

Clinical Communications

Recent dramatic increase in patients with food protein–induced enterocolitis syndrome (FPIES) provoked by hen's egg in Japan

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Clinical Implications

This study revealed that cases of food protein–induced enterocolitis syndrome provoked by hen's egg increased dramatically in Japan in 2018–2019. This increase may be associated with a change in policy to early introduction of hen's egg to high-risk infants.

Food protein–induced enterocolitis syndrome (FPIES) is a non–IgE-mediated gastrointestinal food allergy that occurs predominantly in infants and young children.¹ Since the international consensus guideline for FPIES was released in 2017,¹ epidemiological studies were conducted in many countries. However, there have been few longitudinal studies of FPIES, so we have lacked knowledge regarding possible changes in the trends of offending foods over the years. Recently, some case series of hen's egg–induced FPIES (hen's-egg FPIES) were reported from Japan;^{2–4} such cases had rarely been reported previously. This suggests that hen's-egg FPIES is increasing in Japan. Therefore, to better clarify this, we performed a multicenter retrospective cohort study of patients with FPIES.

This was a multicenter, 10-year retrospective cohort study that used data obtained from the medical records of patients ≤15 years old who had visited or been referred to allergists in 6 secondary- or tertiary-care hospitals in 5 different Japanese prefectures (Saitama City Hospital, Tsukuba Medical Center Hospital, Tokyo Metropolitan Children's Medical Center, Tochigi Medical Center, Keiyu Hospital, and Jikei University Katsushika Medical Center) between January 2010 and December 2019. Patients suspected of FPIES based on such clinical symptoms as vomiting and/or diarrhea were enrolled in this study. We investigated the offending foods, clinical symptoms, age at onset, comorbidity, and blood test and skin test results. This study was approved by the Ethics Review Board of Saitama City Hospital (A3138).

A total of 141 patients were studied. Fifteen of those patients could not be diagnosed as having FPIES because of a lack of data about the interval between the last ingestion and vomiting, which is an indispensable major criterion. Thirty-eight patients did not fulfill the diagnostic criteria or did not undergo oral food challenge tests for diagnosis. Finally, 88 patients (97 cases) were diagnosed as having FPIES who met the international consensus diagnostic criteria (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org).

Repetitive vomiting was the most frequent symptom (100%), followed by lethargy (77%) and pallor (65%), all of which were typical symptoms described in an earlier report.¹ Hyperthermia is not a typical symptom in western countries, but it was observed in 12 cases (12%), as in previous reports from Japan (Table E1, available in this article's Online Repository at www.jaci-inpractice.org),^{2,4} suggesting that it may be a specific feature in Japan. Hen's egg was the most common offending food (42%), followed by cow's milk (23%) in this decade (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). A comparison of the total number of cases every 2 years revealed a sharp increase in the number after 2016–2017 (Figure 1). When classified by each offending food, the number of cases with hen's-egg FPIES increased dramatically, especially in 2018–2019, whereas the number of cases with cow's milk–induced FPIES (cow's-milk FPIES) rose only gradually (Figure 1). Cases induced by soy and wheat also increased in 2018–2019. The increase in total FPIES cases since 2016–2017 may be partly due to increased awareness of the disease because of online posting of the international guidelines in early 2017. However, the ratio of hen's-egg FPIES to cow's-milk FPIES also increased dramatically, especially in 2018–2019. That suggests that cases of hen's-egg FPIES were increasing, especially in 2018–2019. Importantly, several clinical trials showed that early introduction of hen's egg to high-risk infants was protective against development of IgE-mediated hen's-egg allergy. On the basis of these findings, the Japanese Society of Pediatric Allergy and Clinical Immunology recommended early introduction of hen's egg from 6 months of age only to high-risk infants with eczema in 2017.⁵ Although our study could not clarify the timing of hen's egg introduction, the age of onset for hen's-egg FPIES was significantly earlier in 2018–2019 than in 2010–2017, whereas cow's-milk FPIES showed no significant change (Table 1). These findings indirectly suggest that hen's egg was introduced to infants at a younger age in 2018–2019 than in 2010–2017. Given that the number of reported cases of peanut-induced FPIES also increased in the United States after a change in peanut introduction policy supporting early introduction,^{6,7} early introduction may be associated with the increase in hen's-egg FPIES, as postulated by others.^{8,9} In addition, in this study, egg yolk—rather than egg white—was the main causative component of hen's-egg FPIES (Table E1, available in this article's Online Repository at www.jaci-inpractice.org), as previously reported.^{2,3} Notably, it was recommended in Japan that weaning be started with boiled egg yolk, rather than egg white. These facts may also support a possible association.

