrome (OAS), also known as pollen-food syndrome, is a type of contact allergic reaction that mainly occurs on oral contact with raw fruit, vegetables, or nuts.<sup>1</sup> The symptoms are manifested in the oropharynx, at the site of food contact, and include itching of the lips, tongue, and throat, and is sometimes accompanied by swelling of the lips and tongue.<sup>2,3</sup> It is caused when an inflammatory reaction is triggered due to cross-reactivity between birch pollen allergens and food proteins, leading to an allergic reaction.

**Author Contributions**

Conceptualization: Chang YS, Kim JH, Kim SH. Data curation: Chang YS, Kim JH. Formal analysis: Chang YS, Kim JH, Kim SH, Park HW, Cho SH. Writing - original draft: Chang YS, Kim JH, Kim SH, Park HW, Cho SH. Writing - review & editing: Chang YS, Kim JH.

The most common type of pollen-fruit cross-reaction is the birch pollen-related food allergy. The major birch pollen allergen, *Bet v 1*, belongs to the pathogenesis-related (PR) 10 protein family, and is recognized by immunoglobulin E (IgE) antibodies in > 90.0% of birch pollen-allergic patients.<sup>4</sup> Other members of the *Bet v 1*-related food proteins are apple (*Mal d 1*), peach (*Pru p 1*), apricot (*Pru ar 1*), cherry (*Pru av 1*), strawberry (*Fra a 1*), and pear (*Pyr c 1*), as well as hazelnut (*Cor a 1*), celery (*Api g 1*), carrot (*Dau c 1*), soybean (*Gly m 4*), celery (*Api g 1*), peanut (*Ara h 8*), and kiwi (*Act d 8*). These molecules cross-react with *Bet v 1* due to the high degree similarity between their amino acid sequences and the major birch pollen allergen, and thus, resulting in highly similar tertiary structure.<sup>3,5,6</sup>

Several studies have shown that  $\geq 50.0\%$  patients with birch pollen allergy develop OAS.<sup>7-9</sup> It is also reported that 75.0% of birch pollinosis patients develop OAS caused by apples.<sup>10</sup>

Although there is an increasing prevalence of birch pollinosis and birch pollen-related food allergy in clinical practice, no recent data on the prevalence and main triggers of this type of food allergy are available.<sup>9,11,12</sup> In addition, epidemiological surveys of OAS to date have been conducted mostly in western countries, such as Northern and Central Europe and North America, and few epidemiological studies have been conducted in Asian countries alone.<sup>13,14</sup> In Korea, epidemiological studies on OAS have not been conducted for the past 10 years.<sup>13</sup> In this study, we investigated the characteristics of OAS in birch pollen-sensitized patients.

**METHODS****Study subjects and baseline data**

To evaluate the prevalence and triggers of birch pollen-related food allergy, a retrospective chart review was conducted on 1,427 patients who underwent a skin prick test (SPT) for inhalant allergens at the Asthma and Allergy Clinic in Seoul National University Bundang Hospital, from January 2011 to December 2016.

Among 1,427 patients, those who presented a wheal > 3 mm and had an allergen-to-histamine wheal size ratio of at least 1 for birch pollen were selected using an electronic medical record system (BESTCare system<sup>®</sup>)<sup>15-17</sup> and analyzed. We evaluated the prevalence of OAS among birch pollen sensitized patients, compared the clinical features of patients with or without OAS, and evaluated the triggering foods of OAS.

