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The First Case of Jujube allergy presented as anaphylaxis in a child sensitized multiple food allergens: A case report

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Short running title: Jujube allergy presented as anaphylaxis

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Abstract

Background: Chinese jujube fruits, called daechu in Korea, have high nutritional and medical value and are consumed worldwide as fresh and dry fruit, but there are few reports of side effects or allergies.

Case presentation: We present the first child's case, having anaphylaxis to this fruit in a patient with no latex allergy, but other food allergy such as pine nuts and kiwi. We took the examination using skin prick test specific immunoglobulin E (IgE) with unicap and indirect enzyme-linked immunosorbent assay (ELISA) to confirm the sensitization of the causative allergen. In the skin test, the result of latex and jujube was negative, and Unicap specific IgE tests for kiwi and pine nut were 2.34 kU/L and 2.87 kU/L, and 0.55 O.D and 0.87 O.D (control group 0.36, 0.4) by indirect ELISA to kiwi and pine nut that we performed. The result of our performing indirect ELISA to jujube was positive as 0.62 O.D. (control group 0.41).

Conclusions: It is thought that research on allergenicity of jujube and the cross-relationship between jujube allergy antigen and food allergens such as kiwi or pine nut will be necessary in the future.

Keywords: Ziziphus, Food hypersensitivity, Cross reactions, Enzyme-Linked Immunosorbent Assay

Background

More than 600 species of jujube trees are grown in many parts of the world, and among them, *Ziziphus jujuba* Mill (Chinese jujube) and *Z. mauritiana* Lam. (Indian jujube or ber) are the most important with respect to distribution and economic significance.[1] The fruit of the jujube tree has an oval shape, tastes like an apple with low acidity before it is ripe, and as it ripens, it turns red, wrinkled, and sweet. In many countries, the fruit of jujube is used as a snack, for cooking, and in medicine in its fresh or dried form.[2] Jujube tree, which is cultivated in South Korea, is a species of Chinese jujube, and the fruit of the tree is called "Daechu" in Korean. It is not only used as medicine but also as a form of tea, unlike in other countries.[3] Although Jujube fruits are used in various forms in many countries, there are next to no reports on jujube side-effect or allergy. However, in Taiwan, there was a report of jujube allergy which appeared

as a cross antigen reaction from a patient with latex allergy[4], and recently in Canada, anaphylaxis symptom due to jujube was reported in an adult without latex sensization[5]. Herein, we report a case of anaphylatic reaction to jujube in a child allergic to pine nuts and kiwi for the first time and suggest the possibility that jujube allergy could be induced by a cross reaction with other food allergies apart from latex.

Case presentation

A 9-year-old girl who had urticaria and respiratory discomfort after drinking jujube tea visited the outpatient pediatric clinic at Kangwon National University Hospital. Fifteen minutes after her mother started to boil jujube in a double boiler to make jujube tea, the patient began scratching around her back and neck. It then spread to the face and a red rash began to appear in the form of urticaria. After drinking some of the boiled jujube tea, her lips and eyelids began to swell and she found it difficult to breathe. Symptoms improved after injection therapy in the emergency room. The patient had taken dried jujube before, and there were no allergic symptoms such as urticaria at that time, and it was her first time having jujube tea. The patient had several types of food allergies, including egg white allergy before she was 1 year old, because of which she had a restricted diet and now shows no symptoms. In addition, the skin around her lips turned red after eating walnuts before, but she now does not show such symptoms and is able to eat walnuts. However, she had a history of treatment for severe urticaria, angioedema, and respiratory distress from both touching and eating pine nuts. She continues to show such symptoms even by just touching pine nuts and still refrains from eating pine nuts. Recently, a tingling mouth and red lips appeared after having a green kiwi, and similar symptoms appeared after having cherry. Often having itchy eyes and nose, she was diagnosed with asthma or allergic rhinitis, and the symptoms were severe enough to require treatment, especially in-between seasons. As for family history, she has a mother with allergic rhinitis symptoms. At the time of the hospital visit, there was no skin lesion of urticaria or angioedema

