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ORIGINAL RESEARCH

Anaphylaxis in Chinese Children: Different Clinical Profile Between Children with and without a History of Asthma/Recurrent Wheezing

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Purpose: Asthma and recurrent wheezing (RW) have been identified as risk factors for anaphylaxis; however, little is known about the characteristics of anaphylaxis in children with a history of asthma or RW in Chinese children.

Patients and Methods: This was a retrospective, observational chart review of children who were diagnosed with anaphylaxis in a tertiary children's hospital between 2014 and 2021. Patients' demographics, symptoms, triggers and presence of physician-diagnosed asthma/RW history were collected from medical charts.

Results: A total of 399 anaphylactic reactions in 264 patients were analyzed; 119 patients (45.1%) had a history of asthma/RW. Food was the most common cause (85.5%, 341/399). Compared with patients without a history of asthma/RW, buckwheat-induced anaphylaxis was significantly more common in the asthma/RW group (9.4% vs 0.5%, $p < 0.001$), patients with a history of asthma/RW had higher rates of oropharyngeal symptoms (17.3% vs 8.6%, $p = 0.011$) and wheezing (34.5% vs 15.9%, $p < 0.001$). Ninety-one reactions (22.8%, 91/399) presented as severe anaphylaxis, but no difference existed between asthma/RW and non-asthma/RW groups. Children with a history of asthma/RW were more likely to receive inhaled β agonists than children without a history of asthma/RW (11.8% vs 2.5%, $p = 0.003$). A larger proportion of children without asthma/RW history were treated with epinephrine (11.7%) than children with asthma/RW history (6.9%).

Conclusion: Our finding revealed that different clinical profiles of anaphylaxis in children with and without a history of asthma/RW. Our study did not find that children with a history of asthma/RW have more severe anaphylactic reactions compared with children without asthma/RW. Buckwheat-induced anaphylaxis was more common in the asthma/RW group, wheezing and oropharyngeal symptoms affected a higher proportion of the asthma/RW group.

Keywords: anaphylaxis, asthma, epinephrine, wheezing, children

Introduction

Anaphylaxis is a severe, potentially life threatening acute allergic reaction.[1] Studies have shown that 11–38% of children who experienced anaphylaxis have a history of asthma or recurrent wheezing (RW).[2–5] Asthma is present in 61–78% of patients with fatal anaphylaxis.[6–9] Asthma is indicated as a risk factor for severe anaphylaxis and fatal anaphylaxis in many consensus statements and guidelines, and RW may have potential risk or associations for developing anaphylaxis in infancy.[1,10–14] However, the relationship between asthma and severe anaphylaxis remains controversial. Recent literature has suggested that asthma itself is not a strong predictor of more severe anaphylaxis. Dribin et al did not find that children hospitalized for anaphylaxis with a history of asthma were not more likely to have severe anaphylactic reactions compared with children without asthma.[5] Recent 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.[15,16]

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Few studies have suggested that the presence of asthma or RW increases the risk of wheezing and respiratory arrest among patients with food-induced anaphylaxis.[17] Life-threatening manifestations in food anaphylaxis are generally caused by respiratory compromise; therefore, underlying bronchial hyperactivity in asthma or RW are likely to be significant risk factors.[18,19] Little is known whether asthma or RW comorbidity is related to the clinical profile of anaphylaxis. The aim of this study was to investigate the characteristics of anaphylaxis in children with asthma or RW compared to patients without asthma or RW and see whether a history of asthma or RW portends an increased risk of more severe anaphylactic reaction.

Methods

Ethics Approval and Informed Consent

This study has been performed in accordance with the principles stated in the Declaration of Helsinki, and the study protocol was approved by the Research and Ethics Board of Beijing Children's Hospital (Approval number:2022-E-023-R). Informed consent was signed by all patients or their parents before participation.

Collection of Data

This was a retrospective chart review study. Medical records were retrospectively analyzed to identify the patients who were diagnosed with "anaphylactic shock", "anaphylaxis", and "severe allergic reactions" from January 2014 to October 2021. The patients' records were manually reviewed and reanalyzed by a pediatric allergy specialist to confirm whether the WAO 2020 diagnostic criteria were met.[20] A detailed history and allergic comorbidities were collected by allergists. Patients were divided into two groups according to presence of physician-diagnosed asthma, or recurrent wheezing (defined as 3 or more episodes of wheezing but not diagnosed asthma by physicians): asthma/RW group and non-asthma/RW group. We extracted information from the electronic medical records, including demographic data, symptoms, suspected triggers, acute management, history of asthma/RW, allergic rhinitis, and atopic dermatitis. Pulmonary function testing variables and fractional exhaled nitric oxide (FeNO) in asthmatic children were also obtained.

