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Changes in clinical features of food-related anaphylaxis in children during 5 years

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ABSTRACT

Background: Despite being frequently recommended, adrenaline auto-injectors (AAIs) are insufficiently prescribed and used for the prehospital management of anaphylaxis.
Objective: This study aimed to investigate recent changes in the clinical features and prehospital management of food-related anaphylaxis in children.
Methods: We retrospectively compared the clinical features of children who were hospitalized for food-related anaphylaxis in 2013 and 2018. The patients' medical records were reviewed for causative foods, triggers, location, AAI prescription, and/or use, wheezing on admission, and treatment.
Results: Overall, 62 consecutive patients (43 males; median age, 5.6 years) hospitalized in 2018 were compared with 57 patients (37 males; median age, 4.3 years) hospitalized in 2013. There were no significant differences between the cohorts in age, gender, causative foods, or wheezing on admission. Cow's milk, wheat, and egg represented over half of the causative foods in both groups. Compared with 2013, the incidence of anaphylaxis decreased at home but increased at nurseries and schools in 2018. Exercise was a significantly more common trigger for anaphylaxis in 2018. Furthermore, a significant increase was observed in AAI administration by lay helpers or the patients themselves and in ambulance transportation. After admission, intramuscular adrenaline was administered to 26 patients in 2013 and 12 patients in 2018. Patients receiving prehospital adrenaline were significantly less likely to require in-hospital adrenaline injections.
Conclusion: Food-related anaphylaxis triggered by exercise and AAI use have increased. Hence, raising awareness and educating caregivers, patients, teachers, and medical professionals are essential for the optimal management of this disorder.

Keywords: Adrenaline auto-injector; Food-related anaphylaxis; Prehospital management; Food allergies; Pediatric patients

INTRODUCTION

Anaphylaxis is a rapidly progressive, systemic allergic reaction that occurs after contact with specific allergens [1]. Food allergy is the leading cause of anaphylaxis in pediatric

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Conflict of Interest
The authors have no financial conflicts of interest.

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patients, followed by medication [2]. An increase in the incidence of anaphylaxis in general, particularly of food-induced anaphylaxis, among children in the industrialized world has been recently suggested [3]. Immediate intramuscular adrenaline injection is the first-line treatment for anaphylaxis [4]. However, numerous studies have reported that adrenaline is underused in anaphylaxis cases [5]. Moreover, despite several recommendations in favor of using adrenaline auto-injectors (AAIs), they are seldom prescribed and administered for prehospital anaphylaxis management [6].

In Japan, a fatal accident occurred in 2012 when a student developed anaphylaxis after ingesting a milk product that was served at a school lunch [7]. This event led to the publication of the anaphylaxis guidelines by the Japanese Society of Allergology. Furthermore, the Japanese Society of Pediatric Allergy and Clinical Immunology proposed a list of symptoms for which AAIs could be administered by individuals other than medical professionals. Information about situations where AAI administration was indicated could help improve awareness among patients and attendees of social education programs. Consequently, pediatric allergists and educated nurses in our hospital have undertaken a concerted effort to manage children at risk of developing anaphylaxis in their homes, nurseries, and schools. We have also advised pediatric practitioners around our hospital to take appropriate approaches toward early treatment of anaphylaxis.

The aim of this study was to examine recent changes in the clinical features and prehospital management of food-related anaphylaxis in pediatric patients.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of pediatric patients hospitalized for anaphylaxis at National Hospital Organization Fukuoka National Hospital, Japan—where pediatricians are also on duty at night—between April 2018 and March 2019.

We then compared the clinical characteristics of food allergy between pediatric patients hospitalized in our institute in 2018 and those hospitalized in 2013. Their medical records were searched for causative foods, place of occurrence, triggers for anaphylaxis, ambulance transportation, AAI prescription, and/or use, respiratory symptoms on admission, and intramuscular adrenaline administration by referring practitioners before admission and in our institute after admission.

Patients' demographic data and clinical characteristics were compared between the cohorts, and categorical data were expressed as percentage, whereas continuous data were presented as median (interquartile range). Quantitative variables were compared using the Mann-Whitney *U* test or Fisher exact test, depending on the number of data. Associations were tested using simple logistic regressions for qualitative variables and quantified by unadjusted odds ratios (ORs) and their confidence intervals. Multivariate logistic regressions were then used to assess associations between in-hospital adrenaline administration and prehospital adrenaline administration, gender, age > 6 years, occurrence in 2013, and ambulance transportation. Statistical analyses were performed using IBM SPSS Statistics ver. 24.0 (IBM Co., Armonk, NY, USA). A p value of <0.05 was considered statistically significant.

This study was approved by the Ethics Board of the National Hospital Organization Fukuoka National Hospital (No. F2-4), which waived informed consent of the children who were studied.

