

# A Single Nonsteroidal Anti-Inflammatory Drugs-Induced Anaphylaxis to Diclofenac Confirmed by Skin Testing

Hana Lee<sup>1,2,3</sup>, Jung-Hyun Kim<sup>3</sup>, Yong-Hyun Kim<sup>1,2</sup>, Bomi Seo<sup>4</sup>, Sae-Hoon Kim<sup>1,2,5</sup>, Yoon-Seok Chang<sup>1,2,5\*</sup>

<sup>1</sup>Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea

<sup>2</sup>Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea

<sup>3</sup>Department of Internal Medicine, The Armed Forces Capital Hospital, Seongnam, Korea

<sup>4</sup>Department of Internal Medicine, Seongnam Citizens Medical Center, Seongman, Korea

<sup>5</sup>Institute of Allergy and Clinical Immunology, Seoul National University Medical Research Council, Seoul, Korea

\*Corresponding author: Yoon-Seok Chang, adchang@snu.ac.kr

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## Abstract

Anaphylaxis is a serious acute systemic allergic reaction that can lead to death, thus requiring immediate diagnosis and treatment. In particular, food is the most common cause of anaphylaxis in children, adolescents, and young adults. In addition to physical contact with food, anaphylaxis can also be induced by exposures other than ingestion, such as the inhalation of aerosolized food proteins. Korean males undergo medical screening prior to a compulsory military service. A history of possible food allergy requires referral to a specialized allergy clinic. It was reported in 2021 that a 19-year-old male patient enlisted in the military was referred to the allergy clinic for an oral provocation test. That case confirmed that anaphylaxis was caused not only by walnut intake, but also by skin contact or by inhaling walnut particles, which will be reviewed in this paper.

## Keywords

Anaphylaxis  
Allergy  
Food allergy  
Walnut

## 1. Introduction

Anaphylaxis is an acute, life-threatening, systemic allergic reaction caused by the sudden release of basophilic and mast cell mediators into the systemic circulation, and it is an emergency condition that can result in death, requiring accurate diagnosis and treatment<sup>[1]</sup>. In children and young adults, food allergy is the most common cause of anaphylaxis and is usually caused by ingestion of immunoglobulin E (IgE)-

mediated allergenic foods<sup>[2]</sup>. Allergic reactions and anaphylaxis induced by inhalation of aerosolized foods are rare<sup>[3]</sup>. A case of allergic reaction and anaphylaxis induced by the inhalation of walnut particles will be analyzed in this paper.

## 2. Case

A 19-year-old male presented with a generalized urticaria with dyspnea. The patient had atopic

**Table 1.** The result of serum specific IgE levels measured by UniCAP (Pharmacia, Uppsala, Sweden)

Allergen	kU/L
Walnut	18.7
Jug r 1	24.5
Jug r 3 (LTP)	2.85
Banana	5.73
Birch	24.8
Bet v 1 (PR-10)	25.4
Bet v 2 (Profilin)	3.24
<i>Dermatophagoides pteronyssinus</i>	> 100
<i>Dermatophagoides farinae</i>	> 100

dermatitis since neonatal period and was continuously treated by a dermatologist, and he developed a nut allergy (choking sensation, cough, dyspnea, angioedema) when he started weaning. He developed symptoms of coughing, breathing difficulties, and angioedema even when other people nearby ate nuts, and had allergic reactions such as facial edema and hives to the smell of bananas. He had experienced anaphylaxis (generalized hives, angioedema around the face and mouth, cough, and difficulty breathing) after eating blue crab; and in 2016, three years prior to this visit, he had developed anaphylaxis after eating chocolate pie containing a small amount of walnuts and was presented the emergency room, which improved after treatment with epinephrine, antihistamines, and steroids. One month prior to this visit, the patient presented to the emergency department with pruritus, dyspnea, and generalized urticaria after walking by a walnut snack, and was treated for anaphylaxis and discharged with improvement. The patient presented to our clinic for a workup prior to his military enlistment physical examination for recurrent anaphylaxis. He had a medical history of allergic rhinitis with year-round clear runny nose, sneezing, and generalized urticaria on exposure to cats. Not known family history of allergic diseases or social history was found.

Upon admission, the patient was alert and conscious with a blood pressure of 125/78 mmHg, heart rate of 95 beats/min, respiratory rate of 18 breaths/min, temperature of 36.6°C, and oxygen saturation of 98%; he had eczematous lesions due to atopic dermatitis on his face, neck, back, hands, and feet, with no other unusual findings.