However, rice, a staple food in Japan, has long been customarily consumed from the early weaning period. Indeed, the age at onset of rice-induced FPIES was significantly earlier than with hen's egg-, soy-, and wheat-induced FPIES (Table E1, available in this article's Online Repository at www.jaci-inpractice.org), suggesting that rice was introduced earlier than these foods. However, rice was not a major offending food (4%) in our study. These findings suggest that not only early introduction but also other factors, including the nature, quantity and combination of foods, and the individual predisposition, may affect development of FPIES.

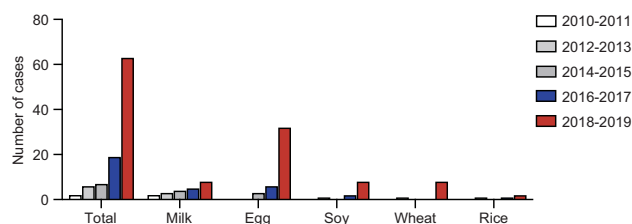


FIGURE 1. Changes in the trends of cases with food protein–induced enterocolitis syndrome (FPIES) in the past decade. The numbers of cases with FPIES in each 2-year period between 2010 and 2019.

TABLE I. Changes in the characteristics of patients with hen's-egg or cow's-milk FPIES between 2010-2017 and 2018-2019

	Hen's egg			Cow's milk		
	2010-2017 (n = 9)	2018-2019 (n = 32)	P value	2010-2017 (n = 14)	2018-2019 (n = 8)	P value
The median age at onset (mo) (IQR)	9 (8-11)	8 (7-9)	.041	1 (0-3.5)	3.5 (1-5.3)	.12
Prevalence of eczema (%)	33% (3/9)	31% (10/32)	.60	21% (3/14)	25% (2/8)	.62
Specific IgE-positive (%)	67% (6/9)	47% (15/32)	.25	54% (7/13)	25% (2/8)	.20

P values were calculated using the Mann-Whitney U test for differences in the age at onset, and the χ^2 test or Fisher's exact test for differences in the prevalence of eczema and specific IgE-positive.

FPIES, Food protein–induced enterocolitis syndrome; IQR, interquartile range.

Early introduction of hen's egg or peanut to high-risk infants was shown to be protective against development of IgE-mediated hen's-egg and peanut allergy, respectively. To ensure greater benefit than risk, further studies are needed to clarify the factors mentioned above that may be associated with development of FPIES.

In summary, our retrospective cohort study revealed a dramatic increase in cases of hen's-egg FPIES in Japan, especially in 2018-2019, after the 2017 recommendation of early introduction of hen's egg to high-risk infants. This study has several limitations: the timing, amount, and frequency of intake of causative foods were not evaluated, and recall bias or physician's awareness of FPIES may have affected the number of patients per year due to the long (10 years) retrospective period. In addition, this study did not prove a causal relationship between early introduction of hen's egg and the increase in hen's-egg FPIES. Further prospective studies may be needed to clearly demonstrate an association.

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REFERENCES

- Nowak-Węgrzyn A, Chehade M, Groetch ME, Spergel JM, Wood RA, Allen K, et al. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: executive summary—workgroup report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol* 2017; 139:1111-1126.e4.
- Toyama Y, Ishii T, Morita K, Tsumura Y, Takahashi T, Akashi M, et al. Multi-center retrospective study of patients with food protein-induced enterocolitis syndrome provoked by hen's egg. *J Allergy Clin Immunol Pract* 2021;9:547-549.e1.
- Nishino M, Sato S, Nagakura KI, Takahashi K, Asaumi T, Ogura K, et al. Food protein-induced enterocolitis syndrome triggered by egg yolk and egg white. *Pediatr Allergy Immunol* 2021;32:618-21.
- Watanabe Y, Sakai H, Nihei M, Miura K, Kumaki S. Early tolerance acquisition in hen's egg yolk-associated food protein-induced enterocolitis syndrome. *J Allergy Clin Immunol Pract* 2021;9:2120-2122.e2.
- Natsume O, Ohya Y. Recent advancement to prevent the development of allergy and allergic diseases and therapeutic strategy in the perspective of barrier dysfunction. *Allergol Int* 2018;67:24-31.
- Lopes JP, Cox AL, Baker MG, Bunyavanich S, Oriel RC, Sicherer SH, et al. Peanut-induced food protein-induced enterocolitis syndrome (FPIES)

- in infants with early peanut introduction. *J Allergy Clin Immunol Pract* 2021;9:2117-9.
7. Robbins KA, Ackerman OR, Carter CA, Uygungil B, Sprunger A, Sharma HP. Food protein-induced enterocolitis syndrome to peanut with early introduction: a clinical dilemma. *J Allergy Clin Immunol Pract* 2018;6:664-6.
 8. Matsumoto K, Mori R, Miyazaki C, Ohya Y, Saito H. Are both early egg introduction and eczema treatment necessary for primary prevention of egg allergy? *J Allergy Clin Immunol* 2018;141:1997-2001.e3.
 9. Caubet JC, Nowak-Węgrzyn A. Reply: To PMID 21851972. *J Allergy Clin Immunol* 2013;131:242.

