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Unusual anaphylaxis induced by food allergen inhalation or skin contact

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To the Editor,

Anaphylaxis is a serious, usually rapid-onset, systemic hypersensitive reaction that may be life-threatening [1]. Food is the most common trigger of anaphylaxis in children. In infants, cow's milk, eggs, and wheat are the most frequently reported food allergens implicated in anaphylactic reactions. In older children and adolescents, our previous study demonstrated that buckwheat, fruit, and vegetables are common food triggers in Chinese children [2]. Most food-induced anaphylactic reactions are triggered by ingestion of the food allergen, and only a few episodes are induced by inhalation or skin contact with food in highly sensitive subjects.

Inhalation or skin contact with food allergens can provoke rhinitis and asthma, especially in occupational environments among adults [3]. However, occupational exposure is uncommon in children, and anaphylactic reactions induced by food inhalation or skin contact are considered to be rare in children. Only a few cases have been reported in the literature. The food triggers were peanuts, soybeans, lupine, fish, shellfish, and cereals [4]. Food-triggered anaphylaxis caused by a noningested route may be under-recognized and underreported. Here, we report a case series of Chinese children who experienced anaphylactic episodes induced by food allergen inhalation or skin contact to raise awareness that respiratory and skin exposure to food allergens may trigger life-threatening allergic reactions, indicating the need to develop protective measures and prompt acute management.

This was a retrospective study of children who experienced anaphylactic symptoms and were referred to a specialized allergy department in a tertiary children's hospital. Medical records were retrospectively analyzed to identify patients who were diagnosed with anaphylactic shock, anaphylaxis, or severe allergic reactions from January 2014 to 2021. Patient records were manually reviewed by 2 pediatric allergists to confirm whether the World allergy organization 2020 diagnostic criteria were met [1]. The exposure route was determined from medical records.

Serum levels of specific IgE were measured to confirm food triggers (Phadia AB, Uppsala, Sweden). The detection limit was 0.35 kU_A/L. The study protocol was approved by the Research and Ethics Board of Beijing Children's Hospital, Beijing, China, on February 16, 2022. (Chairperson Pro. Yongli Guo, Approval number: 2022-E-023-R).

Eighteen patients were enrolled in this case series (Table 1). The patients were mostly male (83.3%, 15/18). The mean age of anaphylactic reactions was 3.9 ± 2.3 years (range: 9 months–9 years). Thirty-three percent of patients (6/18) were 0–2 years old, 50% of patients (9/18) were 3–6 years old, and 16.9% (3/18) were 7–9 years old. In terms of clinical history, 61.1% (11/18) had a history of asthma or recurrent wheezing (RW), 55.6% (10/18) had a history of allergic rhinitis/conjunctivitis, and 33.3% (6/18) had a history of atopic dermatitis (AD).

The most frequently implicated food triggers were wheat (33.3%, 6/18, wheat flour: 6 cases), eggs (22.2%, 4/18, cooked eggs: 1 case; raw eggs: 3 cases), and buckwheat (16.7%, 3/18, buckwheat flour: 1 case; buckwheat pillow: 2 cases). Other food triggers included shrimp (n = 2), peaches (n = 1), and walnuts (n = 1).

Respiratory inhalation was the most common exposure route in 66.7% (12/18) of patients, and skin contact with food allergens triggered 33.3% (6/18) of reactions. Respiratory manifestations were seen in most patients (88.9%, 16/18), followed by skin and mucocutaneous (12/18, 66.7%), oropharyngeal (3/18, 16.7%), gastrointestinal (3/18, 16.7%), and neurological (1/18, 5.6%) manifestations. By comparing symptoms induced by ingestion, 66.7% (12/18) of cases presented with anaphylaxis after ingesting the trigger food, 1 patient (No. 2) tolerated wheat ingestion without an allergic reaction, 1 patient (No. 7) experienced AD exacerbation rather than anaphylaxis after egg intake, and 1 patient (No. 16) presented with acute urticaria after shrimp ingestion compared with anaphylaxis caused by shrimp inhalation (Supplementary Table 1, http://links.lww.com/PA9/A13).

