

Food-Induced Anaphylaxis among Children Weighing <15 kg: A Single-Center Case Series of the Pediatric Emergency Department

Kenshiro Tabata^{a,b} Tatsuki Fukuie^a Masami Narita^a Shinichiro Inagaki^a
Shima Ohnishi^c Satoshi Tsuji^c Mitsuru Kubota^d Akira Ishiguro^b Yukihiro Ohya^a

^aAllergy Center, National Center for Child Health and Development, Tokyo, Japan; ^bCenter for Postgraduate Education and Training, National Center for Child Health and Development, Tokyo, Japan; ^cDivision of Pediatric Emergency and Transport Services, National Center for Child Health and Development, Tokyo, Japan; ^dDepartment of General Pediatrics and Interdisciplinary Medicine, National Center for Child Health and Development, Tokyo, Japan

Keywords

Anaphylaxis · Epinephrine auto-injector · Epinephrine · Food allergy · Infants

Abstract

Introduction: Food-induced anaphylaxis among infants shows an increasing prevalence; however, the prescription of epinephrine auto-injectors (EAI) for children weighing <15 kg is associated with issues of the needle length and the epinephrine dose. Several studies have shown age-related differences in food-induced anaphylaxis, although little is known about the weight-related differences in food-induced anaphylaxis. This study aimed to reveal the incidence, clinical characteristics, and management of food-induced anaphylaxis in children weighing <15 kg. **Methods:** This chart review included children who visited the pediatric emergency department (ED) of the National Center for Child Health and Development (Tokyo, Japan) from January 2014 to December 2016 and were diagnosed with food-induced anaphylaxis. The severity of anaphylaxis was evaluated using the Sampson Grading Scale. **Results:** Of 89,232 ED visits, 444 visits included patients with food-induced anaphylaxis, after excluding cases of food-induced anaphylaxis related to oral desensitization therapy. The incidence was 4.98 per 1,000

visits. More than half of the children ($n = 247/444$, 55.6%) weighed <15 kg. The proportion of grade 3 and higher severity anaphylactic symptoms was 74.5% (184/247) in children weighing <15 kg and 79.2% (156/197) in children weighing 15 kg or more. The recurrence rate of food-induced anaphylaxis was 22.3% (55/247) in children weighing <15 kg and 48.7% (96/197) in children weighing 15 kg or more. Among the children weighing <15 kg, the proportion of those with recurrent food-induced anaphylaxis was 4 times higher in children weighing 10–15 kg than in those weighing <10 kg (32.2% [47/146] vs. 7.9% [8/101]). The proportion of patients who were prescribed EAI before each visit was 25.5% (14/55) in children weighing <15 kg with a history of food-induced anaphylaxis. **Conclusion:** Food-induced anaphylaxis among children weighing <15 kg occurred as frequently and was as severe as that among children weighing 15 kg or more. However, the proportion of patients prescribed EAI was very low in children weighing <15 kg with food-induced anaphylaxis. The potential need for EAI is suggested among children weighing <15 kg, especially among children weighing 10 kg or more but <15 kg.

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Introduction

Food allergies are the commonest trigger for pediatric anaphylaxis and the prevalence of food-induced anaphylaxis is increasing, and especially in infants, the increment in emergency room visits is drawing attention after the publication of early introduction guidelines [1–4]. Epinephrine, administered intramuscularly, is the first-line treatment for anaphylaxis, and a weight-based dose (0.01 mg/kg) is recommended for children [4–9]. Epinephrine auto-injectors (EAI) are the standard method for administering epinephrine as prehospital emergency medication in patients who are at risk of anaphylaxis [4]. International guidelines and the position statement from the American Academy of Pediatrics recommend the prescription of 0.15 mg EAI to at-risk children weighing 10–15 kg (≥ 10 and < 15 kg) in the absence of suitable devices [5–9]. However, there are distinct issues with the needle length and epinephrine dose delivered by EAI in children who weigh < 15 kg [1]. Dreborg et al. [10–13] reported concerns about subcutaneous and intraosseous/periosteal epinephrine injections by high-pressure EAI (HPEAI) in children in a study that used ultrasound to measure the distance from the skin to the muscle and bone. A study by Kim et al. [14] showed that children with food allergies who weigh < 15 kg, especially < 10 kg, have shorter skin-to-bone distances, and are at high risk of intraosseous/periosteal injections when using HPEAI, such as EpiPen® Jr or Allerject® (0.15 mg), which are widely prescribed for pediatric patients with anaphylaxis. The amount of epinephrine administered by these EAI is higher than the recommended weight-based epinephrine dose for children who weigh < 15 kg and is 1.5 times higher for children who weigh approximately 10 kg.

Due to the issues associated with EAI use, clinical judgment is often required for applying the recommendation for prescribing EAI to individual patients who have a history of food-induced anaphylaxis and weigh < 15 kg [1, 7, 13, 15, 16]. In principle, the use of EAI in children who weigh < 15 kg is contraindicated in the EAI package insert in Japan. A 0.1-mg formulation (Auvi-Q 0.1-mg®) is approved for use and is available for children who weigh 7.5–15 kg in the USA; however, this product is not yet generally available worldwide. Thus, weight-related characteristics of food-induced anaphylaxis may facilitate the decision of whether to prescribe EAI to at-risk patients who weigh < 15 kg. Several studies have shown the age-related characteristics of pediatric food-induced anaphylaxis in the emergency department (ED) [17–20]; however, there is limited information about the

weight-related characteristics of pediatric food-induced anaphylaxis. This study aimed to reveal the incidence, clinical characteristics, and management of food-induced anaphylaxis in children weighing < 15 kg. Because it is the weight under which EAI dose and needle length have been pointed out as problematic, we chose 15 kg as the cut-off weight value. Therefore, the primary objective of this study was to provide information on the demographics, clinical features, causes, and management of food-induced anaphylaxis in children who weigh < 15 kg. The second objective was to determine similarities and differences in food-induced anaphylaxis in children who weigh $< \text{or} > 15$ kg.

