Epidemiological Study of Hospital Admissions for Food-Induced Anaphylaxis Using the Japanese Diagnosis Procedure Combination Database

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ABSTRACT

Background: Food allergies are common among children, and food-induced anaphylaxis (FIA) is a serious disease with a risk of death; however, there is yet to be a large-scale epidemiological study on causative foods in Japan. The purpose of this study was to identify foods that cause FIA in Japan.

Methods: We identified 9,079 patients from the Japanese Diagnosis Procedure Combination Database who were admitted for treatment for FIA from April 1, 2014 through March 31, 2017. We extracted data on patient sex, age, use of epinephrine injections on the first day, prescription for epinephrine self-injection on the day of discharge, length of stay, readmission, and causative foods.

Results: The most common causative food was eggs, followed by wheat, milk, peanuts, and buckwheat. The most common causative food in each age group was eggs among 0–3-year-olds, milk among 4–6-year-olds, peanuts among 7–19-year-olds, and wheat among those aged 20 years and older. Epinephrine was used at admission among about 40%, 50%, and over 60% of cases in which the causative food was eggs; wheat, milk and peanuts; and buckwheat, respectively. The proportion of cases with a prescription for epinephrine self-injection at discharge was highest among those in which the causative food was wheat, followed by peanuts, buckwheat, milk, and eggs.

Conclusions: FIA due to peanuts has become as common in Japan as it is in the West. These results suggest the importance of taking measures to prevent peanut allergies because children cannot make adequate decisions regarding food.

Key words: anaphylaxis; child; food hypersensitivity; shock

INTRODUCTION

Food allergy is a common disease in children. A previous study reported that about 8% of children in the United States, Canada, the United Kingdom, and Australia have food allergies. Additionally, about 5% of children under the age of 5 years in East Asian countries and regions, such as Hong Kong, South Korea, and Taiwan, have food allergies. In Japan, an estimated 5% to 10% of infants have food allergies. Further, the prevalence of food allergies is on the rise, with medical costs associated with food allergies having increased in the past decade in Australia, Japan, China, Korea, the United States, and Norway. Evidence also suggests that there is an increase in food allergies in developing countries in Africa and Asia due to lifestyle changes and genetic factors. These results indicate the importance of prevention and the need for proper treatments for food allergies.

Anaphylactic shock is a serious allergic reaction, and food is an important causative factor. A study in Europe demonstrated that food is the most common cause of anaphylactic shock. In the United States, 40% of children with a food allergy experience severe symptoms. Food-induced anaphylaxis (FIA) has increased along with food allergies. In the United Kingdom, hospital admissions due to FIA doubled from 1998 to 2012. In Australia, the number of hospitalizations for anaphylactic shock among patients under the age of 5 years increased from 4.1 to 19.7 per 100,000 people between 1993–1994 and 2004–2005, for which the main cause was noted to be food. FIA can result in sudden death of healthy children and can have a significant social impact. In Japan, a fatal incident due to a milk allergy was reported following consumption of a school meal in 2012. Subsequently, the Japanese government enacted the Basic Law for Allergic Diseases and clarified the responsibilities of the government, local governments, citizens, healthcare workers, and school establishments. The law also promotes epidemiological, basic, and clinical research into allergic diseases.

Past epidemiological studies have shown that foods that cause serious symptoms differ among different regions. In the United States, a cross-sectional study of 3,339 children who had food allergies showed that tree nuts and peanuts are the most common causative food of severe allergic reactions. In Japan, eggs...
followed by milk and wheat are the most common causative foods across all ages. Among those under 20 years old, hen’s eggs, fish, beef, and crustaceans are the most common causative food of new-onset food allergies for those aged 0–1, 2–3, 4–6, and 7–19 years old, respectively. The first- and second-most common causative foods of accidental ingestion are hen’s eggs and cow’s milk, respectively, among those aged 0–19 years old. A Japanese prospective study conducted between 2000 and 2001 reported that the most common causative foods of anaphylactic shock among 395 patients were hen’s egg, cow’s milk, wheat, buckwheat, and peanuts, in that order. However, there is yet to be a large-scale epidemiological survey on foods that cause anaphylactic shock in Japan.