Blood tests were performed on an outpatient basis,

with a peripheral blood count of 8,900/mm<sup>3</sup> white blood cells, 15.1 g/dL hemoglobin, and 273,000/mm<sup>3</sup> platelets, with 54% neutrophils, 30% lymphocytes, 5% monocytes, 9.2% eosinophils, and 0.7% basophils; his alkaline phosphatase was 104 IU/L, aspartate aminotransferase/alanine aminotransferase 29/21 IU/L, and potassium 4.3 mmol/L; his total IgE antibodies were 2,500 IU/mL (reference value < 100 IU/mL), allergen-specific IgE test (R-biopharm AG, Darmstadt, Germany) to European house dust mite (> 100 kU/L), North American house dust mite (> 100 kU/L), cat fur (18.96 kU/L), *Cladosporium* (5.45 kU/L), *Alternaria* (2.23 kU/L), *Aspergillus* (1.55 kU/L), wormwood pollen (1.22 kU/L), walnut (6.94 kU/L); and further allergen-specific IgE tests (UniCAP, Pharmacia, Uppsala, Sweden) was done for walnut (18.7 kU/L), Jug r 1 (24.5 kU/L), Jug r 3 (LTP, 2.85 kU/L), banana (5.73 kU/L), birch pollen (24.8 kU/L), Bet v 1 (PR-10, 25.3 kU/L), Bet v 2 (profilin, 3.24 kU/L) and a serum tryptase of 3.49 µg/L (reference value: < 11 µg/L). The details are found in [Table 1](#).

## 2.1. Food provocation test 1

Oral provocation test was performed with raw walnut, and based on his medical history, the ingestion of this food can cause fatal anaphylaxis even in small amounts, so it was started with a light mouthful. Ten minutes into the test, she developed lip oedema and pruritus, followed by increased pruritus on both cheeks and glabella at 17 minutes, throat tightness at 20 minutes, and dyspnea, facial oedema, eyelid oedema,



**Figure 1.** Walnut induced anaphylaxis at 1st provocation test by lip contact

and generalized urticaria at 30 minutes (Figure 1). His blood pressure was 113/88 mmHg, heart rate was 80 beats/minute, respiratory rate was 17 breaths/minute, and his body temperature was 37.1 °C, with an oxygen saturation of 99%. His symptoms improved after he was given 0.3 mg bolus of epinephrine, 4 mg bolus of pheniramine, and 30 mg bolus of methylprednisolone. The symptoms were observed after a single exposure to walnuts, and there was no re-exposure or dose escalation during the observation period.

## 2.2. Food provocation test 2

The second test was performed with bananas. Similar to the first test, edema of the upper lip started 20 minutes upon rubbing the lip on the banana, followed by a rash, hives, and pruritus on the upper body. There were no complaints of dyspnea or dizziness, but he was lucid. His blood pressure measured at presentation was 115/84 mmHg, with a heart rate 94 beats/minute, respiratory rate of 16 breaths/minute, body temperature of 37.2°C, and oxygen saturation of 98%. His skin symptoms such as pruritus and urticaria gradually improved after treatment with 4 mg pheniramine and 30 mg methylprednisolone.

## 2.3. Outcome and action 1

After two food trigger tests (walnuts, bananas), it was determined that fatal anaphylaxis can occur in daily life even with small exposures to triggers, so the patient was advised to avoid triggers and carry self-injectable epinephrine at all times, and a medical certificate

was written for reference in the military medical examination. However, the physical examination resulted in a “reconsideration” with a recommendation that “more than six months of medical records” and “evidence that the patient show reaction even after avoiding contact with the allergens” were needed to obtain a medical exemption. Based on the patient’s medical history and food provocation tests, it was determined that anaphylaxis could be triggered not only by ingestion of the allergens but also by small exposures such as unintentional cross-contamination, which is difficult to avoid no matter how careful the patient is. This patient’s condition was explained to the military several times, but it was not accepted by the military, and a third food trigger test because the patient and his guardian strongly wanted it.

## 2.4. Food provocation test 3

In the third test, instead of direct contact with the allergens, the allergen was placed in a container and the patient was asked to shake it lightly and smell it to see if the reaction could be triggered by indirect exposure, i.e., inhalation. Twenty minutes into the test, he started experiencing generalized itching, eyelid edema, and throat tightness, followed by hives on the cheeks, ears, neck, back, and hands after 35 minutes. Two hours later, she complained of angioedema, urticaria over the upper body, and dyspnea (Figure 2). His blood pressure



**Figure 2.** Walnut induced anaphylaxis at 3rd provocation test by inhalation.

was 152/63 mmHg, pulse rate was 81 beats/minute, respiratory rate 21 breaths/minute, body temperature 37.0°C, oxygen saturation was 93%, and auscultation revealed no wheezing or stridor. Epinephrine, an antihistamine, and methylprednisolone were immediately administered, and symptoms resolved over the next several hours.

