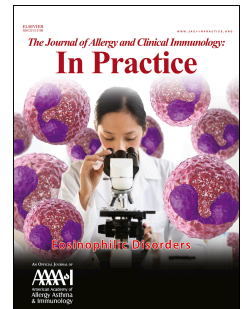


Journal Pre-proof

Early tolerance acquisition in hen's egg yolk-associated food protein-induced enterocolitis syndrome

Yohei Watanabe, MD, PhD, Hideyuki Sakai, MD, Masato Nihei, MD, Katsushi Miura, MD, PhD, Satoru Kumaki, MD, PhD



PII: S2213-2198(21)00043-X

DOI: <https://doi.org/10.1016/j.jaip.2020.12.053>

Reference: JAIP 3363

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 19 September 2020

Revised Date: 18 December 2020

Accepted Date: 18 December 2020

Please cite this article as: Watanabe Y, Sakai H, Nihei M, Miura K, Kumaki S, Early tolerance acquisition in hen's egg yolk-associated food protein-induced enterocolitis syndrome, *The Journal of Allergy and Clinical Immunology: In Practice* (2021), doi: <https://doi.org/10.1016/j.jaip.2020.12.053>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2021 American Academy of Allergy, Asthma & Immunology

Title: Early tolerance acquisition in hen's egg yolk-associated food protein-induced enterocolitis syndrome

Yohei Watanabe, MD, PhD¹⁾, Hideyuki Sakai, MD¹⁾, Masato Nihei, MD¹⁾²⁾, Katsushi Miura, MD, PhD²⁾, and Satoru Kumaki, MD, PhD¹⁾

1) Department of Pediatrics, Sendai Medical Center, Sendai, Japan

2) Department of Allergy, Miyagi Children's Hospital, Sendai, Japan

Correspondence should be addressed to:

Yohei Watanabe

Department of Pediatrics, Sendai Medical Center, 2-11-12, Miyagino, Miyagino-ku, Sendai, 983-8520, Japan

watanabe.yohei.mv@mail.hosp.go.jp

Tel: +81 022 293 1111 Fax: +81 022 291 8114

Email address:

Yohei Watanabe, watanabe.yohei.mv@mail.hosp.go.jp; Hideyuki Sakai, sakai.hideyuki.nf@mail.hosp.go.jp; Masato Nihei, nihei.masato@rouge.plala.or.jp; Katsushi Miura, kmiura@miyagi-children.or.jp; Satoru Kumaki, kumaki.satoru.zh@mail.hosp.go.jp,

Funding sources & COI

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors declare no conflicts of interest associated with this manuscript.

Key words: allergy, non-IgE mediated allergy, hen's egg, egg white, tolerance

Clinical Implication

Our study demonstrated early tolerance acquisition in patients with egg yolk-associated food protein-induced enterocolitis syndrome. We propose the first evaluation of tolerance acquisition earlier than 12months after diagnosis or the most recent reaction, and an early introduction of egg white.

Hen's egg-associated food protein-induced enterocolitis syndrome (FPIES) (hen's egg-FPIES) is not a rare disease^(1, 2). However, the precise mechanism such as which part of the egg—the egg white or egg yolk—triggers FPIES and its clinical course have not been fully understood. Three case reports⁽³⁻⁵⁾ and the most recently published case series⁽⁶⁾ have described the characteristics of patients with egg yolk-associated FPIES (egg yolk-FPIES). Shimomura⁽³⁾ and Toyama⁽⁶⁾ demonstrated that egg yolk-FPIES is distinctly triggered by egg yolk but not by egg white, and that it is the main form of hen's egg-FPIES. However, its clinical course, especially with respect to the age of tolerance acquisition, is still not fully elucidated. Here, we report the characteristics and clinical courses of patients with egg yolk-FPIES and discuss better practices of managing the disease.

Fourteen patients with egg yolk-FPIES, treated at Sendai Medical Center from April 2014 to January 2019, were enrolled in this study. We investigated the clinical symptoms, blood test results, tolerability to egg white, and tolerance acquisition of egg yolk in these patients. The protocol of the oral food challenge (OFC) and measuring laboratory data were described in the Online Repository. This study was approved by the ethics committee of Sendai Medical Center (approval number: RIN 30-2).