Therefore, we investigated the causes and characteristics of patients hospitalized due to FIA using the Diagnosis Procedure Combination (DPC) database, a standardized electronic claims system adopted by hospitals throughout Japan.

**METHODS**

**Study design**

We performed a cross-sectional study using data from the Japanese DPC database from April 2014 to March 2017. All data in the DPC database were gathered by the DPC research group, which receives funding from the Japanese Ministry of Health, Labour and Welfare. A total of 1,478 hospitals completed a survey conducted by the DPC research group during the study period and allowed their DPC data to be used for research purposes. The DPC database harbors inpatient data and comprehensive procedures for the Japanese national health insurance system. This study was conducted with approval from the ethics committee of medical care and research of the University of Occupational and Environmental Health, Japan (approved number R1-067).

**Inclusion and exclusion criteria**

We selected patients whose principal diagnosis was anaphylactic shock due to an adverse food reaction (ICD-10 code T78.0; n = 10,049), including food-dependent exercise-induced anaphylaxis. The diagnosis was determined by the physician when the patient was discharged from hospital. To homogenize patients’ background characteristics, patients who had scheduled hospitalizations were excluded because they may have been hospitalized for an oral food challenge rather than for treatment of the acute phase of anaphylactic shock (n = 970).

**Types of causative food**

We analyzed incidences in which the following seven foods were the cause of anaphylactic shock because labeling for these foods is required by the Food Labeling Act in Japan: eggs, wheat, milk, peanuts, buckwheat, shrimp, and crab. The causative food was identified based on the disease name written in Japanese in combination with the ICD-10 code. A food was considered a causative food only when the principal diagnosis or comorbidity was anaphylactic shock due to adverse food reaction (ICD-10: T78.0) or other adverse food reactions not classified elsewhere (ICD-10: T78.1) and the causal food was clearly indicated in the diagnosis at the time of discharge.

**Other variables and outcomes**

We examined sex and age because the incidence of food-induced anaphylactic shock differs among categories within these variables. IgE testing conducted during hospitalization was examined because it is widely used to confirm a diagnosis of FIA. We also examined tests on breathing and circulation, which are performed on patients with severe symptoms. Use of epinephrine injections, oxygen, and steroids on the first day were examined because these are often used for severe symptoms. Prescription for epinephrine self-injection on the day of discharge was used as a variable because this occurs when symptoms are severe. To determine whether there was a repetition of adverse events, we examined the occurrence of readmission due to another FIA episode regardless of the causative foods. In the case of rehospitalization, we calculated the period between hospitalizations.

**Statistical analysis**

We conducted a descriptive epidemiological study by age group. We also tabulated the findings according to causative foods. All statistical analyses were performed using Stata version 15.1 (StataCorp, College Station, TX, USA).

**RESULTS**

Table 1 shows the characteristics of all patients. The most common causative food among all cases was eggs (n = 608, 6.7%), followed by wheat (n = 436, 4.8%), milk (n = 416, 4.6%), peanuts (n = 287, 3.2%), and buckwheat (n = 185, 2.0%). The causative food for 79% of patients was not listed. We did not separate shrimp and crab into different groups in Table 1 because less than 10 patients were hospitalized for anaphylactic shock due to these foods during the study period. We also did not describe a number of fatal cases because less than 10 patients died in the study period. Table 2 shows the patients’ characteristics by age group. We divided age into the following groups: <1, 1, 2–3, 4–6, 7–19, and ≥20 years old, with reference to Japanese guidelines. Groups younger than the 20-year-old group tended to be comprised of fewer females. Over 30% of the causative foods examined were identified among patients 6 years old or younger. The most common causative food in each age group was eggs among 0–3-year-olds, milk among 4–6-year-olds, peanuts among 7–19-year-olds, and wheat among those 20 years and older. IgE testing was most frequently performed among those under 1 year old, followed by those aged 7–19 years old. The proportion of patients using epinephrine at the time of admission was 38–50%. The proportion who used epinephrine two or more times or oxygen tended to increase with age. Epinephrine self-injection was prescribed to those aged 2–3 years and older, and the rate of prescription increased with age among those under 20 years. The length of hospital stay was approximately 2 days for all age groups. The readmission rate was 2.4%, 5%, 6%, and 3.1% for those aged <1, 1–3, 4–19, and over 20 years old. The period until rehospitalization varied widely.