Clinical Diagnostic Criteria and Severity Grading

Assessment of the outpatients with anaphylaxis was based on WAO 2020 criteria.[20] Based on current diagnostic criteria, anaphylaxis was defined as an acute allergic reaction involving more than two organ systems or life-threatening compromise in breathing and/or circulation alone. The severity of anaphylaxis was stratified into mild-moderate, or severe during a chart review; severe or life-threatening anaphylaxis symptoms or signs included one or more of the following: hypoxia (cyanosis or SpO_2 ≤92%), hypotension (SBP <70 mmHg in infants [1 month–1 year old], <70+[2×age] mmHg in children aged 1–10 years), and <90 mmHg in patients aged >10 years), or neurologic compromise (confusion, collapse, or incontinence).[21]

Identification of Triggers

We conducted serum levels of specific IgE testing (Thermo Fisher Scientific, Uppsala, Sweden), and/or skin prick testing combined confirmed food-triggered reactions to confirm food triggers. The detection limit of specific IgE was defined as 0.35 kUA/L. Skin tests were regarded positive if the mean wheal diameter was ≥3 mm in the prick test. Insects or drugs induced anaphylactic episodes were diagnosed mainly based on history. If the medical record did not suggest a potential trigger and allergen specific tests were negative, the episode was diagnosed as idiopathic.

Measurement of FeNO (Fractional Exhaled Nitric Oxide)

FeNO was measured according to the Guidelines of American Thoracic Society and used an electrochemical method and the NIOX MINO ® FeNO detection system (Aerocrine, Solna, Sweden) according to the manufacturer's instructions. The FeNO measurement was conducted using a mouth pressure of 16 cm H_2O with 50 mL/s expiratory flow for 10 seconds. To obtain three NO values that achieved 5% level, exhalation was repeated in this study. The levels of FeNO were measured in ppb mol/L, where 1 ppb=1×10^{-9} mol/L.

Pulmonary Function Testing

Pulmonary function testing was performed using the MasterScreen™ PAED pulmonary function analyzer and the MasterScreen™ Pneumo von JAEGER™ (CareFusion, Würzburg, Germany), according to the manufacturer's instructions. Measured variables included FVC (forced vital capacity), FEV1 (forced expiratory volume in 1 second), FEV1/FVC (forced expiratory ratio), FEF25, FEF50, FEF75 (forced expiratory flow 25%, 50%, 75% of forced vital capacity, respectively), MMEF (The average mid-maximal expiratory flow) and PEF (peak expiratory flow).

Statistics

All statistical analyses were performed using SPSS 20.0 (IBM Inc., Chicago, IL). A descriptive analysis was used for characterization of the study population. Continuous variables are expressed as the mean±standard deviation and comparisons among groups were performed using two tailed, unpaired *t*-test. Categorical variables are expressed as a percentage or ratio and comparison between groups was performed using the chi-square or Fisher tests. P-values <0.05 were considered statistically significant.

Results

General Characteristics of Studied Patients

There were 264 children who met the inclusion criteria after manual review and reanalyzed using the WAO anaphylaxis criteria, 119 (45.1%) had a history of asthma/RW. Of 119 patients, 91 children with the mean age (7.09±3.4) years was diagnosed with "asthma", and 28 children with the mean age (3.08±2.0) years was diagnosed with "recurrent wheezing". These enrolled children were stratified into two groups based on the history of asthma/RW (Table 1). The data revealed that 53.4% (141/264) of first anaphylactic episodes occurred in children aged 0–2 years; there was no difference between the two groups. Children with asthma/RW were more likely to have a history of allergic rhinitis/allergic conjunctivitis (76.5% vs 64.8%, p = 0.044). Among children with asthma/RW, 14.3% experienced more than three episodes of anaphylaxis compared with 6.9% of non-asthmatic children; however, the difference was not of statistical significance. Children with asthma/RW were more likely to have a family history of allergic disease (48.7% vs 30.3%, p = 0.003). When analyzing the allergen sensitization profile, 61.7% of all enrolled patients were sensitized to at least one aeroallergen, and the most common aeroallergen sensitization was mugwort (38.3%), followed by ragweed (28.0%), and mold (24.6%); there was no difference between the asthma/RW and non-asthma/RW groups. Sensitization to dust mites was more common in the asthma/RW group (25.2% vs 14.5%, p = 0.028).

Food Triggers

The triggers for 399 anaphylactic events are shown in Table 2. The triggers could be determined in 97.5% (389/399) of reactions. Foods were the most common causative agents (85.5%, 341/399), followed by food+exercise/exercise (8.3%, 33/399) and drugs (3.5%, 14/399). There was no case of insect venom-induced anaphylaxis. The triggers were unable to be determined in 2.5% (10/399) of all reactions, which were classified as idiopathic. Overall, the most frequently implicated foods were cow's milk (16.3%, 65/399), fruits/vegetables (15.3%, 61/399), wheat (12.3%, 49/399), and egg (10.8%, 43/399). The most common fruit trigger was peach (n = 12), followed by mango (n = 9) and pitaya (n = 8), and the most common nut trigger was walnut (n = 13), followed by cashew (n = 7) and pistachio (n = 2). When analyzing the differences between triggers with regard to asthma and non-asthma/RW groups, buckwheat-induced anaphylaxis was more common in the asthma/RW group (9.4%, 18/191 vs 0.5%, 1/208; p < 0.001), see Figure 1.

