

DR MAKOTO NISHINO (Orcid ID : 0000-0002-5381-8848)

DR SAKURA SATO (Orcid ID : 0000-0003-3674-0759)

DR KYOHEI TAKAHASHI (Orcid ID : 0000-0003-1220-7386)

MR TOMOYUKI ASAUMI (Orcid ID : 0000-0002-7464-5421)

DR MOTOHIRO EBISAWA (Orcid ID : 0000-0003-4117-558X)

DR NORIYUKI YANAGIDA (Orcid ID : 0000-0001-9643-744X)

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Food protein-induced enterocolitis syndrome triggered by egg yolk and egg white

Makoto Nishino^{1,2} | Sakura Sato^{2,3} | Ken-ichi Nagakura^{1,4} | Kyohei Takahashi^{1,2} | Tomoyuki Asaumi¹ | Kiyotake Ogura¹ | Motohiro Ebisawa³ | Noriyuki Yanagida¹

¹Department of Pediatrics, National Hospital Organization Sagamihara National Hospital, Kanagawa, Japan

²Course of Allergy and Clinical Immunology, Juntendo University Graduate School of Medicine, Tokyo, Japan

³Department of Allergy, Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagamihara National Hospital, Kanagawa, Japan

⁴Department of Pediatrics, Jikei University School of Medicine, Tokyo, Japan

Running title: FPIES due to egg yolk and egg white

Correspondence to:

Noriyuki Yanagida

Department of Pediatrics

National Hospital Organization Sagamihara National Hospital

18-1, Sakuradai, Minami-ku, Sagamihara

Kanagawa 252-0392, Japan

Email: sagami@foodallergy.jp

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Key message: In contrast to IgE-mediated egg allergy, in which egg white induces symptoms, many patients with egg-induced FPIES react only to egg yolk. Performing egg white OFCs in these patients may help prevent unnecessary avoidance of egg white.

To the Editor,

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated food allergy. Acute FPIES is characterized by emesis 1–4 h after ingestion of a certain food.¹ The prevalence of acute FPIES due to hen's egg (HE-FPIES) is reported to be much less common than FPIES due to cow's milk, and the onset of symptoms usually occurs in infancy when eggs are introduced into the diet.^{2,3} While previous reports have confirmed that patients with HE-FPIES react to whole eggs, whether they were reactive to egg white (EW) or egg yolk (EY) remains unclear.^{4,5} This study aimed to specifically evaluate whether children diagnosed with HE-FPIES are reactive to EY or EW by performing oral food challenges (OFCs).

We enrolled Japanese infants who visited our hospital from August 2018 to January 2020 and were diagnosed with HE-FPIES based on their history of egg-induced symptoms. Diagnosis of HE-FPIES was made according to the diagnostic criteria proposed in the international consensus guidelines for the diagnosis and management of FPIES.¹ Serum-specific IgE (sIgE) levels for EW, EY, and ovomucoid were measured at the first visit using ImmunoCAP (Thermo Fisher Scientific/Phadia, Uppsala, Sweden).

The infants enrolled in this study were subjected to OFCs with EY and EW. EY OFCs were performed with EY separated immediately from an egg boiled for 15 min. We initially performed EY OFC with 2 g of EY (333 mg of EY protein); if no symptoms were induced, an OFC with one whole EY (3000 mg of EY protein) was performed within 1 month. EW OFCs were performed within 3 months of the last EY OFC. EW was separated from a whole egg and boiled for 20 min. It was then freeze dried to form EW powder (Kewpie Co. Ltd., Tokyo, Japan). Initial EW OFC was performed with EW powder equivalent to 1/20 of an egg (180 mg of EW protein). If no symptoms were induced, we proceeded to perform an OFC with EW powder equivalent to 1/4 of an egg (900 mg of EW protein). Infants with an apparent episode of EY-induced emesis within 3 months of the first visit were considered to be reactive to EY; they were subjected to only EW OFCs. All OFCs were performed with a single dose in the hospital under the supervision of a physician; the patients were observed for at least 5 h after ingestion. The OFCs were classified as positive when emesis occurred 1–4 h after ingestion and no IgE-mediated skin and/or respiratory symptoms were observed. The study was approved by the ethics committee of National Hospital Organization Sagamihara National Hospital (approval no. 2018-046), and written informed consent was obtained from each patient's guardian.

A total of 12 patients were enrolled, and OFCs were performed as required. Six patients did

not receive an EY OFC because they had experienced an apparent reaction to EY within the previous 3 months. One patient was excluded after the EW OFC owing to a suspected IgE-mediated egg allergy. The patient had EW and ovomucoid sIgE levels of 18.0 and 11.0 kU_A/L, respectively. She reacted to the EY OFC with emesis but developed IgE-mediated skin and respiratory symptoms during the EW OFC. Of the remaining 11 patients, nine reacted to EY alone, one reacted to EW alone, and one reacted to both EY and EW.

The patient characteristics, including symptoms before diagnosis, are shown in Table 1. Seven patients (64%) had atypical FPIES, with median EW and EY sIgE of 2.63 (0.16–4.55) and 0.38 (< 0.1–0.97) kU_A/L, respectively. In this study, 8 patients had consumed only EY and 3 had consumed both EY and EW before the first symptomatic episode. The 8 patients who had consumed only EY reacted with emesis only to EY, whereas of the 3 patients who had consumed both EY and EW, one reacted to EY, one reacted to EW, and one reacted to both EY and EW (Table 2). In the positive OFCs, emesis occurred at a median of 135 min after ingestion. Symptoms observed during the OFCs are shown in Table 2.