Materials and Methods

Study Design and Setting

This retrospective cross-sectional study enrolled patients who visited the pediatric ED over a 3-year period from January 1, 2014 to December 31, 2016. The study setting was the pediatric ED of the National Center for Child Health and Development (NCCHD) in Tokyo, Japan. The NCCHD is an urban, tertiary-care pediatric hospital and the ED receives approximately 30,000 visits per year. We reviewed the medical records of all patients aged 0–18 years who visited the ED with an acute reaction to food or anaphylaxis, regardless of the underlying cause.

Identification of Cases

To identify patients with anaphylaxis, we reviewed the medical records of patients who visited the ED and received a definitive or suspected diagnosis of anaphylaxis. All medical records were reviewed in detail by a trained pediatrician (K.T.) based on the criteria for anaphylaxis that were presented in the World Allergy Organization Anaphylaxis Guidelines [8]. Anaphylaxis was defined as an acute onset of allergic reaction involving 2 or more of the following organ or organ systems: the skin and the respiratory, gastrointestinal, circulatory, and nervous systems after exposure to a likely allergen; or as an acute allergic reaction involving hypotension alone after exposure to a known allergen in that patient. The severity of anaphylaxis was evaluated using the Sampson Grading Scale [21, 22], which is based on the grading of symptoms in the skin, the respiratory organs, the digestive organs, the circulatory system, and the neurological system. The symptom grade was determined according to the organ symptoms of the highest grade. If the patient had only multiple grade-1 symptoms, anaphylaxis was not considered in the differential diagnosis. Tachycardia was defined as an increase of 15 or more beats/min from the upper limit of the normal range at each age [23]. We have defined anaphylaxis caused by the same foods as “recurrent anaphylaxis.” An episode is defined as the first episode of anaphylaxis if the causative food is different from the causative food trigger in previous anaphylactic episodes. The history of anaphylaxis pertained to episodes that occurred before or during the study period. The history of anaphylaxis, the causative food, and whether EAI was prescribed were based on information elicited from the patient’s family.

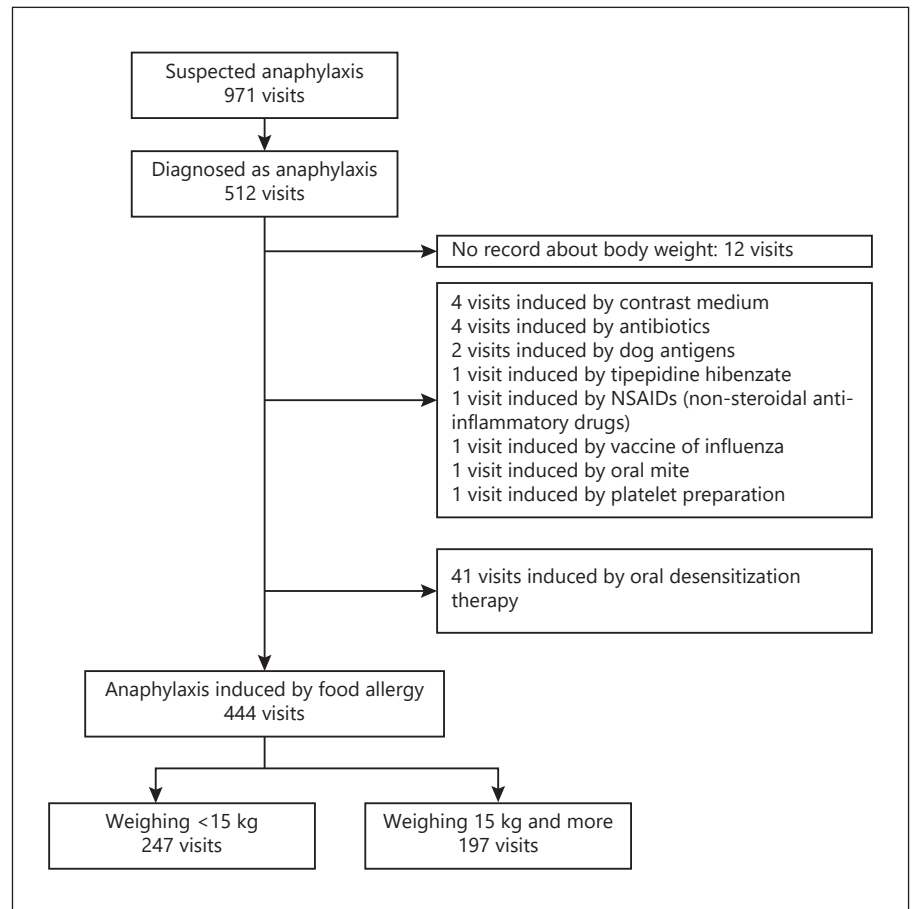


Fig. 1. Flow chart of 971 patients with suspected anaphylaxis. NSAIDs, non-steroidal anti-inflammatory drugs.

Data Collection

All of the described symptoms, signs, and treatments were entered into a database. Details, such as the patient's sex, age, body weight, history of food allergy, probable current eliciting foods, clinical symptoms, and pharmacotherapy (at home, in the ambulance, and at the hospital), were extracted from the medical records. Body weight measured within the last 3 months was recorded; however, if weight was not measured, the body weight reported by the patient's family was recorded. The eliciting agent was recorded as "mixed foods," if no single food could be identified because multiple foods were ingested simultaneously.

Statistical Analysis

We analyzed the visits of patients with anaphylaxis in 2 groups that were stratified by weight: children who weighed 15 kg or more and <15 kg. In addition, we assigned children who weighed <15 kg to 2 subgroups as those weighing: <10 kg or 10–15 kg. The Fisher exact test and the Mann-Whitney U test were used to determine associations between 2 categorical variables. For all analyses, a *p* value of <0.05 was considered statistically significant. In order to assess the weight-related characteristics of food-induced anaphylaxis, we excluded visits from the analysis if there was no record of the patient's weight, or if the cause of anaphylaxis was a non-food trigger. Furthermore, to avoid oversampling the symptoms for certain foods, we excluded cases of anaphylaxis related to oral de-

sensitization therapy. The prevalence rates of eliciting foods, symptoms, and treatment are presented as proportions. The composition ratio was investigated in 4 age categories: infants (<2 years), preschool-aged (2–5 years), school-aged (6–11 years), and adolescents (12–18 years) [17, 18].