Symptoms of Anaphylaxis

Table 3 and Figure 2 summarizes the symptoms of anaphylaxis in which skin symptoms were most frequent (85.7%, 342/399), followed by respiratory system (66.7%, 266/399), gastrointestinal tract (23.1%, 92/399), oropharyngeal (12.8%, 51/399), neurological (9.0%, 36/399), and cardiovascular (8.5%, 34/399) symptoms. When analyzing different clinical patterns between the asthma/RW and non-asthma/RW groups, patients with asthma/RW had higher rates of oropharyngeal symptoms (p = 0.011) and wheezing (p < 0.001), while cyanosis (p = 0.016) and neurologic involvement

Table 1 Characteristics of 264 Children with Anaphylaxis

Characteristics	Total, n=264, n (%)	AS/RW[a], n=119, n (%)	Non-AS/RW, n=145, n(%)	P value (AS/RW vs Non-AS/RW)[d]
Onset age				
0–2y	141 (53.4)	65 (54.6)	76 (52.4)	0.804
3–6y	55 (20.8)	27 (22.7)	28 (19.3)	0.544
7–12y	53 (20.1)	21 (17.6)	32 (22.1)	0.441
13–17y	15 (5.7)	6 (5.0)	9 (6.2)	0.793
Gender				
Male	176 (66.7)	82 (68.9)	94 (64.8)	0.514
Allergic comorbidities				
AR/AC[b]	185 (70.1)	91 (76.5)	94 (64.8)	0.044[e]
AD[c]	95 (36.0)	44 (37.0)	51 (35.2)	0.797
Multiple food allergy (not anaphylaxis)	79 (30.0)	32 (27.9)	47 (32.4)	0.347
Chronic urticaria	15 (5.7)	5 (4.2)	10 (6.9)	0.429
Family history	102 (38.6)	58 (48.7)	44 (30.3)	0.003[f]
Allergen sensitization				
At least 1 areoallergen sIgE positive	163 (61.7)	80 (67.2)	83 (57.2)	0.097
Mold	65 (24.6)	33 (27.7)	32 (22.1)	0.288
Dust mite	51 (19.3)	30 (25.2)	21 (14.5)	0.028[g]
Cat dander	54 (20.5)	26 (21.8)	28 (19.3)	0.611
Dog dander	65 (24.6)	35 (29.4)	30 (20.7)	0.102
Mugwort	101 (38.3)	47 (39.5)	54 (37.2)	0.708
Ragweed	74 (28.0)	40 (33.6)	34 (23.4)	0.067
Birch	44 (16.7)	16 (13.4)	28 (19.3)	0.203
Cockroach	6 (2.3)	5 (4.2)	1 (0.7)	0.057

Notes: [d]Comparison between AS/RW group and non-AS/RW group was performed using the Pearson's chi squared test, or Fisher's exact test; [e]children with asthma/RW were more likely to have a history of allergic rhinitis/allergic conjunctivitis (76.5% vs 64.8%, p = 0.044); [f]children with asthma/RW were more likely to have a family history of allergic disease (48.7% vs 30.3%, p = 0.003); [g]sensitization to dust mites was more common in the asthma/RW group (25.2% vs 14.5%, p = 0.028).
Abbreviations: [a]AS, asthma; RW, recurrent wheezing; [b]AR, allergic rhinitis; AC, allergic conjunctivitis; [c]AD, atopic dermatitis.

(p = 0.005) were more common in non-asthmatic children. Ninety-one reactions (22.8%, 91/399) were classed as severe anaphylaxis, but there was no difference between the two groups.

Acute Management of Anaphylaxis

Table 4 shows the treatments of the 306 anaphylactic episodes. Acute management was not accessible for 93 anaphylactic events. Among the 306 anaphylactic events with detailed management records, 12.1% (37/306) self-resolved and 35.9% (110/399) were home-treated. Antihistamines were the most common medications, especially in patients with