**SPTs**

A SPT was conducted on the upper back using standardized techniques as previously described.<sup>18-20</sup> Positive control tests were performed using histamine (10.0 mg/mL). A positive skin response was defined as a wheal > 3.0 mm and an allergen-to-histamine wheal size ratio of at least 1. All subjects underwent skin prick testing for the following allergens: *Dermatophagoides pteronyssinus* (*Dp*), *D. farina* (*Df*), *Tyrophagus putrescentiae* (*Tp*), cat epithelia, dog epithelia, *Blattella germanica*, *Aspergillus fumigatus*, *Alternaria tenuis*, tree pollens (alder, hazel, poplar, elm, willow, birch, beech, oak, plane tree, Japanese cedar, elder, pine, acacia, and ash), grass pollens (velvet grass, orchard grass, rye grass, timothy grass, Kentucky blue grass, meadow grass, nettle, and Bermuda grass), weeds (mugwort, Japanese hop, dandelion, golden rod, plantain and ragweed), and latex (Allergopharma, Reinbek, Germany).

## OAS

During the study period, all patients who demonstrated a positive response to birch pollen allergen on the SPT were asked whether they experienced oropharyngeal symptoms such as itchiness or swelling of the mouth, face, lip, tongue, and throat during certain food ingestion by an allergist. The allergist inquired about their symptoms and trigger foods, and the patients were clinically diagnosed with OAS.

## Statistical analysis

Differences between the means were assessed using the two-sided t-test and proportions were compared using the two-sided  $\chi^2$  test. A *P* value of < 0.05 was considered to be statistically significant. All analyses were performed using the SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

## Ethics statement

The protocol was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (IRB No. B1703/388-111). Informed consent was waived by the board.

## RESULTS

Among 1,427 patients who underwent a SPT, 125 (8.7%) were positive to birch pollen and **Table 1** shows the baseline characteristics of birch pollen sensitized patients.

In total, 20.8% (n = 26) of the study population experienced food allergy. OAS was the most frequent clinical manifestation (n = 25, 96.2%), and one patient presented with anaphylaxis to persimmon and ginseng. The incidence of OAS was 17.4% (n = 12) in males and 23.2% (n = 13) in females (*P* = 0.418). There was no significant difference between the birch pollen-sensitized patients with and without OAS in age (9.52 ± 13.83 years vs. 41.57 ± 15.58 years, *P* = 0.554) or serum eosinophil counts (206.99 ± 127.35 counts/μL vs. 247.37 ± 208.98 counts/μL, *P* = 0.412). The patients with OAS demonstrated a higher prevalence of asthma (20.0% vs. 45.0%, *P* = 0.024) and low serum total IgE levels, although these levels were not statistically significant (180.07 ± 164.99 U/mL vs. 380.98 ± 467.03 U/mL, *P* = 0.062). The percentage of patients with OAS who had rhinoconjunctivitis was 70% (n = 18), 20.0% (n = 5) patients had asthma, and 12.0% (n = 3) patients had chronic urticaria as comorbid diseases (**Table 2**).

**Table 1.** Baseline characteristics of birch pollen sensitized patients (n = 125)

Characteristics	Birch pollen sensitized patients
Age, yr	41.16 ± 15.398
Gender (% of male)	44.8 (n = 56)
Serum total IgE, IU/mL	341.19 ± 431.44
Blood eosinophil counts, No./μL	239.30 ± 195.51
Birch pollen mono-sensitive, %	2.4 (n = 3)
Comorbidities, %	
Asthma	40.0 (n = 50)
Rhinoconjunctivitis	76.0 (n = 95)
Chronic urticaria	8.0 (n = 10)
Atopic dermatitis	3.2 (n = 4)
Anaphylaxis	4.0 (n = 5)
Others <sup>a</sup>	5.6 (n = 7)

Data presented as means ± SD (range) or number (%).

SD = standard deviation, IgE = immunoglobulin E.

<sup>a</sup>Others include chronic cough, drug hypersensitivity, and dermatographism.