Total and specific IgE were determined by Immuno CAP. The mean level of total IgE was 731 ± 756 kUA/L (range: 76–2573 kUA/L). Specific IgE against wheat ranged from 12.2 to >100 kUA/L (No. 1, 12.2 kUA/L; No. 2, 25.6 kUA/L; No. 3–5, >100 kUA/L; and No. 6, 28.7 kUA/L). The mean level of specific IgE against eggs was 3.3 ± 2.0 kUA/L (range: 0.77–5.26 kUA/L) (No. 7, 0.77 kUA/L; No. 8, 5.26 kUA/L; No. 9, 2.69 kUA/L; and No. 10, 4.62 kUA/L). Specific IgE against milk was 1.5 kUA/L (No. 11). Specific IgE against shrimp was >100 kUA/L (No. 16 and 17). In total, 61.1% (11/18) of cases were co-sensitized to aeroallergens, and 77.8% (14/18) of cases had multi-food allergen sensitization.

Acute management was not accessible in 6 patients' medical records. Among the 12 anaphylactic events with detailed

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Table 1.

Clinical characteristics of 18 patients with anaphylaxis

Case No.	Age (years)	Sex	Food Trigger	Exposure Route	Symptom (Skin or Inhalation)	Symptoms (ingestion)	sIgE to Food (kU_A/L)	Allergic Comorbidities
1	9 M	Male	Wheat flour	Inhalation	Facial flushing, dyspnea	Anaphylaxis	Wheat-12.2	RW
2	2 Y	Male	Wheat flour	Inhalation	U, dyspnea	Tolerance	Wheat-25.6	AD, anaphylaxis (egg ingestion)
3	2 Y	Male	Wheat flour	Inhalation	Facial Angioedema, U, C, W, dyspnea	Unrecorded	Wheat>100	RW
4	4 Y	Male	Wheat flour	Inhalation	Conjunctival congestion and edema, persistent cough	Anaphylaxis	Wheat>100	AR, AS
5	5 Y	Male	Wheat flour	Skin contact	U, conjunctival congestion and edema,V	Anaphylaxis	Wheat->100	AR,AS
6	6 Y	Male	Wheat flour	Inhalation	U, W	Anaphylaxis	Wheat-28.7	FA (milk)
7	2 Y	Male	Egg (raw)	Skin contact	Pr, periorbital edema, W	AD exacerbation	Egg-0.77	AR,RW,AD
8	2 Y	Male	Egg (raw)	Skin contact	facial angioedema, dyspnea	Anaphylaxis	Egg-5.26	AR, anaphylaixis(wheat)
9	3 Y	Male	Egg (cooked)	Skin contact	U, dyspnea	Anaphylaxis	Egg-2.69	RW
10	3 Y	Female	Egg (raw)	Inhalation	A, W, C	Anaphylaxis	Egg-4.62	AD, anaphylaxis (Wheat ingestion)
11	2 Y	Female	Milk	Skin contact	U,V	Anaphylaxis	Milk-1.5	AR
12	3 Y	Male	Buckwheat (flour)	Inhalation	Laryngeal obstruction, W, dyspnea	Anaphylaxis	Buckwheat-15.6	AR, AS
13	5 Y	Male	Buckwheat (pillow)	Inhalation	laryngeal obstruction, SOB, AP, LOC	Anaphylaxis	Buckwheat-36.7	AD, AS,AR, FA(egg, milk ingestion)
14	7 Y	Male	Buckwheat(pillow)	Inhalation	Hoarseness, SOB,C,W;	Anaphylaxis	Buckwheat-23.8	AR,AS
15	8 Y	Male	Peach	Inhalation	Laryngeal obstruction, SOB	Unrecorded	-	AR, anaphylaxis (pear)
16	3 Y	Female	Shrimp	Inhalation	Laryngeal obstruction, W; dyspnea	U	Shrimp->100	AR, AS, FA (walnut, egg ingestion)
17	3 Y	Male	Shrimp	Inhalation	U, Pr,C,W	Anaphylaxis	Shrimp->100	AD, AS
18	9 Y	Male	Walnut	Skin contact	facial angioedema, SOB	unrecorded	-	AD, EGE