Table 2 Triggers of 399 Anaphylactic Reactions

Suspected Triggers	Total n= 399, n (%)[g]	AS/RW, n=191, n (%)	Non-AS/RW, n=208, n (%)	P value (AS/RW vs Non-AS/RW)[h]
Foods	341 (85.5)	163 (85.3)	178 (85.6)	1
Milk	65 (16.3)	28 (14.7)	37 (17.8)	0.418
Egg	43 (10.8)	23 (12.0)	20 (9.6)	0.519
Wheat	49 (12.3)	27 (14.1)	22 (10.6)	0.29
Buckwheat	19 (4.8)	18 (9.4)	1 (0.5)	0.00 [i]
Corn	1 (0.3)	0 (0)	1 (0.5)	1.00
Peanut	8 (2)	2 (1.0)	6 (2.9)	0.288
Nuts/seeds	33 (8.3)	15 (7.9)	18 (7.7)	0.856
Walnut	14 (3.5)	7 (3.7)	7 (3.4)	0.661
Cashew nut	7 (1.8)	2 (1.0)	5 (2.4)	0.302
Other nuts/seeds[a]	13 (3.3)	6 (3.1)	7 (2.4)	0.900
Soybean	6 (1.5)	3 (1.6)	3 (1.4)	1
Fruit /vegetable	61 (15.3)	26 (13.6)	35 (16.8)	0.221
Peach	12 (3.0)	6 (3.1)	6 (2.9)	0.881
Mango	9 (2.3)	3 (1.6)	6 (2.9)	0.377
Pitaya	8 (2.0)	0 (0)	8 (3.8)	0.006
Lychee	8 (2.0)	3 (1.6)	5 (2.4)	0.302
Other fruit/vegetable[b]	24 (6.3)	14 (7.9)	10 (4.8)	0.531
Seafoods	16 (4.0)	9 (4.7)	7 (3.4)	0.612
Spices	6 (1.5)	4 (2.1)	2 (1.0)	0.432
Mix foods[c]	19 (4.8)	8 (4.2)	11 (5.3)	0.501
Foods unclear[d]	15 (3.8)	3 (1.6)	12 (5.8)	0.021
Foods+exercise /exercise	33 (8.3)	16 (8.4)	17 (8.2)	1
Drug[e]	14 (3.5)	9 (4.7)	5 (2.4)	0.278
Idiopathic	10 (2.5)	3 (1.6)	7 (3.4)	0.342
Other trigger[f]	1 (0.3)	0 (0)	1 (0.5)	1

Notes: [a]Other nuts/seeds include: pistachio nut (n = 2), almond (n = 2), hazelnut (n = 2), sesame (n = 1), sunflower seed (n = 1), not specified (n = 4); [b]other fruits and vegetables include: pear (n = 4), physalis peruviana L (n = 3), longan (n = 2), kiwifruit (n = 2), apple (n = 2), rambutan (n = 2), pineapple (n = 1), cauliflower (n = 1), melon (n = 1), blueberry (n = 1), orange (n = 1), grape (n = 1), seabuckthorn (n = 1), watermelon (n = 1), cherry (n = 1); [c]mix foods represented that the offending foods may contain multiple potential allergens several food allergens, such as cake, cookies, pizza. [d]Food unclear represented the food triggers were not determined during chart review, such as the reactions occur just after a meal that may ingest several foods; [e]Drug triggers included: vaccines [n = 5, comprising DTaP (n = 2), group A+C meningococcal polysaccharide vaccine (n = 1), Sabin vaccine (n = 1), and not specified (n = 1)], propofol (n = 1) antibiotics (n = 4), probiotics (n = 2), methylprednisolone (n = 1), lacidophilin tablets (n = 1); [f]Other trigger: one episode triggered by cat dander exposure. [g]A total of 399 anaphylactic reactions in 264 patients were analyzed; [h]comparison between AS/RW group and non-AS/RW group was performed using the Pearson's chi squared test or Fisher's exact test. [i]Buckwheat-induced anaphylaxis was more common in the asthma/RW group 9.4% vs 0.5%, $p < 0.001$).

asthma/RW. Sixty-one percent of anaphylactic events were treated in the emergency department, 27.8% (85/306) received glucocorticoids, and only 9.5% (29/399) were treated with epinephrine. When analyzing differences regarding treatment between the two groups, children with asthma were more likely to receive inhaled beta agonists during