The results by causative food are shown in Table 3. Regardless of the causative food, women comprised around 40% and length of stay was about 2 days. Epinephrine was used at admission among about 40%, 50%, and over 60% of cases in which the causative food was eggs; wheat, milk, and peanuts; and buckwheat, respectively. About 8% of cases among whom the causative food was buckwheat used epinephrine two or more times. Cases among whom the causative food was eggs had the lowest rates of epinephrine, oxygen, and steroid use. The
### Table 1. Characteristics of patients, type of causative food and treatment

| Characteristics                              | Number or mean | % or SD |
|----------------------------------------------|----------------|---------|
| **Sex, female**                              | 3,930          | 43%     |
| **Causative food**                           |                |         |
| Seven items required by law<sup>a</sup>      | 1,862          | 21%     |
| Other items                                  | 52             | 0.6%    |
| Not specified                                | 7,165          | 79%     |
| **Type of causative food**                   |                |         |
| Hen's egg                                    | 608            | 6.7%    |
| Wheat                                        | 436            | 4.8%    |
| Cow's milk                                   | 416            | 4.6%    |
| Peanuts                                      | 287            | 3.2%    |
| Buckwheat                                    | 185            | 2.0%    |
| **Clinical test**                            |                |         |
| Blood gas analysis, yes                      | 4,160          | 46%     |
| Percutaneous arterial oxygen saturation, yes | 4,040          | 44%     |
| Respiratory and heart rate monitoring, yes   | 4,959          | 55%     |
| Non-specific IgE, yes                        | 2,776          | 31%     |
| Specific IgE, yes                            | 2,898          | 32%     |
| **Treatment on the first day**               |                |         |
| Use of epinephrine injections, yes           | 4,191          | 46%     |
| Use of epinephrine injections 2 times or more, yes | 243      | 2.7%    |
| Use of oxygen, yes                           | 2,775          | 31%     |
| Use of steroids, yes                         | 6,023          | 66%     |
| Prescription for epinephrine self-injection on the day of discharge, yes | 427 | 4.7% |
| **Length of stay, days, mean (SD)**          |                |         |
| <1 years old <sup>n = 838</sup>             | 2.1            | (1.5)   |
| 1 years old <sup>n = 618</sup>              | 2.1            | (1.5)   |
| 2–3 years old <sup>n = 1,050</sup>          | 2.1            | (1.5)   |
| 4–6 years old <sup>n = 845</sup>            | 2.1            | (1.5)   |
| 7–19 years old <sup>n = 2,140</sup>         | 2.1            | (1.5)   |
| ≥20 years old <sup>n = 3,587</sup>          | 2.1            | (1.5)   |

IgE, immunoglobulin E; SD, standard deviation.

<sup>a</sup>Seven items required by law: hen's egg, wheat, cow's milk, peanuts, buckwheat, shrimp and crab.