A, angioedema; AD, atopic dermatitis; AP, abdominal pain; AR, allergic rhinitis; AS, asthma; C, cough; EGE, eosinophilic gastroenteritis; FA, food allergy; LOC loss of consciousness; Pr, pruritus; RW, recurrent wheezing; SOB, shortness of breath; U, urticarial; V, vomiting; W, wheeze.

management records, 1 reaction (8.3%, 1/12) was self-resolved (No. 8), 6 anaphylactic events (50%, 6/12) were treated with oral antihistamine (No. 1, 5, 7, 12, 14, and 17), 2 episodes (16.7%, 2/12) received oral antihistamine and nebulized β-agonist (No. 2 and 3), 2 reactions (16.7%, 2/12) received corticosteroid (No. 9 and 16), and only 1 episode (8.3%, 1/12) received epinephrine (No. 18).

Anaphylactic reactions induced by food allergen inhalation or skin contact are typically rare outside of occupational settings. Here, we report 18 cases of Chinese children who experienced anaphylaxis triggered by food allergens through noningested routes. In our case series, 61% of children with anaphylaxis had a history of asthma or RW. Asthma and RW are risk factors for anaphylaxis and fatal anaphylaxis [5]. Our previous study reported that 45% of children with anaphylaxis have a history of asthma or RW [5]. The underlying bronchial hyperactivity in asthma or RW is likely to be a significant risk factor for severe anaphylaxis. We reviewed allergic asthma (AS)/RW patients (7 AS and 4 RW) and found that only 3 children received asthma maintenance therapy (daily inhaled corticosteroids [ICS] or ICS +LABA, No. 5, No.14, and No. 16). Studies of fatal and near-fatal reactions to allergen immunotherapy suggest that suboptimal asthma control, rather than just the presence of asthma, may increase a patient's likelihood of having severe anaphylaxis [6, 7]. Therefore, suboptimal asthma control is currently recognized as a risk factor for severe and fatal anaphylaxis [8]. We suggest that clinicians should be cautious and continue to focus on asthma control status when approaching patients with asthma at risk of anaphylaxis.

In our cohort, 33.3% (6/18) of patients had a history of &&AD. The association between AD and food allergy has been well-documented due to skin barrier dysfunction [9]. However, the association between AD and anaphylaxis is not clear. A study by Hoffman et al [10] suggests that patients with AD and egg or milk allergy are at significantly higher risk for anaphylaxis compared with patients without AD. This indicates that AD may be an additional risk factor for anaphylaxis. However, this association is not universal for all food allergens, as AD with peanut allergy did not show the same risk. Additional studies are needed to validate these results.

Wheat flour was the most common food trigger in our case series (inhalation: n = 5 and skin contact: n = 1). Our previous study suggested that wheat is the third most common food allergen in infants [2]. Specific IgE against wheat was >100 kUA/L in 3 patients (No. 3–5), indicating that the extremely high level of specific IgE was likely to be a risk factor for triggering anaphylaxis through inhalation. Eggs were the second most common food allergen (skin contact: n = 3 and inhalation: n = 1). Of 4 episodes induced by eggs, 3 (3/4) episodes were triggered by raw eggs. Ando et al suggested that specific IgE against egg greater than 7 kUA/L is highly indicative of an allergy to raw eggs [11]. However, in our study, egg-specific IgE in 4 cases was less than 7 kUA/L. Therefore, the correlation was not high between the egg-specific IgE level and clinical anaphylaxis. Hence, it is necessary to carefully interpret the results of low egg-specific IgE in patients who show suspicious symptoms of egg anaphylaxis, especially infants [12]. Buckwheat was the third most common food trigger in the current case series. Buckwheat has been confirmed to be a common cause of anaphylaxis in Asian countries [13]. Furthermore, buckwheat is a potential allergen that may induce severe and even fatal allergic reactions [14]. Park et al. [14] showed that 66% of patients with a buckwheat allergy have had anaphylaxis. Two patients in our case series (No. 12

and 13) experienced severe anaphylaxis after buckwheat pillow exposure. Pillows filled with buckwheat husks have been popular in China and Korea for a long time. These pillows can cause persistent exposure to airborne buckwheat allergens when sleeping on the pillows. A study from an allergy clinic in China identified 7 patients with buckwheat allergies, 6 of whom had a history of asthma, and 5 used buckwheat husk pillows. The authors concluded that such pillows can be a major route of exposure to buckwheat allergens in China [15].