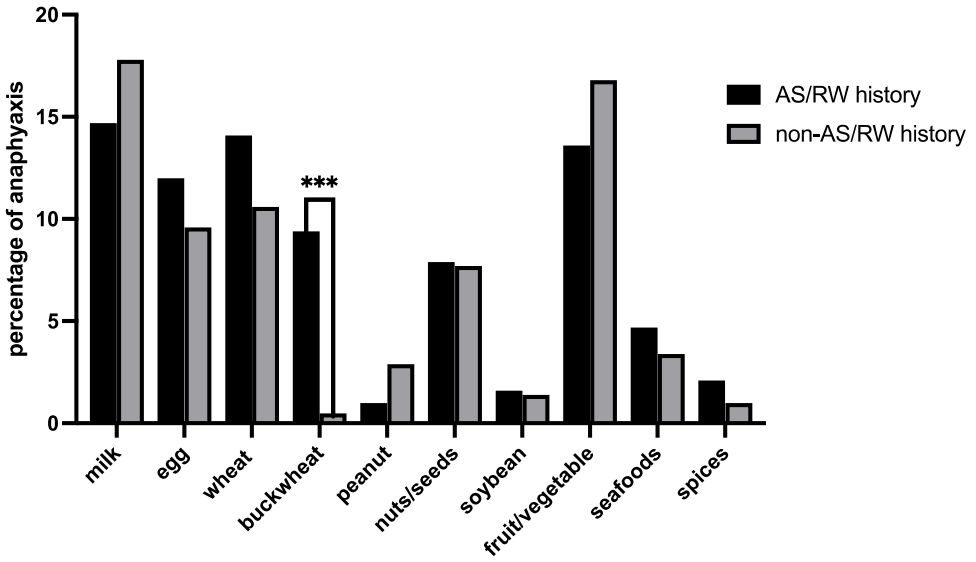

Figure 1 Food triggers in AS/RW and non-AS/RW group. A total of 399 anaphylactic reactions in 264 patients were analyzed and comparison between AS/RW group and non-AS/RW group was performed using the Pearson's chi squared test, or Fisher's exact test. ***Buckwheat-induced anaphylaxis was more common in the asthma/RW group (9.4% vs 0.5%, $p < 0.001$).

emergency treatment (11.8%, 17/144) than children without asthma/RW (2.5%, 4/162). A higher proportion of children without a history of asthma/RW (11.7%) than children with a history of asthma/RW (6.9%) received epinephrine; however, the difference was not of statistical significance.

Comparison of FeNO (Fractional Exhaled Nitric Oxide) and Pulmonary Function Test Results Between Severe and Mild-Moderate Anaphylaxis

FeNO values were evaluated in the severe anaphylaxis and mild-to-moderate anaphylaxis groups. The results showed that the FeNO value was not significant difference. Moreover, there were no significant differences in the FVC% predicted value, FEV1% predicted value, EFV1/FVC ratio, or peak expiratory flow (PEF)% predicted value between the severe and mild-to-moderate anaphylaxis groups ($p > 0.05$) (Table 5).

Discussion

Life-threatening hypersensitivity conditions, such as anaphylaxis and asthma, can coexist or worsen each other. Although asthma and RW have been indicated as risk factors for severe anaphylaxis,[1,10–14] our study did not find that children with a history of asthma/RW have more severe anaphylactic reactions compared with children without asthma/RW. Moreover, the present study also revealed that different clinical profiles of anaphylaxis in children with and without a history of asthma/RW. Buckwheat-induced anaphylaxis was more common in the asthma/RW group, wheezing and oropharyngeal symptoms affected a higher proportion of the asthma/RW group.

In the present study, we did not find a correlation between a clinical history of asthma/RW and severity of anaphylaxis. Studies revealed that asthma seems to be associated with the risk of anaphylaxis. An epidemiologic study in the UK conducted by González-Pérez et al demonstrated that patients with asthma have a greater risk of anaphylaxis than those without asthma, and the risk is greater in patients with severe asthma.[27] Patients with a history of asthma have been considered to be at risk for serious and fatal anaphylactic reactions; in a case series of fatal or near-fatal anaphylaxis, almost all patients had a history of asthma.[8,22,23] However, the relationship between asthma and severe or fatal anaphylaxis remains controversial. Recently, the report by Dribin et al investigated the association between history of asthma and anaphylaxis severity in children.[5] The authors concluded that children hospitalized for anaphylaxis with a medical history of asthma were not more likely to have severe anaphylactic reactions than children without asthma. Interestingly, a multivariable analysis