### Table 2. Characteristics of patients, type of causative food and treatment by age group

| Characteristics                              | <1 years old <sup>n = 838</sup> | 1 years old <sup>n = 618</sup> | 2–3 years old <sup>n = 1,050</sup> | 4–6 years old <sup>n = 845</sup> | 7–19 years old <sup>n = 2,140</sup> | ≥20 years old <sup>n = 3,587</sup> |
|----------------------------------------------|---------------------------------|-------------------------------|----------------------------------|---------------------------------|----------------------------------|----------------------------------|
| Sex, female                                  | 346 (41%)                       | 217 (35%)                     | 358 (34%)                        | 266 (31%)                       | 875 (41%)                        | 1,869 (52%)                      |
| **Causative food**                           | 367 (44%)                       | 203 (33%)                     | 351 (33%)                        | 268 (32%)                       | 347 (16)                         | 326 (9.1)                       |
| Seven items required by law<sup>a</sup>      | 228 (27%)                       | 109 (18%)                     | 108 (10%)                        | 68 (8.0)                        | 74 (3.5)                         | 21 (0.6)                        |
| Hen's egg                                    | 56 (6.7)                        | 39 (6.3)                      | 62 (5.9)                         | 49 (5.8)                        | 59 (2.8)                         | 171 (4.8)                       |
| Wheat                                        | 92 (11)                         | 59 (9.5)                      | 105 (10)                         | 77 (9.1)                        | >70 (3)                         | <3 (1)                           |
| Cow's milk                                   | 0 (1.8)                         | 11 (1.8)                      | 66 (6.3)                         | 73 (8.6)                        | 96 (4.5)                         | 11 (1.1)                        |
| Peanuts                                      | <10 (<1)                        | 30 (2.9)                      | 14 (1.7)                         | 50 (3.2)                        | 23 (2.3)                        | 9 (0.3)                         |
| Buckwheat                                    | <10 (<1)                        | 30 (2.9)                      | 14 (1.7)                         | 50 (3.2)                        | 23 (2.3)                        | 9 (0.3)                         |
| **Clinical test**                            | 451 (54%)                       | 341 (55%)                     | 561 (53%)                        | 410 (49)                        | 978 (46)                        | 1,419 (40)                      |
| Blood gas analysis, yes                      | 317 (38%)                       | 240 (39)                      | 422 (40)                         | 353 (42)                        | 951 (44)                         | 1,757 (49)                      |
| Percutaneous arterial oxygen saturation, yes | 353 (42)                       | 232 (38)                      | 442 (42)                         | 361 (43)                        | 1,146 (54)                      | 2,425 (68)                      |
| Respiratory and heart rate monitoring, yes   | 505 (60%)                       | 251 (41)                      | 333 (32)                         | 235 (28)                        | 748 (35)                        | 704 (20)                        |
| Non-specific IgE, yes                        | 519 (62%)                       | 239 (39)                      | 336 (32)                         | 209 (25)                        | 744 (35)                        | 851 (24)                        |
| Specific IgE, yes                            | 11 (1.3)                        | 12 (1.9)                      | 20 (1.9)                         | 21 (2.5)                        | 52 (2.4)                        | 127 (3.5)                       |
| **Treatment on the first day**               | 318 (38%)                       | 261 (42)                      | 508 (48)                         | 350 (41)                        | 947 (44)                        | 1,888 (50)                      |
| Use of epinephrine injections, yes           | 11 (1.3)                        | 12 (1.9)                      | 20 (1.9)                         | 21 (2.5)                        | 52 (2.4)                        | 127 (3.5)                       |
| Use of epinephrine injections 2 times or more, yes | 105 (13)                  | 103 (17)                      | 230 (22)                         | 202 (24)                        | 630 (29)                        | 1,505 (42)                      |
| Use of oxygen, yes                           | 462 (55)                        | 378 (61)                      | 606 (58)                         | 492 (58)                        | 1,383 (65)                      | 2,702 (75)                      |
| Use of steroids, yes                         | <10 (<1)                        | 30 (2.9)                      | 55 (6.5)                         | 160 (7.5)                       | 176 (7.5)                       | 223 (9.4)                       |
| Prescription for epinephrine self-injection on the day of discharge, yes | <10 (<1)                  | 30 (2.9)                      | 55 (6.5)                         | 160 (7.5)                       | 176 (7.5)                       | 223 (9.4)                       |
| **Length of stay, days, mean (SD)**          | 2.2 (0.7)                      | 2.1 (0.6)                     | 2.1 (1.2)                        | 2.1 (0.5)                       | 2.1 (0.8)                       | 2.2 (2.3)                       |
| Readmission (excluding scheduled hospitalization), yes | 20 (2.4)                 | 32 (5.2)                      | 50 (4.8)                         | 52 (6.2)                        | 136 (6.4)                       | 110 (3.1)                       |
| Period until rehospitalization, days         | 170 (153)                      | 314 (254)                     | 323 (301)                        | 264 (260)                       | 266 (283)                       | 227 (238)                       |

IgE, immunoglobulin E; SD, standard deviation.