Results

Study Population

The total number of ED visits during the study was 89,232 visits, of which 971 visits were identified in patients who were diagnosed with or suspected of having a food allergy and/or anaphylaxis. All ED records of these 971 visits were reviewed. A flow chart of the visit inclusion is shown in Figure 1. In 512 visits, the patients were diagnosed with anaphylaxis, irrespective of the cause. The incidence of anaphylaxis from any cause in all ED visits was 5.74/1,000 visits. Twelve visits were excluded because the patients' body weights were not recorded, and 15 visits were excluded because of non-food-based causative

Table 1. Comparison of the characteristics of food-induced anaphylaxis episodes between children weighing ≥ 15 kg and children < 15 kg

	Total, (n = 444)	15 kg and more (n = 197), 44.4%	< 15 kg (n = 247), 55.6%	< 15 kg between 10 and 15 kg (n = 146/444), 32.9%	< 10 kg (n = 101/444), 22.7%	recurrent anaphylaxis (n = 55), 22.3%	first-time anaphylaxis (n = 192), 77.7%
Male, sex, n (%)	277 (62.4)	136 (69.0)	141 (57.1)*	85 (58.2)	56 (55.4)	33 (60.0)	108 (56.3)
Age, median (range), months	39 (2–215)	104 (27–215)	20 (2–67)	28 (9–67)	11 (2–34)	29 (8–66)	18 (2–67)
Infant, < 2 years, n (%)	140 (31.5)	0 (0)	140 (56.7) [†]	45 (30.8)	95 (94.1) ^{††}	17 (30.9)	123 (64.1) ^{†††}
Preschool-aged, 2–5 years, n (%)	158 (35.6)	51 (25.9)	107 (43.4) [†]	101 (69.2)	6 (5.9) ^{††}	38 (69.1)	69 (35.9) ^{†††}
School-aged, 6–11 years, n (%)	100 (22.5)	100 (50.8)	0 (0) [†]	–	–	–	–
Adolescents, 12–18 years, n (%)	46 (10.4)	46 (23.4)	0 (0) [†]	–	–	–	–
Weight, median (range), kg	14.0 (5.2–74)	23.8 (15.0–74)	10.0 (5.2–14.8) [§]	12.0 (10–14.8)	9.0 (5.2–9.0) ^{§§}	11.5 (8–14.5)	10 (5.2–14.8) ^{§§§}
Previously known food allergy, n (%)	249 (56.1)	137 (69.5)	112 (45.3) [†]	80 (54.8)	32 (31.7) ^{††}	55 (100.0)	57 (29.7) ^{†††}
Intramuscular injection of epinephrine [†] , n (%)	210 (47.3)	108 (54.8)	102 (41.3) [†]	72 (49.3)	30 (29.7) ^{††}	21 (38.2)	81 (42.2)
Recurrent anaphylaxis for the known allergen, n (%)	151 (34.0)	96 (48.7)	55 (22.3) [†]	47 (32.2)	8 (7.9) ^{††}	55 (22.3)	–
Children, n prescribed EAls before recurrent anaphylaxis in recurrent cases, n (%)	72/151 (47.7)	58/96 (60.4)	14/55 (25.5) [†]	14/47 (29.8)	0/8 (0.0) ^{††}	14 (25.5)	–
EAI, n uses among patients who were prescribed EAI in advance in recurrent cases, n (%)	41/72 (56.9)	34/58 (58.6)	7/14 (50.0)	7/14 (50.0)	0/8 (0.0) ^{**}	7/14 (50.0)	–

EAI, epinephrine auto-injector; IM, intramuscular; ED, emergency department. [†]Epinephrine given at home before admission, during ambulance transport, or at hospital. * $p < 0.05$. [†] $p < 0.01$, the Fisher exact test was used to compare the categorical variables between 2 groups: children weighing ≥ 15 kg and children weighing < 15 kg. ** $p < 0.05$. ^{††} $p < 0.01$, the Fisher exact test was used to determine associations between two categorical variables between 2 groups: children weighing ≥ 10 kg and < 15 kg, and children weighing < 15 kg. ^{†††} $p < 0.01$, the Fisher exact test was used to determine associations between two categorical variables: recurrent anaphylaxis and first-time anaphylaxis. [§] $p < 0.01$, the Mann-Whitney U test was used to compare the categorical variables between 2 groups: children weighing ≥ 15 kg and children weighing < 15 kg. ^{§§} $p < 0.01$, the Mann-Whitney U test was used to compare the categorical variables between 2 groups: children weighing ≥ 10 kg and < 15 kg, and children weighing < 15 kg. ^{§§§} $p < 0.01$, the Mann-Whitney U test was used to determine associations between 2 categorical variables: recurrent anaphylaxis and first-time anaphylaxis.