detected during physical examination, and no abnormal findings such as wheezing on chest auscultation. To find causes of anaphylaxis, a blood test was performed to examine the number of eosinophils, the total density of immunoglobulin E (IgE), and any specific IgE test for egg white, pine nuts, walnut, and kiwi (Unicap, Pharmacia, Uppsala, Sweden). A skin prick test was performed using 40 standardized antigens (house dust mites, animal hair, tree, weed, lawn, latex (Lofarma, Milano, Italy)). From the result of the blood test, among 5,300/mm^3 leukocytes, the number of eosinophils was 190/mm^3, and total IgE was 358.3 IU/mL (reference value, 1.5–158.0). Specific IgE (Unicap F1) for egg white was <0.35 kUA/L, that for kiwi (Unicap F84) was 2.34 kUA/L, that for pine nuts (Unicap F253) was 2.87 kUA/L, and that for walnut (Unicap F256) was <0.10 kUA/L. From the skin prick test using standardized antigens, only *Dermatophagoides farina* (Df, W = 7.5 mm) showed a positive result by showing a bigger wheal size compared with that shown for histamine (histamine 1 mg/mL, wheal size (W) = 4.5 mm; 0.9% saline, W = 0 mm) which was a positive control. In addition, *Dermatophagoides pteronyssinus* (Dp, W = 4 mm), Japanese alder, and Asian hazel (W = 2 mm, respectively), white birch (W = 3 mm), beech (W = 3.3 mm), and kiwi (W = 3.5 mm) showed wheals even though they were smaller compared with those shown for histamine. Skin prick test result of latex, which is known to be associated with jujube allergy, was negative. Since there is no standardized antigen for jujube, the skin prick test was performed by prick-to-prick method using liquid obtained from brewing crushed jujube for over 30 min at 70°C. The result was negative. (Figure 1).

To identify jujube-specific IgE from the serum of the patient, indirect enzyme-linked immunosorbent assay (indirect ELISA) was used. First, jujube, pine nuts, and kiwi were each ground with distilled water. The solutions were then serial distilled from 1:10 to 1:10^5 by 10 times each using bicarbonate buffer (pH 9.6). Approximately 100 uL of each was dispensed into wells in the Nunc Maxisorb 96 well plate and cultured and attached at 4℃ overnight. To

95 prevent a non-specific reaction, 100 uL of blocking buffer (Blocker™ BSA in phosphate
96 buffered saline (PBS) (10×) Cat no. 37525, Thermo Fisher Scientific, Cleveland, OH, USA)
97 was dispensed into each well, cultured at room temperature for 3 h, and washed thrice by PBS.
98 Serum from the patient and serum from negative control group that did not have a history of
99 allergy were diluted, dispensed into each well (100 uL), cultured for 1 h, and washed thrice
100 using PBS. Next, horseradish peroxidase (HRP)-conjugated IgE (Goat anti-Human IgE
101 Secondary Antibody, HRP, Cat no. A18793, Invitrogen, Waltham, USA) was dispensed,
102 cultured for 1 h, and washed thrice using PBS. Approximately 50 uL of tetramethylbenzidine
103 (TMB; 1mM), a chromogenic substrate, was added to each well and maintained for 10 min and
104 the reaction was terminated by adding 50 uL of H_2SO_4 (2 M). Next, the absorbance (O.D.,
105 Optical Density) of each well was measured at 450 nm using a spectrophotometer
106 (SpectraMax® ABS Plus, Molecular Devices, CA, USA). Results demonstrated that the IgE for
107 jujube in the serum of the patient was 0.62 O.D., which was higher than 0.33 and 0.42 O.D.
108 found in the control group (Table 1).

109 Symptoms of the patient were diagnosed as an anaphylaxis by jujube-specific
110 immunoglobulin E mediated reaction. Because pine nuts and kiwi allergies were found from
111 both the medical history and blood tests, instructions were given to avoid eating jujube, pine
112 nuts and kiwi. Epinephrine auto-injector was prescribed after giving instructions on how to use
113 it. Also, we will plan the allergen immunotherapy to house dust mite and birch, if she has
114 persistent moderate to severe symptoms of allergic rhinitis, and to observe if there is to
115 disappear its symptom to jujube after it or not.

116 **Discussion and Conclusions**

117 There was previously a report on jujube allergy caused by latex-fruit syndrome[4], and a recent
118 report of IgE-mediated anaphylaxis without latex sensitization in an adult[5]; however, our study
119 is the first to report an anaphylaxis induced by jujube via IgE-mediated immune response in a

120 child. In addition, unlike previous reports that were about allergy symptoms by Indian jujube
121 (*Z. mauritiana*), this study is the first to report about Chinese jujube (*Z. jujuba* Mill). More
122 specifically, allergic symptoms to antigen released in vapor form were detected in a child, who
123 did not eat jujube often but had a history of anaphylaxis or oral allergy symptoms from allergy
124 to certain foods such as kiwi and pine nuts.

125 To confirm that Chinese jujube was the cause of anaphylaxis symptoms in the patient,
126 IgE was measured using a skin prick test and indirect ELISA from serum. Because there was
127 no commercially available skin prick test reagent, the skin prick test was performed by the
128 prick-to-prick method and the result was negative (Fig 1). In addition, as the result from the
129 skin prick test to examine the reaction to latex was negative, it was concluded that there was no
130 sensitization to latex. However, from the indirect ELISA test, not only was the jujube-specific
131 IgE measured at a similar density as that for pine nuts or kiwi, which induced allergic symptoms
132 in the patient, but also at a significantly higher density compared with that in the control group
133 (Table 1). Although an oral challenge for food allergy diagnosis was not performed, it was
134 assumed that the patient had an IgE-mediated allergic reaction to jujube.