<sup>a</sup>Seven items required by law: hen's egg, wheat, cow's milk, peanuts, buckwheat, shrimp and crab.
The proportion of cases with a prescription for epinephrine self-injection at discharge was highest among those in which the causative food was wheat, followed by peanuts, buckwheat, milk, and eggs. The readmission rate was highest in cases in which the causative food was wheat, followed milk and eggs.

**DISCUSSION**

This study used the Japanese DPC database to investigate the patient characteristics, causative food, and treatment for patients hospitalized due to FIA. We found that the proportion of cases in which the causative food was eggs, wheat, and milk decreased with increasing age. Cases due to peanuts peaked in those aged 4–6 years before declining. Buckwheat was the causative food in over 2% cases among 2–3-year-olds and remained at this rate thereafter.

Our study has three strengths. First, we analyzed a large sample from the Japanese DPC database, which includes a cumulative total of 33 million hospital admissions for all conditions across 4 years. A systematic review showed that there are 1 to 77 per 100,000 person-years of FIA. Large databases are useful for examining the epidemiology of rare diseases. A descriptive study conducted for 12 years since the 1990s with a sample size of about 6,000 is the largest study to date. The largest sample size in a published report since the 2010s is about 2,000 in the United States and about 3,000 in Europe. In contrast, the prevalence of immediate wheat, milk, peanut, and buckwheat allergies is 30%, 55%, 13%, and 5.6% of that for eggs in the guidelines, compared to 72%, 68%, 47%, and 30% of that for eggs for FIA in our study. This result suggests that the severity of symptoms may vary depending on the causative food.

In analysis by age, peanuts, like milk, were the most common causative food among children aged 1 and 3 years old. In contrast, the prevalence of immediate wheat, milk, peanut, and buckwheat allergies is 30%, 55%, 13%, and 5.6% of that for eggs in the guidelines, compared to 72%, 68%, 47%, and 30% of that for eggs for FIA in our study. This result suggests that the severity of symptoms may vary depending on the causative food. In analysis by age, peanuts, like milk, were the most common causative food among children aged 1 and 3 years old. In contrast, the prevalence of immediate wheat, milk, peanut, and buckwheat allergies is 30%, 55%, 13%, and 5.6% of that for eggs in the guidelines, compared to 72%, 68%, 47%, and 30% of that for eggs for FIA in our study. This result suggests that the severity of symptoms may vary depending on the causative food.
the importance of social strategies for preventing FIA in older children and young adults.

There were several limitations in this study. First, we used discharge diagnosis to identify causative foods. Previous studies have used the results of oral food challenge tests, skin prick tests, or other measures of food-specific IgE. In our study, laboratory test results were not available. In addition, the percentage of foods that were actually identified as being causative among the listed potential causative foods decreased with increasing age. Second, we may have underestimated the readmission rate because, while we could identify cases of readmission to the same hospital due to assignment of the same anonymized ID in the DPC database, it was impossible to capture rehospitalization when patients visited a different hospital. However, this problem can be solved by conducting a study using the National Database of Health Insurance Claims and Specific Health Checkups of Japan, the Japanese government’s repository for all health insurance claims data. Third, our study did not include patients who were judged not to require hospitalization after an emergency department visit. Therefore, we were unable to calculate population-based prevalence in the same way as epidemiological studies conducted in the United Kingdom that included inpatients. However, identifying the proportion of cases with relatively severe symptoms that require hospitalization due to certain foods is important for preventing death from FIA. Fourth, we were unable to examine any known factors that affect food allergy or FIA that were not indicated in the DPC data. A previous cohort study showed that parents’ history of allergies affects their children’s allergies. Further, a cohort study conducted in Japan has revealed the epidemiology of parental history of allergies. Future studies should use these data in an FIA study.

In summary, we identified the causative foods, details of treatment, and readmission rate of patients hospitalized for anaphylactic shock using data from the DPC database. While the breakdown of causative foods was similar to that reported by previous studies, a novel finding was that peanuts were a common causative food of FIA in children and teenagers in Japan, as they are in the West. These results suggest the importance of taking measures to prevent peanut allergies in preschool or school as well as FIA due to the three major causative foods. In the future, government efforts are needed to improve the reporting rate of causative foods for more accurate statistics.

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