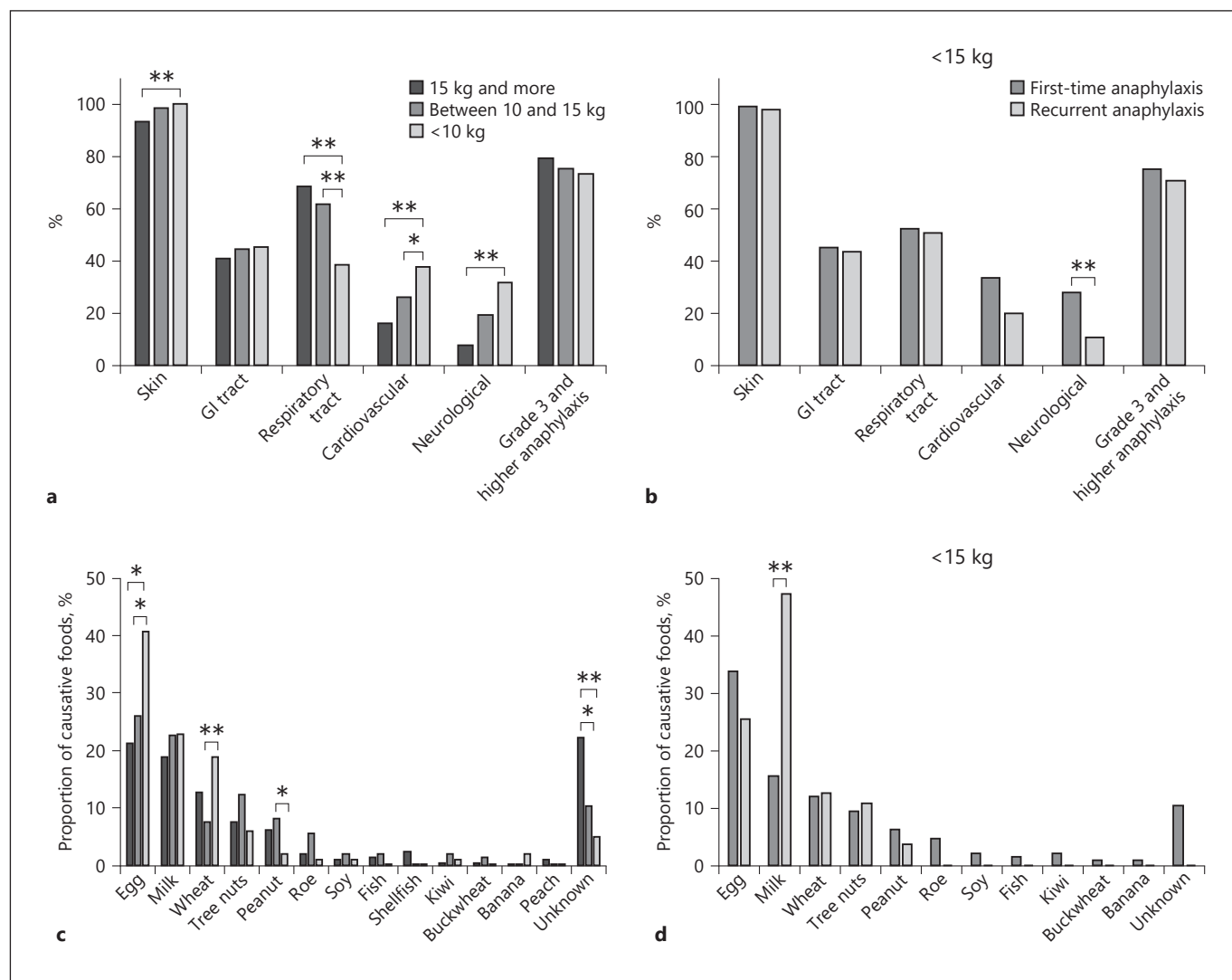


Fig. 2. Proportions of anaphylactic symptoms, by organ and causative food. **a** Differences by organ between the 3 groups: children weighing ≥ 15 kg; children weighing ≥ 10 kg and < 15 kg; and children weighing < 10 kg. **b** Differences by organ between the first and recurrent anaphylaxis episodes among children who weighed < 15

kg * $p < 0.05$; ** $p < 0.01$. **c** Differences by causative food between 3 groups: children weighing ≥ 15 kg; children weighing ≥ 10 kg and < 15 kg; and children weighing < 10 kg. **d** Differences by causative food between the first and recurrent anaphylaxis among children who weighed < 15 kg * $p < 0.05$; ** $p < 0.01$.

factors. We analyzed 444 ED visits for food-induced anaphylaxis, after excluding 41 visits related to oral desensitization therapy. The incidence of food-induced anaphylaxis, except those related to oral desensitization therapy, in all ED visits was 4.98 per 1,000 visits.

Demographics

Table 1 presents a comparison of the demographics, type of symptom, and treatment history between children who weighed < 15 kg and those who weighed 15 kg or more. Of the 444 visits, 247 (55.6%) included children

who weighed < 15 kg; patients who weighed < 10 kg accounted for 22.7% (101/444) of the total visits, and most of them ($n = 91/101$, 90.1%) weighing 7.5 kg or more. A history of food allergies at the time of each visit was noted in a lower proportion of patients who weighed < 15 kg ($n = 112/247$, 45.3%) than in those who weighed 15 kg or more ($n = 137/444$, 69.5%) ($p < 0.01$). The proportion of patients who weighed 15 kg or more who received an intramuscular injection of epinephrine was higher than that of children who weighed < 15 kg ($p < 0.01$) but did not differ from that of children who weighed between 10 and

<15 kg ($p = 0.33$). The proportion of patients with recurrent anaphylaxis was lower in children who weighed <15 kg than in children who weighed 15 kg or more (22.3% [55/247] vs. 48.7% [96/197], $p < 0.01$). Among patients who weighed <15 kg, the proportion of those with recurrent anaphylaxis was 4 times higher in children in the 10 to <15 kg weight group ($n = 47/146$, 32.2%) than in those who weighed <10 kg ($n = 8/101$, 7.9%) ($p < 0.01$). A lower proportion of patients were prescribed EAI before each visit in children who weighed <15 kg ($n = 14/55$, 25.5%) than in those who weighed 15 kg or more ($n = 58/96$, 60.4%) ($p < 0.01$). The number of children who had been prescribed EAI before their first anaphylaxis episode was 6, and 2 of them were administered epinephrine by EAI. Nine children who weighed <15 kg who were administered the 0.15-mg EAI (Epipen Jr) dose had no obvious complications and showed effective therapeutic responsiveness after administration of EAI.