The inconsistent symptoms experienced by the same patient when ingesting versus not ingesting a particular allergen can be attributed to several factors. One reason is the varying sensitization profiles of individual allergen components. For instance, in cases of Baker's asthma, inhalation of wheat allergen components such as α-Amylase inhibitors and nslipid transfer protein group is common. On the other hand, Tri a 37, a plant defense protein found in wheat, is highly stable and resistant to heat and digestion. Patients with IgE antibodies against Tri a 37 are at a 4-fold increased risk of severe allergic symptoms when they consume wheat [16]. Another contributing factor is the difference in allergens present in raw versus cooked materials. Raw eggs, for example, may contain more allergens that are sensitive to digestive enzymes, such as ovalbumin, ovotransferrin, and lysozyme, compared with cooked eggs [17].

The most common symptoms in the present case series were respiratory tract symptoms. Conversely, previous studies have demonstrated that skin symptoms were the most frequent manifestations in most food-induced anaphylaxis episodes [18]. The high percentage of respiratory symptoms may be attributed to the exposure route, and the underlying bronchial hyperactivity in individuals with asthma and wheezing may be a risk factor for developing respiratory symptoms. Moreover, we observed several differences between inhalation or skin exposure and ingestion. One patient (No. 2) had tolerance when ingesting wheat products, and patients 7 and 16 experienced mild skin symptoms when ingesting the trigger food. Similar findings in 1 report described an 11-year-old boy who had anaphylaxis while his mother was cooking rice. He was able to consume rice without any symptoms, but the bronchial challenge with rice induced anaphylaxis [19]. The possible reason for this is that patients may be sensitized to molecular allergens that differ from those that elicit allergic reactions through the ingestion route, as observed in some patients with work-related asthma [20]. Another possibility is that food protein allergenicity may be reduced by processing or gastric digestion [21], leading to loss of their capacity to induce allergic reactions, whereas intact allergens may elicit reactions in the airways.

Epinephrine was underused in the current series. Only 1 case received epinephrine as an emergency treatment. Current treatment recommendations for anaphylaxis highlight prompt intramuscular epinephrine injection as the gold standard to reduce morbidity, mortality, and hospitalization. However, the use of epinephrine has been insufficient in almost all Chinese population studies of anaphylaxis (percentage of epinephrine administration: 9.3% of 177 children in an allergy clinic, 25% of 907 pediatric and adult patients in a cohort, and 14.2% of 819 reported cases) [2, 22]. The present case series and previous studies highlight that education and training on the initial treatment of anaphylaxis are strongly suggested for healthcare providers in China.

A major limitation of the study was the lack of information on skin prick testing of food allergens. Additionally, due to limitations in the detection reagent for allergen-specific IgE and the allergen component panel, we were unable to measure specific IgE levels against peaches, walnuts, and relevant allergen components. Furthermore, the diagnosis of anaphylaxis was based on reported information rather than laboratory testing and challenge tests. There may be some risk factors associated with different exposure routes (airborne, cutaneous, and ingestion) that induce anaphylaxis, such as allergen component sensitization and allergic comorbidities. However, this case series is too small to conduct univariate/multivariate regression analyses, and we have not enrolled enough "control cases" to perform statistical analysis.

In conclusion, inhalation and skin contact reactions to food allergens can be severe and even life-threatening and should be promptly recognized. Food trigger identification is necessary to avoid all possible exposure routes (e.g., ingestion, inhalation, and skin contact). Additionally, effective acute management of anaphylaxis is needed. Furthermore, education of children and caregivers is necessary to improve the quality of life of patients at risk of reactions to food allergen inhalation or skin contact.

Conflicts of interests

The authors report no conflicts of interest in this work.

Author contributions

Nan Nan Jiang analyzed and interpreted the data and drafted the article. Li Xiang made substantial contributions to conception and design, made major contributions to acquisition of the cases, and gave final approval of the version to be published. Hui Jie Huang and Xiao Ling Hou performed *in vitro* allergy diagnostics and made contributions to acquisition of the cases.

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