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TABLE E1. Demographic characteristics of the study patients

Characteristics	Total (97 cases [88 patients])	Hen's egg (41/97, 42%) (EY: 33 cases; EW: 2 cases; whole egg: 6 cases)	Cow's milk (22/97, 23%)	Soy (11/97, 11%)	Wheat (9/97, 9%)	Rice (4/97, 4%)	Others (10/97, 10%) (fish: 3 cases; quail's egg: 3 cases; clam, almond, chickpeas, persimmon: 1 case each)
Sex (male) (%)	53% (47/88) [§]	56% (23/41)	55% (12/22)	36% (4/11)	78% (7/9)	50% (2/4)	30% (3/10)
The median age at onset (mo) (IQR)*	7 (6-9)	8 (7-9)	1 (0-4.75)	6 (6-7.5)	8 (7-8)	5 (5-5.25)	42 (17.25-57)
Multiple triggers (%)	10% (9/88) [§]	15% (6/41)	14% (3/22)	36% (4/11)	33% (3/9)	0% (0/5)	50% (5/10)
Other allergic diseases [†]							
Eczema (%)	25% (22/88) [§]	32% (13/41)	23% (5/22)	9% (1/11)	33% (3/9)	0% (0/4)	0% (0/10)
Asthma (%)	2% (2/88) [§]	5% (2/41)	0% (0/22)	0% (0/11)	0% (0/9)	0% (0/4)	0% (0/10)
Symptoms							
Repetitive vomiting (%)	100% (97/97)	100% (41/41)	100% (22/22)	100% (11/11)	100% (9/9)	100% (4/4)	100% (10/10)
Extreme lethargy (%)	77% (75/97)	81% (33/41)	64% (14/22)	91% (10/11)	78% (7/9)	100% (4/4)	70% (7/10)
Marked pallor (%)	65% (63/97)	68% (28/41)	50% (11/22)	73% (8/11)	67% (6/9)	50% (2/4)	80% (8/10)
Diarrhea (%)	43% (42/97)	32% (13/41)	64% (14/22)	73% (8/11)	44% (4/9)	50% (2/4)	10% (1/10)
Hypotension (%)	2% (2/97)	2% (1/41)	5% (1/22)	0% (0/11)	0% (0/9)	0% (0/4)	0% (0/10)
Hypothermia (%)	2% (2/97)	2% (1/41)	5% (1/22)	0% (0/11)	0% (0/9)	0% (0/4)	0% (0/10)
Hyperthermia (%)	12% (12/97)	12% (5/41)	27% (6/22)	0% (0/11)	11% (1/9)	0% (0/4)	0% (0/10)
Blood stool (%)	6% (6/97)	2% (1/41)	14% (3/22)	18% (2/11)	0% (0/9)	0% (0/4)	0% (0/10)
Acute treatments (97 cases)							
Emergency department visit (%)	56% (54/96)	68% (28/41)	64% (14/22)	36% (4/11)	63% (5/8)	50% (2/4)	10% (1/10)
Intravenous fluid support (%)	35% (34/97)	22% (9/41)	64% (14/22)	27% (3/11)	11% (1/9)	75% (3/4)	40% (4/10)
Laboratory data [‡]							
Positive for specific IgE (%)	35% (31/89)	51% (21/41)	43% (9/21)	0% (0/11)	11% (1/9)	0% (0/4)	0% (0/3)
Positive skin prick test (%)	0% (0/4)	—	—	—	—	—	0% (0/4)

EW, Egg white; EY, egg yolk; IQR, interquartile range.

*The median age at onset in patients with cow's-milk food protein–induced enterocolitis syndrome (FPIES) was earlier than in patients with hen's-egg FPIES, soy FPIES, and wheat FPIES ($P < .001$). The median age at onset in patients with rice FPIES was earlier than in patients with hen's-egg FPIES ($P = .001$), wheat FPIES ($P = .004$), and soy FPIES ($P = .04$). The median age at onset in patients with soy FPIES was earlier than in patients with hen's-egg FPIES ($P = .002$) and wheat FPIES ($P = .02$). The Mann-Whitney U test was used for analyses.

[†]The number of patients diagnosed based on the initial medical history and examination findings.