RESULTS

A total of 62 consecutive patients (43 males; median age, 5.6 years) admitted for anaphylaxis in 2018 were compared with 57 patients (37 males; median age, 4.3 years) admitted in 2013 (**Table 1**). The cohorts did not differ significantly in terms of age, gender, causative foods, and wheezing on admission. Cow's milk and hen eggs accounted for approximately half of the causative foods in both patient groups. In the 8 cases whose causative food was unknown in 2018, only 2 cases had anaphylaxis by exercising after ingesting food. In 2018, the incidence of anaphylaxis declined at homes but increased in nurseries and schools compared with that in 2013 ($p < 0.01$).

Exercise was a significantly more common trigger for anaphylaxis in 2018 than in 2013 ($p < 0.05$) (**Table 2**). Among the 16 cases in 2018, none were diagnosed as food-dependent exercise-induced anaphylaxis (FDEIA) by provocation tests. The causative foods were identified as cow's milk (n = 4), wheat (n = 4), hen's egg (n = 3), barley (n = 1), crab (n = 1), and soybean (n = 1). The causative foods could not be determined in the remaining 2 cases. Hot bathing would be a type of exercise as the enhancing factor for allergic reaction. Two cases of anaphylaxis after bathing were caused by hen's eggs. We confirmed that these 2 cases did not develop anaphylactic symptoms after bathing when they did not ingest hen's eggs. In the 2013 cohort, only 1 patient consumed the causative food for oral immunotherapy (OIT).

The rate of patients prescribed with AAIs increased from 21% in 2013 to 47% in 2018. With respect to prehospital management, there was an increase in AAI use ($p < 0.01$) and ambulance transportation ($p < 0.001$). In-hospital intramuscular adrenaline was administered to 12 patients (7 of whom had already been prescribed with AAIs, but only 1 used) in 2018 and 26 patients (20 of whom had not already been prescribed with AAIs) in 2013 ($p < 0.05$).

Table 1. Subject characteristics and differences of causing foods and incident places in pediatric anaphylaxis patients between 2018 and 2013

Parameter	2018	2013	*p* value
No. of cases	62	57	
Male sex	43 (69)	37 (65)	0.60
Age (yr)	5.6 (2.7–9.5)	4.3 (2.3–8.0)	0.13
Causing food			0.61
Cow's milk	16 (25)	21 (37)	
Wheat, barley	16 (25)	4 (7)	
Hen's egg	13 (21)	13 (23)	
Salmon roe	3 (5)	0 (0)	
Walnut	2 (3)	0 (0)	
Peanut	1 (2)	6 (11)	
Soybean	1 (2)	1 (2)	
Crab	1 (2)	0 (0)	
Fish	1 (2)	0 (0)	
Unknown	8 (13)	10 (18)	
Place of incidence			0.004
Own home, relative's house	32 (52)	44 (77)	
Nurseries, schools, sports clubs	22 (35)	6 (11)	
Restaurants	8 (13)	7 (12)	

Values are presented as number (%) or median (interquartile range).

Table 2. Differences of trigger and pre and in-hospital care of pediatric anaphylaxis patients between 2018 and 2013

Parameter	2018	2013	*p* value
Trigger of anaphylaxis			0.014
Accidental ingestion	34 (55)	47 (82)	
Exercise	16 (26)[+]	4 (7)	
First ingestion	5 (8)	1 (2)	
Others	3 (5)	3 (5)	
Unknown	4 (6)	2 (4)	
Ambulance transportation to hospital	54 (87)	26 (46)	<0.001
Prescription of adrenaline auto-injector	29 (47)	12 (21)	0.004
Use of adrenaline auto-injector	17 (27)	4 (7)	0.004
Respiratory symptom at admission	29 (47)	29 (51)	0.65
Intramuscular adrenaline treatment			0.02
By medical practitioner before admission	11 (18)	10 (18)	
In-hospital after admission	12 (19)	26 (46)	
In both of practitioner and hospital	0 (0)	1 (2)	

Values are presented as number (%).
[+]Containing 2 cases after hot bathing.

In the 2013 cohort, 36 patients (63%) received corticosteroids; 34 (60%), antihistamines; 8 (14%), β2-agonists; and 7 (12%), intravenous fluids, and/or oxygen. In the 2018 cohort, 43 patients (69%) were treated with corticosteroids; 43 (69%), antihistamines; 12 (19%), β2-agonists; and 10 (16%), intravenous fluids, and/or oxygen. Other than AAI administration, no significant differences were observed regarding pre and in-hospital treatments between the 2013 and 2018 cohorts.

In 2013, only 3 patients with anaphylaxis—triggered by accidental ingestions (n = 2) and unknown factors (n = 1)—were transported from nurseries. In 2018, an increase was observed in the number of cases transported from schools (n = 12) and nurseries (n = 8). AAIs had already been prescribed to 10 of the 12 patients transported from schools in 2018, and 9 of them used AAIs. Of the cases that occurred in schools, 11 were triggered by exercise and 1 by unknown factors, without any case of anaphylaxis resulting from first ingestion. Of the 8 cases that occurred in nurseries in 2018, 2 were triggered by first ingestion (walnuts); 5, accidental ingestion; and 1, unknown factors.