## 2.5. Outcome and action 2

In the third provocation test, the patient developed anaphylaxis, including dyspnea, angioedema, and generalized urticaria, just by smelling walnuts, and the symptoms did not resolve quickly despite treatment with epinephrine, antihistamines, and steroids. This confirms that aerosolized allergens could also trigger fatal anaphylaxis.

## 3. Case review

Anaphylaxis is a severe systemic allergic reaction that can be fatal and requires immediate diagnosis and treatment. Patients who experience anaphylaxis should be accurately diagnosed and evaluated to identify the trigger, avoidance, and treatment<sup>[3]</sup>. Anaphylaxis is characterized by signs and symptoms in one or more systems within minutes to hours of exposure to the trigger, and it is important to determine the history of exposure in order to estimate the cause of the reaction<sup>[4-5]</sup>. Food is the most common trigger in children and young adults, whereas drugs and insect stings are more common triggers are more common in middle-aged and elderly people, although food is also possible<sup>[6]</sup>. In Korea, there are differences between etiology of food-induced of different ages, with milk, egg white, wheat, walnut, peanut, buckwheat, and shrimp being the main triggers in children and young adults, and peanut, shellfish, nuts, and fish being the most common in adults. Food allergy are usually IgE-mediated reactions upon ingestion of allergens, but anaphylaxis can also be triggered by exposures other than ingestion, such as inhalation of aerosolized food proteins, as well as physical contact with the food, as in this case<sup>[7]</sup>. In cases of peanut allergies, the risk of inhalation has been demonstrated by bronchial provocation tests, in which a three-year-old boy developed an allergic reaction on board a Singapore

Airlines flight in July 2017 after a passenger opened a bag of peanuts Another case of peanut allergic reaction was also reported in an Australian woman on board a Singapore flight in 2016, which resulted in a medical emergency. In response to these incidents, major airlines around the world have recently stopped serving peanuts on board, including Korean Air in 2019<sup>[8,9]</sup>.

Military service in South Korea is generally compulsory for young men in their early to mid-20s. They will undergo a pre-enlistment physical examination to determine their type of service, including active duty, supplementary service, wartime labor service, exemption, and re-examination<sup>[10]</sup>. Among them, men with anaphylaxis can be exempted from military service the following three requirements are met: (i) a confirmed history of recurrent anaphylaxis, (ii) unavoidable causes during daily life or outdoor activities, or unknown causes, and (iii) fatal anaphylaxis (when medical evidence of decreased oxygen saturation or respiratory distress is confirmed, or a decrease in blood pressure equivalent to shock is observed and recovery is achieved through emergency treatment); if any of these are applies to the candidate, the patient will be given an option of active service or supplementary service depending on the severity<sup>[11]</sup>.

The primary treatment for food allergy is by avoiding the allergen<sup>[12]</sup>. Patients that need to strictly avoid the allergens should be given extensive education, including reading food labels on processed foods, preparing meals safely at home, and avoiding food allergens in restaurants and other settings<sup>[13]</sup>. Particularly in the case of this patient, inhalation of the allergen alone can trigger a severe respiratory reaction, so any situation where aerosolized food can be inhaled should be avoided, including exposure to the cooking or a dish. However, as is commonly known, nuts such as walnuts, peanuts, and pine nuts are often mixed in common foods, and even if care is taken to avoid them in the cooking process, anaphylaxis can occur due to cross-contamination of knives, chopping boards, bowls and other utensils, or if they are produced

on the same line in the food processing stage of a factory. It is therefore very difficult for individuals to completely avoid exposure to an allergen, no matter how hard they try.

Anaphylaxis is a fatal systemic allergic reaction that can lead to death, and this case is unique in that a young patient with recurrent anaphylaxis due to food allergy was subjected to three oral provocation tests to determine his fitness for military service. The patient demonstrated that anaphylaxis can be triggered not only by ingestion, but also by skin contact and airborne exposure to food particles. Therefore, it is important to raise awareness of food allergies in society and airlines around the world, including Korean Air, to stop serving peanuts on board. This study has clearly showed that individuals have different thresholds for allergic reactions, and that exposure to even trace amounts of the offending food can cause a fatal anaphylaxis.

Given the nature of military service, active avoidance of certain foods (especially aerosolized food proteins) and the potential for cross-contamination may be difficult, and several treatments are still under research, including oral immunotherapy (OIT), low-dose OIT, sublingual immunotherapy, and epicutaneous immunotherapy. Given that there is still no definitive treatment for anaphylactic patients due to their limited application, there is a need for more expert opinions of allergists in the assessment the severity of military personnel who experience food-induced anaphylaxis<sup>[14-15]</sup>.

However, provocation testing in patients with a history of anaphylaxis can be risky and burdensome for healthcare providers. We report this case with the patient's informed consent for publication because of its significance in determining the risk of food allergy and anaphylaxis and in raising public awareness.

### Disclosure statement

The authors declare no conflict of interest.

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