Table 3 Symptoms of 399 Anaphylactic Reactions

Symptoms, n (%)	Total, n=399, n (%)[a]	AS/RW, n=191, n (%)	Non-AS/RW, n=208, n (%)	P value (AS/RW vs Non-AS/RW)[b]
Skin and mucocutaneous (any)	342 (85.7)	158 (82.7)	184 (88.5)	0.116
Hives	247 (61.9)	113 (59.2)	134 (64.4)	0.303
Itching	41 (10.3)	23 (12)	18 (8.7)	0.322
Redness/rash	8 (2.0)	6 (3.1)	2 (1.0)	0.16
Angioedema	109 (27.3)	48 (25.1)	61 (29.3)	0.37
Oropharyngeal (any)	51 (12.8)	33 (17.3)	18 (8.6)	0.011[c]
Throat closing or swelling	38 (9.5)	23 (12.0)	15 (7.2)	0.124
Difficulty swallowing	5 (1.3)	5 (2.6)	0 (0)	0.024
Throat tingling or itching	7 (1.8)	6 (3.1)	1 (0.5)	0.058
Hoarseness	7 (1.8)	5 (2.6)	2 (1.0)	0.267
Respiratory(any)	266 (66.7)	131 (68.6)	135 (64.9)	0.458
Wheezing	99 (24.8)	66 (34.5)	33 (15.9)	0.00[d]
Shortness of breath	58 (14.5)	34 (17.8)	24 (11.5)	0.088
Breathing difficulty	128 (32.1)	62 (32.5)	66 (31.7)	0.915
Cough	68 (17.0)	29 (15.2)	39 (18.8)	0.355
Cyanosis	22 (5.5)	5 (2.6)	17 (8.2)	0.016[e]
Gastrointestinal (any)	92 (23.1)	48 (25.1)	44 (21.2)	0.405
Nausea	2 (0.5)	1 (0.5)	1 (0.5)	1
Pain	29 (7.3)	15 (7.9)	14 (6.7)	0.703
Vomiting	59 (14.8)	31 (16.2)	28 (13.5)	0.481
Diarrhea	9 (2.3)	3 (1.6)	6 (2.9)	0.506
Cardiovascular (any)	34 (8.5)	13 (6.8)	21 (10.1)	0.16
Hypotension	5 (1.3)	1 (0.5)	4 (1.9)	0.374
Loss of consciousness/Confusion	31 (7.8)	13 (6.8)	18 (8.7)	0.576
Incontinence	1 (0.3)	0 (0)	1 (0.5)	1
Neuologic (any)	36 (9.0)	9 (4.7)	27 (13.0)	0.005[f]
Persistent crying or restlessness	17 (4.3)	4 (2.1)	13 (6.3)	0.048
Drowsiness	10 (2.5)	0	10 (4.8)	0.002
Faintness	4 (1.0)	1 (0.5)	3 (1.4)	0.624
Amaurosis	3 (0.8)	1 (0.5)	2 (1.0)	1
Seizure	2 (0.5)	2 (1.0)	0 (0)	0.229
Severe anaphylaxis [g]	91 (22.8)	37 (19.4)	54 (25.9)	0.122

Notes: [a]A total of 399 anaphylactic reactions in 264 patients were analyzed; [b]comparison between AS/RW group and non-AS/RW group was performed using the Pearson's chi squared test or Fisher's exact test. [c]Patients with asthma/RW had higher rates of oropharyngeal symptoms (17.3% vs 8.6%, p = 0.011); [d]patients with asthma/RW had higher rates of wheezing (34.5% vs 15.9%, p < 0.001); [e]cyanosis was more common in non-AS/RW patients (8.2% vs 2.6%, p = 0.016); [f]neurologic involvement was more common in non-AS/RW children (13.0% vs.4.7%, p = 0.005). [g]The frequency of severe anaphylaxis was no difference between AS/RW group and non-AS/RW group (19.4% vs 25.9%, p = 0.122).

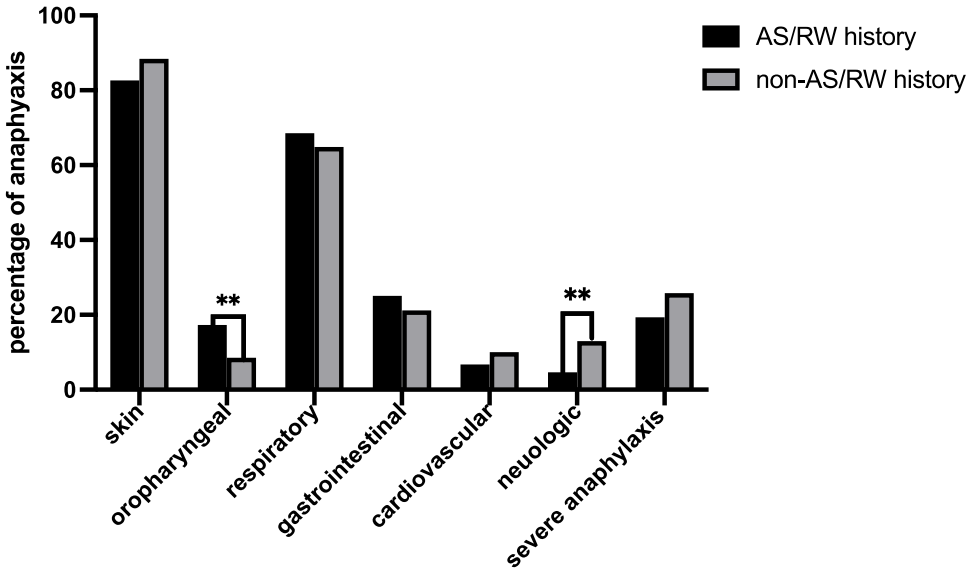

Figure 2 Systems involvement in AS/RW and non-AS/RW group. A total of 399 anaphylactic reactions in 264 patients were analyzed and comparison between AS/RW group and non-AS/RW group was performed using the Pearson's chi squared test, or Fisher's exact test. **Patients with asthma/RW had higher rates of oropharyngeal symptoms (17.3% vs 8.6%, p = 0.011); Neurologic involvement was more common in non-AS/RW children (13.0% vs.4.7%, p = 0.005).