Of the 14 patients with egg yolk-FPIES, 8 (57.1%) met the criteria of international consensus guidelines⁽⁷⁾, and the other 6 (42.9%) were diagnosed based on positive OFC results exhibiting delayed abdominal reactions after consuming egg yolk. The patients' characteristics are summarized in Table 1. The median ages at onset and diagnosis were 8 [interquartile range (IQR): 8–9] and 10.5 (IQR: 9–12) months, respectively. At a median of 7.5 months (IQR: 6.0–11.5) after complete elimination of egg yolk, 13 patients underwent an egg yolk OFC for the evaluation of tolerance acquisition and one patient attempted to consume egg yolk at home (Figure 1). Nine of 14 patients (64.3%) tolerated the full dose of boiled egg yolk by the median age of 18 months (range: 12–24) [early tolerance acquisition (ET) group] and at a median of 7 months after complete elimination. They could subsequently consume a whole egg yolk at home. Five patients (35.7%) did not pass the first OFC and were required to continue the complete elimination of egg yolk [non-early tolerance acquisition (non-ET) group]. A median age of 14 months after the first failed OFC (IQR: 10.8–20.3, range: 7–33), four of them underwent a second OFC, but all of them failed the OFC again (Figure 1). We compared the clinical characteristics and laboratory data of 9 patients in the ET group with those of 5 patients in the non-ET group (Table E1). The proportion of male patients (55.6%) in

the ET group was significantly higher than that (0%) in the non-ET group ($p < 0.05$, chi-square test). Between the ET and non-ET groups, there were no significant differences in the rates of egg yolk-specific IgE positivity. These results are different from those reported previously⁽²⁾ which indicated that patients with atypical FPIES are more likely to have a persistent disease. Further studies are needed to clarify the factors influencing patient prognosis.

In our study, 64.3% of the patients achieved remission by the age of 2 years at a median of 7 months after diagnosis or the most recent reaction. Tolerance of egg yolk in children with egg yolk-FPIES in our cohort was achieved early childhood, similar to reported resolution rates in cow's milk- and soy-associated FPIES^(8, 9). Therefore, we suggest that the duration from the most recent reaction to the first egg yolk OFC for tolerance evaluation should be set between 6 and 12 months, which is earlier than that recommended in the United States (12 to 18 months)⁽⁷⁾.

In contrast, most patients in the non-ET group failed the series of OFCs, and some of them were compelled to undergo long-term elimination. Thus, if the first OFC is positive, then it is better to set a longer interval than the recommended 12 to 18 months in the subsequent OFC.

Egg white OFCs were performed before tolerance acquisition of egg yolk in 5

patients who consented to the plan (Group 1). If not, the OFCs were performed after tolerance acquisition of egg yolk (Group 2). In both groups, no patients exhibited any delayed abdominal reactions to egg white (Table E₂). A total of three patients with positive egg white-specific IgE exhibited immediate reactions to boiled egg white in the OFCs. The other 11 patients could pass the OFCs and increase the amount of egg white consumed at home except for one patient, with positive IgE, exhibiting urticaria after consuming an insufficiently heated whole egg product at home.

Similar to the previous reports^(3, 6), no FPIES responses to egg white occurred among the patients with egg yolk-FPIES in the present study. The reactions caused by egg white were only immediate reactions in the patients who tested positive for egg white-specific IgE. This finding indicates that a large proportion of patients with egg yolk-FPIES, especially those who test negative for egg white-specific IgE, can consume egg white safely.

The limitation of this study was that there were differences in each patient's timing when the OFC was performed to evaluate the tolerance acquisition to egg yolk. A targeted study to determine firm resolution is needed.