**Table 2.** Characteristics of the study participants according to OAS

Characteristics	OAS (+, n = 25)	OAS (-, n = 100)	P value
Age, yr	39.52 ± 14.83	41.57 ± 15.58	0.554
Gender (% of male)	52 (n = 13)	43 (n = 43)	0.502
Serum total IgE, IU/mL	180.07 ± 164.99	380.98 ± 467.03	0.062
Blood eosinophil counts, No./ $\mu$ L	206.99 ± 127.35	247.37 ± 208.98	0.412
Comorbidities, %			
Asthma	20 (n = 5)	45 (n = 45)	0.024
Rhinoconjunctivitis	72 (n = 18)	77 (n = 77)	0.607
Chronic urticaria	12 (n = 3)	7 (n = 7)	0.417
Atopic dermatitis	4 (n = 1)	3 (n = 3)	1.000
Anaphylaxis	12 (n = 3)	2 (n = 2)	-
Others <sup>a</sup>	0 (n = 0)	7 (n = 7)	-

Data presented as means ± SD (range) or number (%).

OAS = oral allergy syndrome, IgE = immunoglobulin E, SD = standard deviation.

<sup>a</sup>Others include chronic cough, drug hypersensitivity, and dermatographism.

There was no difference in the prevalence of OAS between birch pollen-sensitized patients with allergic rhinoconjunctivitis (n = 95, 19.0%) and birch pollen sensitized patients without rhinoconjunctivitis (n = 30, 23.3%) ( $P = 0.601$ ). The prevalence of OAS was significantly lower in birch pollen-sensitized asthma patients (n = 50) than that in asthma-free patients (n = 75) (10.0% vs. 26.67%,  $P = 0.022$ ).

Apple (68.0%), peach (56.0%), nuts (36.0%), kiwi (20.0%), persimmon (20.0%), plum (16.0%), and cherry (16.0%) were frequent triggers; however, Chinese yam, kudzu vine, bellflower root, codonopsis, and ginseng were also reported to be triggers (Table 3). In addition, 60.0% of patients demonstrated OAS with  $\geq 3$  foods at the same time.

Of the 125 birch pollen-sensitive patients, only 3 were mono-sensitive to birch pollen, while the other patients exhibited multi-sensitivity to trees, grasses, weeds, or house dust mite allergens. In addition, birch pollen multi-sensitive patients were frequently sensitized to beech (71.2%), alder (68.0%) in tree pollens, velvet (22.4%) in grass pollens, and mugwort (32.8%) and Japanese hop (32.8%) in weed pollens. Patients sensitized to house dust mite allergens accounted for 58.4% (n = 73). Patients with OAS were more sensitized to willow trees (32.0% vs. 13.0%,  $P = 0.023$ ) and less sensitized to *Dp* (32.0% vs. 60.0%,  $P = 0.012$ ) than patients without OAS. Fig. 1 shows allergen sensitization profiles compared by presence of OAS.

## DISCUSSION

In this study, we investigated the unique triggers of OAS in Korea, such as persimmon, Chinese yam, kudzu vine, bellflower root, and ginseng, as well as well-known triggers, such as apple. Approximately 34.6% of pollen-sensitized patients and 48.0% of birch-sensitized patients are reported to exhibit symptoms of OAS.<sup>13</sup> In this study, the prevalence of OAS in birch pollen-sensitized patients (20.0%) was lower than that observed in the Western study population (50.0%–75.0%)<sup>7,10</sup>; however, it remains sufficiently high to warrant the clinician's attention.

In a previous Korean study, all patients sensitized to birch antigens were simultaneously sensitized to 5–6 types of tree pollen. In this study, the features of pollen sensitization were similar to those reported in previous studies, and only 3 patients were mono-sensitized to birch pollen alone.<sup>13</sup>