In this study, we found that many of the Japanese infants with HE-FPIES reacted only to EY, although one patient reacted only to EW and another reacted to both EW and EY. In previous reports, most patients with HE-FPIES have been diagnosed based on their reactivity to whole egg or to EY or EW alone.⁴⁻⁸ Three patients with HE-FPIES have previously been evaluated with OFCs using boiled EY and EW. All three patients reacted to EY but not to EW.⁹ Evaluating reactivity to EY and EW separately may be useful in children with HE-FPIES, thereby enabling them to consume foods that do not contain the egg antigen to which they react.

Notably, we also found that ingestion of the antigen before the first symptomatic episode may be necessary for FPIES to develop. The 8 patients who had not consumed EW before the first episode of symptoms did not react to EW, whereas of the 3 patients who had consumed EW, 2 reacted to EW. However, further studies with a larger number of patients would be needed before drawing conclusions.

A limitation of the study is that the EW OFCs were performed with a maximum dose of 1/4 of an egg, which leaves the possibility that patients with a negative EW OFC may actually be reactive to larger amounts. We chose this maximum dose to ensure that infants as young as 7 months could consume the dose and because infants rarely consume food products containing only EW that exceeds this amount. Another limitation is that there was a maximum interval of 3 months between the EY and EW OFCs. Since majority of patients with HE-FPIES are known to

resolve by 5 years of age, a few may have resolved during the interval.¹⁰ In addition, as 64% of the patients were sensitized to egg, it can be argued that they had IgE-mediated egg allergy presenting with gastrointestinal symptoms. However, all patients met the diagnostic criteria, and delayed emesis was observed in those with positive OFCs. Hsu and Mehr⁵ have reported that two of the four patients with HE-FPIES were sensitized to EW, which is comparable to the prevalence of sensitization observed in our study.

In conclusion, symptoms of HE-FPIES were induced by EY in most of the Japanese infants in our study. Performing EW OFCs on EY-reactive patients with HE-FPIES may be useful in preventing unnecessary avoidance of EW, especially in patients who have not consumed EW before the first symptomatic episode. Further studies from other countries with different ways of introducing hen's egg to infants are necessary because the percentage of HE-FPIES patients reactive to EY and/or EW may differ from that found in our study.

Makoto Nishino^{1,2}, MD; Sakura Sato^{2,3}, MD; Ken-ichi Nagakura^{1,4}, MD, PhD; Kyohei Takahashi^{1,2}, MD; Tomoyuki Asaumi¹, MD; Kiyotake Ogura¹, MD; Motohiro Ebisawa³, MD, PhD; Noriyuki Yanagida¹, MD

¹Department of Pediatrics, National Hospital Organization Sagamihara National Hospital, Kanagawa, Japan

²Course of Allergy and Clinical Immunology, Juntendo University Graduate School of Medicine, Tokyo, Japan

³Department of Allergy, Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagamihara National Hospital, Kanagawa, Japan

⁴Department of Pediatrics, Jikei University School of Medicine, Tokyo, Japan

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Table 1. Characteristics of the patients with food protein-induced enterocolitis syndrome due to hen's egg

	N = 11
Male, n (%)	5 (45%)
Age of onset (months)	8 (7–10)
Age at first visit (months)	10 (7–22)
Total IgE (IU/L)	12.7 (<5–84.6)
EW sIgE (kU _A /L)	0.16 (<0.10–7.27)
EY sIgE (kU _A /L)	<0.10 (<0.10–1.86)
Ovomucoid sIgE (kU _A /L)	<0.10 (<0.10–0.56)
Complications, n (%)	
Atopic dermatitis	5 (45%)
Recurrent wheezing	0 (0%)
Other food allergy †	2 (18%)
Egg-induced FPIES reactions before diagnosis	
Vomiting 2-4 hours after consumption of food containing egg	11 (100%)
Two or more episodes of vomiting after eating the same food	7 (64%)
Vomiting 1-4 hours after eating 2 or more different foods	5 (45%)
Number of vomiting episodes	2 (2-3)
Extreme lethargy	10 (91%)
Marked pallor	5 (45%)
Diarrhea	7 (64%)
Hypotension	0 (0%)
Hypothermia	0 (0%)
IgE-mediated skin and/or respiratory symptoms	0 (0%)
Required visit to emergency department	3 (27%)
Required intravenous fluid support	2 (18%)

Data are shown as n (%) or median (range)

† Other food allergy includes one patient with IgE-mediated cow's milk allergy, and one patient with FPIES due to soybean.

EW, egg white; EY, egg yolk; FPIES, food protein-induced enterocolitis syndrome; sIgE, specific IgE

Table 2. Relationship between egg yolk and egg white consumption before the first symptomatic episode and oral food challenge results

Patient	EY ingestion before initial symptoms	EW ingestion before initial symptoms	EY OFC result	EW OFC result
1	+	–	N/A [†]	–
2	+	–	N/A	–
3	+	–	N/A	–
4	+	–	N/A	–
5	+	–	N/A	–
6	+	–	N/A	–
7	+	–	Vomit × 6, lethargy (Onset: 117 min)	–
8	+	–	Vomit × 7, pallor, lethargy, diarrhea (Onset: 140 min)	–
9	+	+	Vomit × 3, pallor (Onset: 135 min)	–
10	+	+	Vomit × 5, lethargy (Onset: 135 min)	Vomit× 8, lethargy (Onset: 150 min)
11	+	+	–	Vomit× 4 (Onset: 190 min)

[†] OFCs with EY were not performed in patients 1–6 because they were considered to be reactive to EY due to an apparent episode of EY consumption-induced emesis at home within 3 months of

the first visit.

EY, egg yolk; EW, egg white; N/A, not applicable; OFC, oral food challenge