135 Plant food allergen is classified by structure or biological function of the protein.
136 Antigens that are taxonomically different but have homologous structures may cause cross
137 reactions leading to allergic symptoms such as pollen-fruit, latex-fruit cross-reactive syndrome,
138 and celery-mugwort-spice syndrome, among others. Allergic symptoms-inducing components
139 could be seed-storage proteins, enzyme activity or proteins which work as defense system
140 against other living creature such as pathogenesis-related proteins (PRs).[7] In a Taiwanese report
141 on a patient with latex allergy who showed allergy symptoms to Indian jujube, the main allergen
142 was Ziz m 1 (30 KD), which is similar to plant class III chitinase which works as PRs [8,9]. This
143 report showed that symptoms could have appeared in the patient with latex allergy by cross
144 reaction.[4]

145 However, although the patient in our study showed sensitization to kiwi and pine nuts
146 from the skin prick test and clinically, the result from the skin prick test to latex was negative,
147 this implied a chance of cross reaction of symptom-inducing Chinese date with components of
148 kiwi or pine nuts. Particularly in the case of an adult patient in Canada[5], who often had Indian
149 jujube as dessert but did not take it at all after moving to Canada, symptoms appeared after re-
150 intake after a certain period of time. The skin prick test for jujube was positive, which suggested
151 induction of allergy symptom by sensitization to jujube itself without sensitization to other
152 antigens. However, the patient in our study did not take jujube or jujube tea often, and symptoms
153 appeared by inhaling antigen while boiling jujube tea, implying a possibility of cross reaction
154 with other food antigens. Clinical symptoms, Unicap test results, and indirect IgE test results
155 showed that Chinese jujube may have cross reacted with pine nuts rather than with kiwi. Until
156 now, there has been no report of allergy antigenicity for Chinese date that induced symptoms
157 in the patient in our study. Inferring from the research on how Indian jujube and Chinese jujube
158 are taxonomically similar but have different structural composition or biological functions due
159 to differences in environment[10], there must be differences in allergens as well. Although there
160 is no report on jujube allergy in South Korea, in the national large-scale survey research on
161 patients with pollen food allergy syndrome[11], 8.9% had jujube allergy symptoms, and jujube
162 accounted for 15.9% of food antigens that induced symptoms by cross reaction with tree pollen.
163 Also, in terms of correlation between aeroallergen and food antigens, jujube showed a high
164 correlation with chestnut and showed higher correlation with pine nut than with kiwi,
165 suggesting that symptoms from the patient in this study could be induced by cross reaction with
166 other foods or aeroallergens.

167 Therefore, future research should be focused on identifying antigen proteins of
168 Chinese jujube and investigating whether it has cross-reactivity with other food items such as
169 pine nuts or other aeroallergens.

170 **List of abbreviations**

171 ELISA: Enzyme-linked immunosorbent assay

172 HRP: Horseradish peroxidase

173 Ig E: Immunoglobulin E

174 O.D.: Optical density

175 PBS: Phosphate buffered saline

176 PRs: Pathogenesis-related proteins

177 TMB: Tetramethylbenzidine

178 W: Wheal size

179 **Declarations**

180 *Ethics approval and consent to participate*

181 This study was approved by the Institutional Review Board of Kangwon National University
182 Hospital (KNUH-2021-05-003). As a retrospective case report, written consent was waived.

183 *Consent for publication*

184 Written informed consent for publication of their clinical details and clinical image was
185 obtained from the patient and parent regardless of the approval of the institutional review board
186 of our hospital.

187 *Availability of date and materials*

188 Not applicable

189 *Competing interests*

The authors have no potential conflicts of interest to disclose.

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Authors' contributions

Kang TS contributed to this work as first authors. Author contributions are as followed: Conceptualization: Kim JK. Investigation: Kim H and Suh IB. Writing - original draft: Kang TS. Writing - review & editing: Kim JK. All authors read and approved the final manuscript.

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Figure 1. Skin prick test and prick to prick test of jujube.

After crushing the dried jujube, it was infused in water at 70°C for 30 mins and the water was used for a prick-to-prick test. Wheal and flare reaction was found by house dust mites, tree pollens, and kiwi, and latex and jujube showed a negative reaction.

233 **Table 1**. Results of Indirect ELISA to confirm Ig E to Jujube in this patient

Classification	Jujube (O.D.)	Pine nut (O.D.)	Kiwi (O.D.)
Patient	0.62	0.87	0.55
Control 1	0.33	0.30	0.36
Control 2	0.42	0.50	0.40

234 ELISA, enzyme-linked immunosorbent assay; Ig, immunoglobuline; O.D., optical density