Type of Anaphylactic Symptoms

Dermatological, cardiovascular, and neurological symptoms were more common in children who weighed less than 15 kg than in those who weighed 15 kg or more ($p < 0.01$; Fig. 2a). Respiratory symptoms were less common in children who weighed <15 kg than in those who weighed 15 kg or more (52.2% [129/444] vs. 68.5% [135/444]). The proportion of children with grade 3 or higher severity anaphylaxis did not differ significantly between the groups of children who weighed <15 kg and those who weighed 15 kg or more (74.5% [184/247] vs. 79.2% [156/197]), although the severity tended to be higher when the age at the time of the emergency visit was older (data not shown). There were no clinical records of children who suffered a cardiac arrest, a fatal course, or adverse events following the administration of epinephrine during the study period.

Eliciting Foods

Egg and milk were the commonest triggers in all the groups (Fig. 2c). Only in the group of children who weighed 10 kg or more and <15 kg were tree nuts ($n = 18/146$, 12.3%) and peanuts ($n = 12/146$ 8.2%) more common triggers than wheat ($n = 11/146$, 7.5%). In 14.6% (64/444) of the total visits, no specific food trigger could be identified because the ingested meal contained several food items.

Comparison between the First and Recurrent Anaphylaxis among Children Who Weighed <15 kg

Fig. 2b, d shows a comparison of the clinical features of children who weighed <15 kg with the first and recur-

rent anaphylactic episodes. The majority ($n = 38/55$, 69.1%) of recurrent cases among children who weighed <15 kg included preschool-aged (2–5 years) participants. There was no difference in the proportion of children who received an intramuscular injection of epinephrine between the recurrent and first anaphylaxis groups (38.2% [21/55] vs. 42.2% [81/192], Table 1). Dermatological symptoms were the commonest presenting symptom in both groups. Neurological symptoms were seen less frequently in the recurrent anaphylaxis group than in the first anaphylaxis group (10.9% [6/55] vs. 28.1% [54/192], $p < 0.01$); however, the severity of anaphylaxis did not differ between the 2 groups (Fig. 2b). Milk was the most common causative food for recurrent anaphylaxis, and 3-quarters of cases of recurrent anaphylaxis were induced by milk or eggs. No recurrence due to roe, soy, fish, kiwi, buckwheat, or banana was observed (Fig. 2d).

Discussion

It is valuable to describe the weight-related characteristics of pediatric food-induced anaphylaxis to facilitate optimal treatment. We identified 3 novel findings in terms of the weight-related characteristics of pediatric food-induced anaphylaxis. First, the proportion of children with food-induced anaphylaxis who weighed <15 kg and presented to the pediatric ED was similar to the proportion of those who weighed 15 kg or more. Second, the symptoms of food-induced anaphylaxis were as severe in children who weighed 15 kg or more as they were in those who weighed <15 kg, with several patterns in the symptoms of food-induced anaphylaxis depending on the weight of the children. Third, among children who weighed <15 kg, the proportion of children with recurrent food-induced anaphylaxis was approximately 20%, of which children who weighed 10 kg or more and <15 kg had a particularly higher recurrence rate than children who weighed <10 kg.

Our study showed that children with food-induced anaphylaxis who weighed <15 kg in the pediatric ED presented as frequently as those who weighed 15 kg or more. Data on the epidemiology of food-induced anaphylaxis in the pediatric ED are sparse because of the influence of study design and study period. The proportion of children with food-induced anaphylaxis in the pediatric ED was reported to be 2.41 per 1,000 visits in a single-center study conducted in Canada from 2011 to 2015 [24]. Choi et al. [25] reported that the proportion of children with food-induced anaphylaxis in the pediatric ED was

1.52/1,000 visits (121/79,676 visits) in a single-center study in South Korea from 2012 to 2016. In our study, this proportion was 4.98 per 1,000 visits, which is higher than the previously reported proportion. The proportion of children who weighed <15 kg among patients with food-induced anaphylaxis has not been investigated, although the age composition of this group was investigated in a population-based study of pediatric EDs in 2007 in Stockholm [19]. In their study, Vetander et al. [19] reported that 40.6% (52/128) of children aged 0–17 years who had food-induced anaphylaxis were 3 years old or younger. In another study that investigated children with food-induced anaphylaxis in a single-center pediatric ED between 2008 and 2012 in the USA, Dyer et al. [26] reported that 44.4% (840/1,894) of those children were 4 years old or younger. According to population-based surveys in Sweden and the USA [27, 28], the average weight of both boys and girls exceeds 15 kg by age 3 or 4. Aggregating the evidence from these studies and surveys, it is estimated that children who weigh <15 kg account for approximately 40% of children with food-induced anaphylaxis in the pediatric ED. Our study group had a slightly higher proportion of children who weighed <15 kg than the above-mentioned estimate, and this may be because Japanese children usually weigh less than Swedish and American children. Moreover, children with multiple food allergies or milk allergies experience an impact on growth [29, 30], which may be one of the causes of this gap. Although age and weight physiologically increase in parallel, the incidence of food-induced anaphylaxis among children who weigh <15 kg, as incurred solely from the age composition, may also be potentially underestimated. In turn, this may lead to an underestimation of the demand for appropriate EAI in children weighing <15 kg. Even of the same age, in populations with a small body frame like in Japan, there may be more patients with food-induced anaphylaxis who weigh <15 kg than in populations with a larger body frame such as in Sweden and the USA [27, 28].