**Table 3.** Trigger foods of OAS in the study subjects

Food	No. (%)
Apple	17 (68.0)
Peach	14 (56.0)
Nuts	9 (36.0)
Almond	3
Peanut	4
Chestnut	2
Persimmon	5 (20.0)
Kiwi	5 (20.0)
Plum	4 (16.0)
Cherry	4 (16.0)
Watermelon	3 (12.0)
Apricot	3 (12.0)
Celery	2 (8.0)
Blueberry	2 (8.0)
Kudzu vine	2 (8.0)
Chinese yam	2 (8.0)
Melon	2 (8.0)
Ginseng	1 (4.0)
Sweet potato	1 (4.0)
Bellflower root	1 (4.0)
Mango	1 (4.0)
Strawberry	1 (4.0)
Pomegranate	1 (4.0)
Orange	1 (4.0)
Tangerine	1 (4.0)
Banana	1 (4.0)
Pear	1 (4.0)
Honey	1 (4.0)
Codonopsis	1 (4.0)
NT 3 or more	15 (60.0)
NT 2 or less	10 (40.0)

NT = numbers of trigger foods.

Interestingly, in addition to the foods commonly reported as triggers of OAS, such as apple and peach in western countries and previous studies, persimmon, Chinese yam, kudzu vine, bellflower root, codonopsis, and ginseng were revealed as trigger foods in this study. In persimmon, the *Dio k 4* allergen is known as the homolog of *Bet v 1*, and cross-reactivity with pollen allergens as a result of the presence of a profilin and *Bet v 6*- and *Bet v 1*-like allergens has been reported.<sup>21</sup> On the other hand, the bellflower root may cross-react with mugwort and birch pollen.<sup>22,23</sup> Studies have shown that immunoblotting with Chinese bellflower, birch, and mugwort revealed a common 40–55-kDa protein band that was very similar to the high-molecular-weight allergen responsible for the celery–birch–mugwort-spice syndrome.<sup>22,23</sup> Another possible protein that could cross-react with birch is an allergen of 14 kDa<sup>22</sup>; however, further studies are needed to investigate this. In a study involving 80 Korean birch-positive patients, 45% reported OAS to ginseng, but the exact allergen that caused the cross-reactivity was not determined.<sup>24</sup> There have been no reports on hypersensitivity reactions or studies of kudzu vine allergens. Kudzu vine belongs to the pea family, Fabaceae. *Bet v 5* and isoflavone reductase homolog proteins are present in pea, which are known as birch pollen minor allergens.<sup>25</sup> These could be involved in the cross-reactivity of kudzu vine and birch pollen. In addition, pomegranate has been reported to contain PR-4 protein, PR-14 protein (pomegranate allergy and PR protein 4 and 14), and *Pru p 3* allergen that cross-reacts with peach; it has a 29-kDa protein and 9–12-kDa protein as an allergen. However, the cross-reactivity of these proteins with the birch allergen has not yet been proved.<sup>26</sup> Chinese yam is rarely used as food in western countries, but it is often used in Asian countries, such as Korea, China, and Japan. Chinese yam-induced anaphylaxis has also been reported.<sup>27</sup>