conducted by Motosue et al found that asthma was less likely to be a predictor of hospital admission, ICU admission, and endotracheal intubation.[24] However, studies of fatal and near-fatal reactions to allergen immunotherapy suggest that suboptimal asthma control, rather than the presence of asthma, may increase a patient's likelihood of having severe anaphylaxis.[23,25,26] Furthermore, poor asthma control has been associated with more severe anaphylaxis reactions during

Table 4 Treatment of Anaphylactic Reactions

Treatment	Total n=306, n (%)[a]	AS/RW, n=144, n (%)	Non-AS/RW, n=162, n (%)	P value (AS/RW vs Non-AS/RW)[b]
Treatment at home	110 (35.9)	57 (39.6)	53 (32.7)	0.37
Self-relief	37 (12.1)	14 (9.7)	23 (14.2)	0.229
Oral antihistamines	67 (21.9)	39 (27.1)	28 (17.3)	0.081
Nebulized β-agonist	7 (2.3)	6 (4.2)	1 (0.6)	0.058
Oral montelukast	2 (0.7)	1 (0.7)	1 (0.6)	1.00
Treatment in ED	186 (60.8)	80 (55.6)	106 (65.4)	0.072
Epinephrine	29 (9.5)	10 (6.9)	19 (11.7)	0.176
Systemic corticosteroid	85 (27.8)	39 (27.1)	46 (28.4)	0.715
Antihistamines	55 (18.0)	21 (14.6)	34 (21.0)	0.146
Nebulized β-agonist	21 (6.9)	17 (11.8)	4 (2.5)	0.003[c]
Oxygen supplement	3 (1.0)	0 (0)	3 (1.9)	0.249
Unclear	28 (9.2)	8 (5.6)	20 (12.3)	0.048
Hospitalization	7 (2.3)	4 (2.8)	3 (1.9)	0.714

Notes: [a]Acute management was not accessible for 93 anaphylactic events and a total of 306 anaphylactic events with detailed management records were analyzed; [b]comparison between AS/RW group and non-AS/RW group was performed using the Pearson's chi squared test or Fisher's exact test; [c]children with asthma were more likely to receive nebulized β–agonists during emergency treatment than children without asthma/RW (11.8% vs 2.5%, p = 0.003).

Table 5 Comparison of FeNO and Pulmonary Function Test Results Between Severe and Mild-Moderate Anaphylaxis

	Severe Anaphylaxis in AS/RW Patients	Mild-Moderate Anaphylaxis in AS/RW Patients	P-value (Severe Anaphylaxis vs Mild-Moderate)[a]
FENO (ppb)	48.6±35.3	45.2±31.9	0.778
FVC% predicted value (%, x±s)	101.8±12.3	96.8±11.5	0.188
FEV_1%predicted value (%, x±s)	98.3±14.7	93.0±14.1	0.254
FEV_1/FVC (%, x±s)	94.8±7.8	93.5±9.5	0.654
PEF%predicted value (%, x±s)	86.0±11.1	84.0±14.9	0.656
FEF_{25} (%, x±s)	82.1±13.0	78.5±20.0	0.546
FEF_{50} (%, x±s)	75.0±18.1	66.7±22.0	0.228
FEF_{75} (%, x±s)	59.5±23.4	53.8±21.2	0.416
MMEF 75/25 (%, x±s)	71.7±19.7	65.2±22.2	0.355

Notes: [a]Comparison between AS/RW group and non-AS/RW group was performed using the two tailed, unpaired *t*-test.
Abbreviations: FENO, fractional exhaled nitric oxide; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; FEV1/FVC, the ratio of the FEV_1 to the FVC; PEF, peak expiratory flow; FEF, forced expiratory flow; MMEF, the average mid-maximal expiratory flow.

an oral food challenge in patients with an allergy to peanut or nuts.[27] These findings require further studies to examine the complex interactions between anaphylaxis and asthma. Data on cases of fatal anaphylaxis in the UK between 1992 and 2006 suggest that overuse of salbutamol, lack of daily inhaled steroid, and asthma exacerbation were associated with fatal food allergic reactions.[6] Therefore, suboptimal asthma control currently is recognized as a risk factor for severe and fatal anaphylaxis.[28] With this background, although controversial, we suggest that clinicians should be cautious and continue to focus on asthma control status when approaching patients with asthma at risk of anaphylaxis.[29] Unfortunately, asthma control status at the time of anaphylaxis was not determined in this study, moreover, given that our study was based on medical records from allergy clinic, so the percentage of severe reactions may be lower than emergency department.