The second finding is that the symptoms of food-induced anaphylaxis were equally severe in children who weighed 15 kg or more and those who weighed <15 kg, with several patterns in the symptoms of food-induced anaphylaxis depending on the weight of the children. There are challenges in identifying the symptoms of an allergic emergency in infants because they cannot describe the symptoms [1]. In infants, allergic symptoms overlap with certain normal behaviors or non-allergic symptoms such as viral infection, reflux, and constipation [1, 31]. A recent expert panel consensus [1] emphasized that the context is crucial to distinguish between allergic

symptoms and normal behavior in infants. The symptoms are more likely to suggest anaphylaxis in combination with other potential symptoms or within close temporal proximity to a potential allergen ingestion exposure [1, 32]. In our study, 1 trained pediatrician reviewed all medical records and confirmed that anaphylaxis was the most suspected diagnosis in all visits. In addition, by diagnosing anaphylaxis in patients with multiple grade 2 or higher symptoms, we attempted to eliminate as much normal behavior and symptoms induced by non-allergic etiology. Few studies have investigated the severity of anaphylaxis in infants. In a study that investigated age-related differences in anaphylaxis in a pediatric ED between 2007 and 2011, Topal et al. [33] categorized 104 children with anaphylaxis of various causes into 3 severity groups according to a position paper of the European Academy of Allergology and Clinical Immunology on the management of anaphylaxis in childhood [34]. The study included children aged 3 months to 17 years and found no significant difference between the proportion of patients with moderate or severe anaphylaxis in infants aged 1 year or less and patients who were older than 1 year (52.2% [12/23] vs. 70.4% [57/81]) [33]. Severe anaphylaxis is common in younger children, which is consistent with our findings.

The present study showed that dermatological, cardiovascular, and neurological symptoms were seen more frequently, and respiratory symptoms were less common in children with food-induced anaphylaxis weighed <15 kg than in those who weighed 15 kg or more. In a study of 2 large North American EDs, Rudders et al. [17] reported that respiratory symptoms were observed less frequently in infants aged <2 years than in preschool children aged 2–5 years, which is similar to our findings. Furthermore, the author noted that cardiovascular symptoms were rarely reported in infants aged <2 years, but the interpretation was complicated due to less frequent measurement of blood pressure [17]. Goh et al. [18] reported that 21% (4/19) of anaphylactic children aged <2 years had cardiovascular symptoms but also noted that blood pressure measurements were infrequent. Similarly, in our study, blood pressure was not measured in almost all infants; therefore, the interpretation of the frequency of cardiovascular symptoms needs to be prudent. We judged that tachycardia above the upper limit of normal heart rate according to age by 15 bpm or more was a cardiovascular symptom, although this carries the risk of overestimation. Tachycardia and behavioral changes may suggest compensated shock in certain contexts [1, 35]; however, in infants, these are often normal reactions and can lead

to misdiagnosis of anaphylaxis. Caution is needed to avoid misinterpretation of simple tachycardia and behavioral changes as more concerning than warranted. In practice, accurate blood pressure measurements for infants are sometimes difficult because proper cuff size is essential, and automated machines have difficulty obtaining valid readings for fussy infants [1]. As with all allergy assessments, the timing of onset and the presence of other organ symptoms are important to assess the reaction of tachycardia as anaphylaxis.

Third, we showed the incidence of recurrent food-induced anaphylaxis in children who weighed <15 kg. Since age and weight increase in parallel physiologically, it is not surprising that the lower the weight, the shorter the duration of the disease and the lower the recurrence rate, but it is noteworthy that the recurrence rate differed about 4 fold between children under 10 kg and those between 10 and 15 kg. The likelihood of recurrence in children who weighed <15 kg is important information in prescribing EIAs for those with a history of food-induced anaphylaxis; however, little is known about the recurrence of food-induced anaphylaxis in infants. In a prospective multicenter study from Canada by O'Keefe et al. [36], the annual recurrence rate of anaphylaxis was 17.6% in children younger than 18 years. In this study, food was the commonest cause of recurrent anaphylaxis, accounting for 84.6% (39/47) of cases. The population in the study was not stratified by age or weight and did not describe the recurrence rate of food-induced anaphylaxis in infants. In the study by Andrew et al. [36], milk and tree nuts were the commonest causative foods of recurrent food-induced anaphylaxis, accounting for 15.4% (6/39) of all visits. Eggs and wheat accounted for 4.6% (2/39) and 1.5% (1/39) of allergies, respectively [36]. The proportion of milk and eggs was higher in our study than in the study by O'Keefe et al. [36]. This seems to reflect differences in age and food culture among the surveyed population. Combining the findings of the frequency of recurrent food-induced anaphylaxis and the proportion of causative foods in our study, the potential need for EIAs may be high, especially in children weighing 10 kg or more and >15 kg with anaphylaxis induced by milk and eggs.

Our study also showed that the prevalence of EAI among children with recurrent food-induced anaphylaxis weighing 10 kg or more and <15 kg was only 25% (14/55). Kilger et al. [37] reported that the prevalence of EIAs among children with a history of anaphylaxis was 23% (14/61) in a questionnaire-based study conducted in 2011 and pointed out the clinical discrepancy with the recommendation on the management of anaphylaxis in

childhood [34]. Although this study was conducted in a different setting than our study, the prevalence of EIAs among children with a history of food-induced anaphylaxis was similarly low. Diwakar et al. [38] reported that the prescriptions of EIAs are increasing, especially for children aged 1 year or less in the UK between 2000 and 2012, but the potential demand may still be high. Although the fatalities due to food-induced anaphylaxis are rare in infants and preschool children, a recent expert panel consensus recommended they should be prescribed EIAs because delay in treatment is widely presumed to be associated with severe reaction and death [1]. Some cost-effectiveness analyses of EIAs in children with food allergy suggested that the use of EIAs is cost effective in patients with anaphylaxis unless it is highly expensive [39]. However, the analysis has not sufficiently focused on the infancy period, and more detailed examination is warranted in the future. Underlying the clinical gap between the recommendation of prescribing the 0.15 mg EIAs for children who weigh <15 kg and the real-world prescriptions of EIAs for those patients, the proviso of contraindications or cautions regarding the use of EIAs and the potential issues of the needle length of EIAs and the amount of epinephrine persist. Our findings indicate the potential demand for appropriate EIAs for children weighing <15 kg. In our study, 9 patients weighing <15 kg who were administered the 0.15-mg EAI (Epipen Jr) had no obvious complications and showed effective therapeutic responsiveness. However, as stated in the study by Dreborg et al. [12], clinicians should be aware that currently available EIAs are not appropriate for all patients. Auvi-Q 0.1-mg[®] HPEAI is intended for use in small children, weighing 7.5–15 kg, to avoid periosteal or intraosseous injection of epinephrine. However, there is a high risk of subcutaneous injection, as indicated in a study using ultrasound for measuring the distance from the skin to the muscle and bone [12]. Dreborg et al. [10] proposed that the only proper solution is to perform ultrasound determination of skin-to-bone distance and skin-to-muscle distance every time an EAI is prescribed.