[‡]A specific IgE antibody titer in serum higher than 0.35 UA/mL or a wheal diameter larger than 3 mm in the skin prick test was considered positive. Hen's-egg specific IgE antibodies were considered positive when causative antigen specific IgE antibodies were 0.35 UA/mL or higher. For each individual patient, the maximum values measured during the study observation period were adopted.

[§]The denominator shows the number of patients. The other denominators show the number of cases.

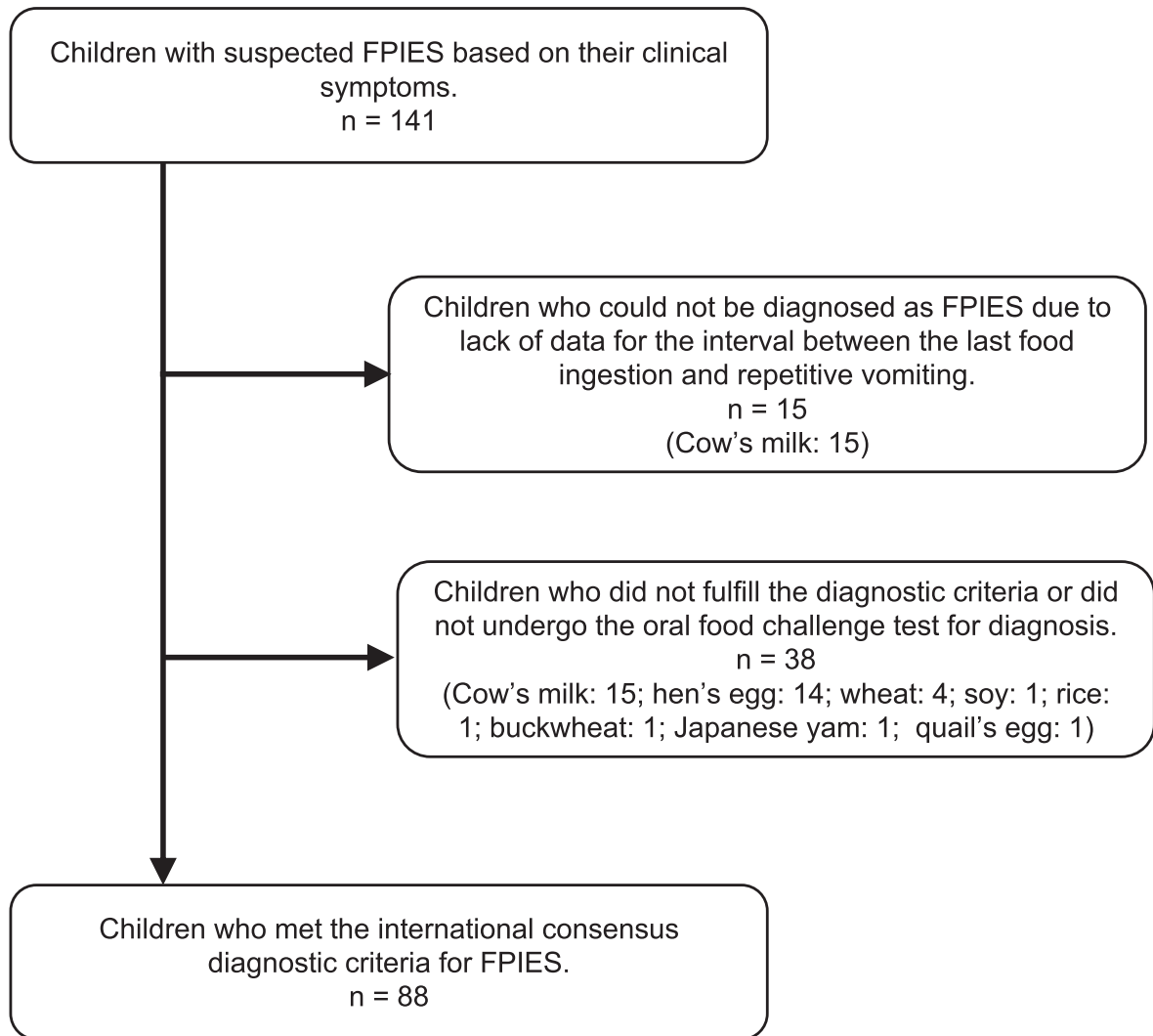


FIGURE E1. Flowchart of the study population. A total of 141 patients were suspected of food protein–induced enterocolitis syndrome (FPIES) based on their clinical symptoms. Among them, 15 patients could not be diagnosed as having FPIES because of a lack of data for the interval between the last food ingestion and repetitive vomiting, and 38 patients did not fulfill the diagnostic criteria or did not undergo the oral food challenge test for diagnosis. A total of 88 patients were diagnosed as having FPIES who met the international consensus diagnostic criteria.