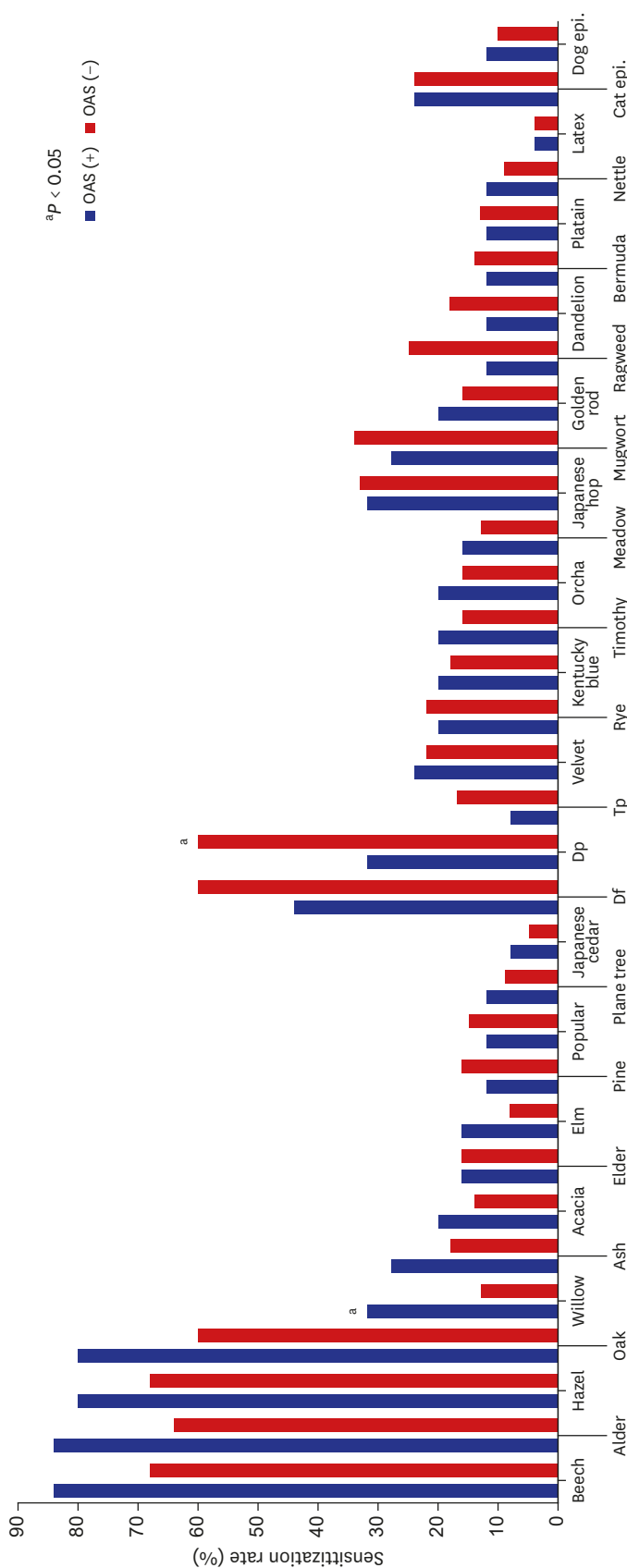


Fig. 1. Allergen sensitization profiles compared by presence of OAS. Patients with OAS were more sensitized to willow trees and less sensitized to Dp than patients without OAS. OAS = oral allergy syndrome, Dp = *Dermatophagoides pteronyssinus*, Df = *Dermatophagoides farrina*, Tp = *Tyrophagus putrescentiae*, epi. = epithelium.

Symptoms of OAS caused by fruits and vegetables are mild. However, laryngeal edema, and rarely, systemic anaphylaxis are reported to occur.<sup>28,29</sup> In this study, 1 patient presented anaphylaxis to persimmon and ginseng. In addition, rhinoconjunctivitis, asthma, generalized urticaria, conjunctivitis, and angioedema have been reported to concurrently occur with OAS, in addition to mild food-pollen syndrome.<sup>29</sup>

Although OAS can be prevented by avoiding consumption of the triggers, immunotherapy for pollinosis could be helpful. However, more prospective studies investigating this treatment are needed.<sup>2,30-32</sup>

This study has some limitations. This study was a retrospective chart review conducted at a university hospital. This could explain the low prevalence of OAS. Because this is a small one-center study, our result can not represent OAS in Korea. However, this study provided an insight into the characteristics of OAS in birch pollen-sensitized patients, and revealed other unique triggers of OAS in Korea, in addition to the well-known triggers.

Second, we only used SPT to confirm birch pollen sensitization, because SPTs are more sensitive than allergen-specific IgE test. However, more information about birch pollen specific IgE like *Bet v1*, *Bet v2*, and *Bet v6* may show some correlation with certain trigger food and it will help to find out allergen component of those food. Further research is needed in this area.

In conclusion, it was found that birch pollen sensitization rate was 8.7% by SPT with inhalant allergens. And the prevalence of OAS among birch pollen-sensitive patients was 20%. In addition to the well-known OAS triggers, Chinese yam, kudzu vine, bellflower root, and ginseng are also reported as triggers of OAS in Korean.

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