Our study has some limitations. First, our study was conducted in a single tertiary-care pediatric hospital in Japan. There may be a sampling bias wherein patients with severe anaphylaxis were sampled. In addition, the proportion of causative foods for food-induced anaphylaxis may be influenced by the Japanese food culture. Second, the information relies entirely on the accuracy of clinical records. In addition, although specific IgE tests or skin prick tests are usually required for the diagnosis of food allergy, we were not able to present such data since

this was a retrospective study of children who visited our ED. Third, the analysis was limited to patients with food-induced anaphylaxis to maintain population uniformity. Anaphylaxis caused by non-food causes has not yet been analyzed. In the future, we will prospectively collect clinical information on children with anaphylaxis weighing <15 kg and 15 kg or more. This may provide more accurate clinical information for children weighing <15 kg, which may contribute to the development of more appropriate EAI and the dissemination of 0.1 mg EAIs.

Conclusions

We determined the incidence, recurrence, and clinical characteristics of food-induced anaphylaxis in children weighing <15 kg in a pediatric ED setting. We also found that children weighing <15 kg with food-induced anaphylaxis had similar severity and had a low proportion of EAI prescriptions compared to those weighing 15 kg or more. Taken together, our results suggest a potential need for the development of EAIs that are suitable for children who weigh <15 kg, especially children weighing between 10 kg and 15 kg, i.e., an EAI delivered with a 0.1-mg dose and an appropriate needle length. Additionally, further studies are warranted to characterize and to validate the diagnosis and treatment of anaphylaxis in children weighing <15 kg.

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References

- Greenhawt M, Gupta RS, Meadows JA, Pistiner M, Spergel JM, Camargo CA Jr, et al. Guiding principles for the recognition, diagnosis, and management of infants with anaphylaxis: an expert panel consensus. *J Allergy Clin Immunol Pract*. 2019;7(4):1148–56.
- Motosue MS, Bellolio MF, Van Houten HK, Shah ND, Campbell RL. National trends in emergency department visits and hospitalizations for food-induced anaphylaxis in US children. *Pediatr Allergy Immunol*. 2018; 29(5):538–44.
- Parrish CP, Kim H. Food-induced anaphylaxis: an update. *Curr Allergy Asthma Rep*. 2018;18(8):41.
- Shaker MS, Wallace DV, Golden DBK, Oppenheimer J, Bernstein JA, Campbell RL, et al. Anaphylaxis—a 2020 practice parameter update, systematic review, and grading of recommendations, assessment, development and evaluation (GRADE) analysis. *J Allergy Clin Immunol*. 2020;145(4):1082–123.
- Muraro A, Roberts G, Worm M, Bilò MB, Brockow K, Fernández Rivas M, et al. Anaphylaxis: guidelines from the European academy of allergy and clinical immunology. *Allergy*. 2014;69(8):1026–45.
- Posner LS, Camargo CA Jr. Update on the usage and safety of epinephrine auto-injectors, 2017. *Drug Healthc Patient Saf*. 2017;9:9–18.
- Sicherer SH, Simons FER; Section On Allergy And Immunology. Epinephrine for first-aid management of anaphylaxis. *Pediatrics*. 2017; 139(3):e20164006.
- Simons FE, Ebisawa M, Sanchez-Borges M, Thong BY, Worm M, Tanno LK, et al. Update of the evidence base: world allergy organization anaphylaxis guidelines. *World Allergy Organ J*. 2015;8(1):32.
- Halbrich M, Mack DP, Carr S, Watson W, Kim H. CSACI position statement: epinephrine auto-injectors and children <15 kg. Allergy, asthma, and clinical immunology. *Allergy Asthma Clin Immunol*. 2015; 11(1):20.

Statement of Ethics

Study approval statement: This study protocol was reviewed and approved by the Regional Ethical Review Board of NCCHD, approval number: 2020-014. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Consent to participate statement: The publication of this study protocol was posted to ensure that patients had the opportunity to refuse to participate in the study by using an opt-out method. The need for informed consent was waived by the approving authority in view of the study's retrospective design. The study does not include any personal information which can identify specific participants.

Conflict of Interest Statement

K.T., T.F., M.N., S.O., S.I., S.T., and M.K. declare that they have no conflicts of interest. Y.O. received speaker honoraria from Maruho and Mylan and research funding from Yakult.

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Author Contributions

K.T., M.N., and T.F. designed the study and wrote the manuscript. S.O., S.T., and S.I. contributed to data collection. K.T. performed the statistical analysis, and M.K., A.I., and Y.O. interpreted the results.

Data Availability Statement

The data that support the findings of this study are not publicly available due to ethical board (the data is stored on a stand-alone PC) but are available from the corresponding author (T.F., E-mail: fukuie-t@ncchd.go.jp).