As shown in **Table 3**, patients receiving prehospital AAIs (OR, 0.18; $p = 0.032$) or intramuscular adrenaline (OR, 0.12; $p = 0.008$) were significantly less likely to be treated with adrenaline after admission.

Table 3. The variables affecting intramuscular adrenaline treatment in-hospital after admission in all patients

Variable	Univariate			Multivariate		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Male sex	1.56	0.67–3.67	0.31	-	-	-
Aged >6 yr	1.06	0.49–2.31	0.88	-	-	-
Occurrence in 2013	3.50	1.54–7.92	0.003	2.19	0.84–5.71	0.11
Ambulance transportation to hospital	0.23	0.10–0.53	0.001	0.64	0.24–1.71	0.37
Use of adrenaline auto-injector	0.18	0.04–0.82	0.027	0.18	0.04–0.86	0.032
Intramuscular adrenaline treatment by medical practitioner before admission	0.12	0.03–0.56	0.006	0.12	0.02–0.57	0.008

OR, odds ratio; CI, confidence interval.

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DISCUSSION

The incidence of anaphylaxis in nurseries and schools was found to be higher in 2018 than 2013. As the ways of providing lunch boxes in school and nursery differ from the necessary minimum elimination conducted in the home setting, the highest priority should be given to ensuring food safety, and the alternative of complete elimination or release of food elimination is recommended. We prepared the "certificate for school and nursery life management (for allergic diseases)" to advance activities for anaphylaxis management [8]. Improved awareness among first responders from 2013 to 2018 could have contributed to a more frequent detection of symptoms that progress to anaphylaxis.

Exercise is a common cofactor in anaphylaxis, with 2%–15% of anaphylactic episodes caused by or associated with exercise [9]. In 266 cases of AAI use by Japanese patients from 2014 to 2016, exercising after food intake was associated with the onset of anaphylaxis in 19 cases (7%) [7]. FDEIA is induced by exercise after food ingestion, but does not occur after either food ingestion or exercise alone in restrict definition [8]. In cases that already experienced food-induced allergic symptoms, FDEIA with strict definition has not been diagnosed even if exercise after food ingestion causes anaphylaxis. Kubota et al. [10] reported that exercise-induced allergic reactions were observed after slow OIT for cow's milk and wheat. Exercise-induced allergic symptoms in children with food allergies in this study should be called exercise-induced allergic reaction rather than FDEIA. In the 16 cases, there were no cases with anaphylaxis induced by exercise only. Exercise-induced anaphylaxis unrelated to food ingestion is rare [11]. In this study, cases with exercise as the trigger of anaphylaxis in children with food allergy increased significantly from 7% to 26% over a period of 5 years. Eleven of the 12 anaphylaxis cases that occurred in school in 2018 were induced by exercise. In Japan, school children can exercise immediately after eating because lunch time is followed by a lunch break. At home, hot bathing after meals is also a common cofactor for food-related anaphylaxis [12]. Two cases after hot bathing as the trigger of anaphylaxis were observed in 2018. Pediatric allergists need to recognize the importance of exercise and hot bathing as a trigger for anaphylaxis at schools and home.

Self- or other-administered AAIs rates ($p < 0.01$) were increased from 7% in 2013 to 27% in 2018 along with an increase in ambulance transportation ($p < 0.001$). The increased AAI administration can be attributed to improved awareness among first responders. The European Anaphylaxis Registry [13] reported that the percentage of patients treated with AAI by lay helpers or themselves was relatively stable at 15.4% during 2006–2008 and 12.9% during 2015–2017. Another reason for the increased use of AAIs in anaphylaxis is that the rate of patients prescribed with AAIs grew from 21% in 2013 to 47% in 2018. There was no case of AAI administration to patients without prescription, as it is not legally permitted in Japan. More frequent allergy referrals by medical practitioners around our institution may have increased AAI prescriptions.

Historically, the trend analysis of anaphylaxis has been complicated by several factors, including inconsistent use of available diagnostic codes and the lack of a universally accepted clinical definition. A strength of our study, compared with others that rely exclusively on diagnostic codes or patient report, was that each case was reviewed by a pediatric allergist. The retrospective design of our study allowed for case verification with allergy testing or food challenges.

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In summary, our study demonstrated that the incidence of anaphylaxis in schools increased from 2013 to 2018, and exercise became a more common trigger for anaphylaxis. Additionally, there was an increase in the rates of patients with prescribed AAIs, self- or other-administered AAIs and ambulance transportation over the same period. In 2018, fewer patients required intramuscular adrenaline treatment after admission compared with 2013. Patients treated with prehospital AAIs or adrenaline were significantly less likely to receive in-hospital adrenaline. Raising awareness and education of caregivers, patients, teachers, and medical professionals play a key role in the optimal management of food-related anaphylaxis in children.

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