Foods were found to be the most frequent trigger of anaphylaxis in the current study. In general, milk was the predominant food trigger, followed by fruits/vegetables, wheat, and egg, consistent with a recently published study in Chinese children.[4] Anaphylaxis triggers in Asia, such as the predominance of wheat and buckwheat, differ from those seen in Western countries, where peanut and tree nuts are the primary food allergens, especially in older children.[29] Buckwheat is a common cause of anaphylaxis in Asian countries; the current study suggested that buckwheat was the fifth most common food trigger, consistent with a multicenter study in Korea where buckwheat was also the fifth leading cause of anaphylaxis in children.[30] Furthermore, buckwheat is a potential allergen that may induce severe, even fatal, allergic reactions. The study conducted by Park et al showed that 66% of patients with buckwheat allergy had anaphylaxis.[31] Noma et al reported an 8-year-old girl in Japan developed fatal anaphylaxis induced by ingestion buckwheat noodles and exercise.[32] A similar pattern in offending food was seen between asthma/RW and non-asthma /RW groups except for buckwheat; our study found that buckwheat-induced anaphylaxis was more common in the asthma/RW group. The higher rate in the asthma/RW group may be partially related to the fact that buckwheat can be an airborne allergen that induces asthma. Pillows filled with buckwheat husk have been popular in China and Korea for a long time but are nowadays used in other parts of the world as well. These pillows can cause domestic exposure to airborne buckwheat allergens when sleeping on pillows. One study from an allergy clinic in China identified seven patients with buckwheat allergies, six of whom had a history of asthma and five used buckwheat husk pillows; the authors concluded that such pillows can be an important route of exposure to buckwheat allergens in China.[33]

In this study, children had a lower frequency of cardiovascular system involvement and hypotension than that reported for adolescents and adults.[34,35] Cardiovascular involvement was possibly underdiagnosed because blood pressure is not generally measured.[14] We observed several differences in the asthma/RW group; wheezing and oropharyngeal symptoms affected a higher proportion of the asthma/RW group, which supports a recently published report describing that wheezing and stridor

were more likely to be observed in asthmatic children.[5] Similar findings were confirmed in the study conducted by González-Pérez et al who found that respiratory signs and symptoms were more common in the asthma cohort (severe, 46%; non-severe, 36%) than the no asthma cohort (15%).[36] Asthma was a risk factor for developing respiratory symptoms during anaphylactic episodes. Therefore, patients with asthma should be educated about the common manifestations of anaphylaxis so that appropriate, early action may be taken on signs of their appearance. Cyanosis and neurologic symptoms have been identified as characteristics of severe anaphylaxis; however, these reactions were not more common among children with a history of asthma/RW. Several studies showed that neurologic symptoms were more likely to be reported in infants.[4,37] We speculated this discrepancy may be because of differences in the age of the populations and the kind of food allergy evaluated, in addition to the coexistence of asthma/RW.

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 is still insufficient in almost all Chinese population studies (percentage of epinephrine administration: 9.3% of 177 children in an allergy clinic, 25% of 907 pediatric and adult patients in a cohort, 14.2% of 819 reported cases).[4,38,39] The low rate of epinephrine utilization and its lack of use as the first-line therapy in our study could be attributed to an initial failure to recognize anaphylactic reactions or worrying adverse reactions associated with the use of epinephrine. The present study did not find any difference in epinephrine administration between children with and without AS/RW. In contrast, a recently published study from the Portuguese Anaphylaxis Registry data showed that the use of AAIs (adrenaline autoinjector device) was higher in patients with asthma (14% of patients with asthma vs 5% of patients without asthma).[40] A possible reason for the higher administration rate in patients with asthma may be that asthma is usually identified as a risk factor of severe or fatal anaphylaxis. Similar to previous studies,[4,38,39] our study suggested that overuse of glucocorticoids was also major problem, in addition to underuse of epinephrine, in the emergency treatment of anaphylaxis. Children with asthma were more likely to receive inhaled beta agonists, consistent with recently published data showing that 31.2% asthma patients receive inhaled β-agonists compared with 16.9% of patients without asthma. The present study and previous published studies highlight that education and training on the initial treatment of anaphylaxis is strongly suggested for health-care providers in China.

This study had several limitations. The study was performed in a single center in China; hence, our findings may not apply to the general population. A major limitation was that all the data presented were collected retrospectively and thus prone to reporting bias. Furthermore, we did not analyze separately asthma and recurrent wheezing because of the retrospective type of research that rendered us unable to distinguish some asthma patients from "recurrent wheezing" based on medical record.

In summary, we did not find correlation between a history of asthma/RW and severity of anaphylaxis. Buckwheat-induced anaphylaxis was more common in patients with asthma/RW patients. Wheezing and oropharyngeal symptoms were also more commonly reported in patients with asthma/RW. The use of epinephrine is still insufficient in our cohort. Recognition of clinical patterns in patients with AS/RW can aid allergists and emergency physicians in acute management.

Data Sharing Statement

The data and materials are available from the corresponding authors based on reasonable requirement.

Consent for Publication

All authors have approved the manuscript and agree with its submission to Journal of Asthma and Allergy.

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Disclosure

The authors report no conflicts of interest in this work.

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