- 10 Dreborg S, Tsai G, Kim H. Epinephrine auto-injector needle length: The impact of winter clothing. *Allergy Asthma Clin Immunol*. 2020;16:24.
- 11 Dreborg S, Wen X, Kim L, Tsai G, Nevis I, Potts R, et al. Do epinephrine auto-injectors have an unsuitable needle length in children and adolescents at risk for anaphylaxis from food allergy? *Ann Allergy Asthma Immunol*. 2016;12:11.
- 12 Dreborg S, Kim L, Tsai G, Kim H. Epinephrine auto-injector needle lengths: Can both subcutaneous and periosteal/intraosseous injection be avoided? *Ann Allergy Asthma Immunol*. 2018;120(6):648–e1.
- 13 Dreborg S, Tsai G, Kim H. Implications of variation of epinephrine auto-injector needle length. *Ann Allergy Asthma Immunol*. 2019;123(1):89–94.
- 14 Kim L, Nevis IF, Tsai G, Dominic A, Potts R, Chiu J, et al. Children under 15 kg with food allergy may be at risk of having epinephrine auto-injectors administered into bone. *Allergy Asthma Clin Immunol*. 2014;10(1):40.
- 15 Simons FE, Gu X, Silver NA, Simons KJ. EpiPen JR versus EpiPen in young children weighing 15 to 30 kg at risk for anaphylaxis. *J Allergy Clin Immunol*. 2002;109(1):171–5.
- 16 Simons FE, Peterson S, Black CD. Epinephrine dispensing for the out-of-hospital treatment of anaphylaxis in infants and children: a population-based study. *Ann Allergy Asthma Immunol*. 2001;86(6):622–6.
- 17 Rudders SA, Banerji A, Clark S, Camargo CA Jr. Age-related differences in the clinical presentation of food-induced anaphylaxis. *J Pediatr*. 2011;158(2):326–8.
- 18 Goh SH, Soh JY, Loh W, Lee KP, Tan SC, Heng WJK, et al. Cause and clinical presentation of anaphylaxis in Singapore: from infancy to old age. *Int Arch Allergy Immunol*. 2018;175(1–2):91–8.
- 19 Vetander M, Helander D, Flodström C, Ostblom E, Alfvén T, Ly DH, et al. Anaphylaxis and reactions to foods in children: a population-based case study of emergency department visits. *Clin Exp Allergy*. 2012;42(4):568–77.
- 20 Grabenhenrich LB, Dölle S, Moneret-Vautrin A, Köhli A, Lange L, Spindler T, et al. Anaphylaxis in children and adolescents: the European anaphylaxis registry. *J Allergy Clin Immunol*. 2016;137(4):1128–37.
- 21 Sampson HA. Anaphylaxis and emergency treatment. *Pediatrics*. 2003;111(33):1601–8.
- 22 Urisu A, Ebisawa M, Ito K, Aihara Y, Ito S, Mayumi M, et al. Japanese guideline for food Allergy 2014. *Allergol Int*. 2014;63(3):399–419.
- 23 Megan M, Tschudy KMA. *The Harriet Lane Handbook 19th (nineteenth) Edition*; Elsevier Inc.; 2011.
- 24 Hochstadter E, Clarke A, De Schryver S, La-Vieille S, Alizadehfar R, Joseph L, et al. Increasing visits for anaphylaxis and the benefits of early epinephrine administration: a 4-year study at a pediatric emergency department in Montreal, Canada. *J Allergy Clin Immunol*. 2016;137(6):1888–90.
- 25 Choi B, Kim SH, Lee H. Missed registration of disease codes for pediatric anaphylaxis at the emergency department. *Emerg Med Int*. 2019;2019:4198630.
- 26 Dyer AA, Lau CH, Smith TL, Smith BM, Gupta RS. Pediatric emergency department visits and hospitalizations due to food-induced anaphylaxis in Illinois. *Ann Allergy Asthma Immunol*. 2015;115(1):56–62.
- 27 Wikland KA, Luo ZC, Niklasson A, Karlberg J. Swedish population-based longitudinal reference values from birth to 18 years of age for height, weight and head circumference. *Acta paediatrNorway*. 2002;91(7):739–54.
- 28 Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, et al. CDC growth charts for the United States: methods and development. *Vital Health Stat*. 2000;11246(246):1–190.
- 29 Berry MJ, Adams J, Voutilainen H, Feustel PJ, Celestin J, Järvinen KM. Impact of elimination diets on growth and nutritional status in children with multiple food allergies. *Pediatr Allergy Immunol*. 2015;26(2):133–8.
- 30 Dupont C, Chouraqui JP, Linglart A, Bocquet A, Darmaun D, Feillet F, et al. Nutritional management of cow's milk allergy in children: an update. *Arch Pediatr*. 2018;25(3):236–43.
- 31 Simons FE, Sampson HA. Anaphylaxis: unique aspects of clinical diagnosis and management in infants (birth to age 2 years). *J Allergy Clin Immunol*. 2015;135(5):1125–31.
- 32 Pouessel G, Antoine M, Lejeune S, Dubos F, Pierache A, Deschildre A, et al. The time course of anaphylaxis manifestations in children is diverse and unpredictable. *Clin Exp Allergy*. 2020;50(1):117–20.
- 33 Topal E, Bakirtas A, Yilmaz O, Ertoý Karagöl IH, Arga M, Demirsoy MS, et al. Anaphylaxis in infancy compared with older children. *Allergy Asthma Proc*. 2013;34(3):233–8.
- 34 Muraro A, Roberts G, Clark A, Eigenmann PA, Halken S, Lack G, et al. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. *Allergy*. 2007;62(8):857–71.
- 35 Robinson M, Greenhawt M, Stukus DR. Factors associated with epinephrine administration for anaphylaxis in children before arrival to the emergency department. *Ann Allergy Asthma Immunol*. 2017;119(2):164–9.
- 36 O'Keefe A, Clarke A, St Pierre Y, Mill J, Asai Y, Eisman H, et al. The risk of recurrent anaphylaxis. *J Pediatr*. 2017;180:217–21.
- 37 Kilger M, Range U, Vogelberg C. Acute and preventive management of anaphylaxis in German primary school and kindergarten children. *BMC Pediatr*. 2015;15:159.
- 38 Diwakar L, Cummins C, Ryan R, Marshall T, Roberts T. Prescription rates of adrenaline auto-injectors for children in UK general practice: a retrospective cohort study. *Br J Gen Pract*. 2017;67(657):e300.
- 39 Shaker M, Greenhawt M. Association of fatality risk with value-based drug pricing of epinephrine autoinjectors for children with peanut allergy: a cost-effectiveness analysis. *JAMA Netw Open*. 2018;21(7):e184728.