In conclusion, our study demonstrates that approximately two-thirds of the

patients with egg yolk-FPIES achieved tolerance by the age of 2 years at a median of 7 months after diagnosis or the most recent reaction. This was earlier than the recommended timing of OFCs of 12 to 18 months. To avoid unnecessary elimination of hen's egg in patients with egg yolk-FPIES, we suggest an earlier evaluation of tolerance acquisition based on OFCs and the introduction of egg white.

Acknowledgements

We thank Dr. Miki Morikawa at Morikawa Pediatrics & Allergy Clinic and Dr. Takanori Minoura at Kid's Clinic Tago, who referred several patients with egg yolk-FPIES to our facility.

(references)

1. Hsu P, Mehr S. Egg: a frequent trigger of food protein-induced enterocolitis syndrome. *The Journal of allergy and clinical immunology*. 2013;131(1):241-2.
2. Caubet JC, Ford LS, Sickles L, Jarvinen KM, Sicherer SH, Sampson HA, et al. Clinical features and resolution of food protein-induced enterocolitis syndrome: 10-year experience. *The Journal of allergy and clinical immunology*. 2014;134(2):382-9.
3. Shimomura M, Tanaka H, Meguro T, Kimura M. Three cases of food protein-induced enterocolitis syndrome caused by egg yolk. *Allergology international : official journal of the Japanese Society of Allergology*. 2018.
4. Arik Yilmaz E, Cavkaytar O, Uysal Soyer O, Sackesen C. Egg yolk: an unusual trigger of food protein-induced enterocolitis syndrome. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology*. 2014;25(3):296-7.
5. Doi M, Matsubara Y, Iwakoshi N, Furuichi Y. Food protein-induced enterocolitis syndrome caused by egg yolk in an infant. *Pediatrics international : official journal of the Japan Pediatric Society*. 2019.
6. Toyama Y, Ishii T, Morita K, Tsumura Y, Takahashi T, Akashi M, et al. Multicenter retrospective study of patients with food protein-induced enterocolitis syndrome provoked by hen's egg. *The journal of allergy and clinical immunology In practice*. 2020.
7. Nowak-Wegrzyn 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. *The Journal of allergy and clinical immunology*. 2017;139(4):1111-26.e4.
8. Katz Y, Goldberg MR, Rajuan N, Cohen A, Leshno M. The prevalence and natural course of food protein-induced enterocolitis syndrome to cow's milk: a large-scale, prospective population-based study. *The Journal of allergy and clinical immunology*. 2011;127(3):647-53.e1-3.
9. Hwang JB, Sohn SM, Kim AS. Prospective follow-up oral food challenge in food protein-induced enterocolitis syndrome. *Archives of disease in childhood*. 2009;94(6):425-8.

144

Title of Table1: Characteristics of the patients with egg yolk-FPIES

Total, n	14
Male, n (%)	5 (35.7)
Onset, month	8 (8 - 9) [†]
Diagnose, month	10.5 (9 - 12) [†]
Median dose of boiled egg yolk for evoking symptoms, gram	5 (2 - 7.5) [†]
Family history of atopic disease, n (%)	3 (21.4) [†]
Past history of allergy disease	
Atopic disease, n (%)	8 (57.1)
Food allergy, n (%)	0 (0)
Past normal consumption of egg yolk, n (%)	12 (85.7)
Vomiting after consumption of other foods [‡] , n (%)	3 (21.4)
Symptoms	
Delayed vomiting, n (%)	14 (100)
Diarrhea, n (%)	2 (14.3)
Fever, n (%)	4 (28.6)
Gross bloody feces, n (%)	0 (0)
Pallor, n (%)	4 (28.6)
Hypovolemic shock, n (%)	1 (7.1)
Laboratory findings	
Total IgE (IU/ml)	35.03 (6.7 - 44.5) [†]
Eosinophils count, per microliter of blood	204 (5.7 - 41) [†]
Platelets count, per microliter of blood	34.6 (30.4 - 53.2) [†]
Positivity and titer of specific IgE at diagnosis	
Egg yolk, n (%)	5 (35.7) [†]
Titer of egg yolk specific IgE, (kUA/L)	1.15 (0.94 – 1.68) [†]
Egg white, n (%)	6 (42.9)
Titer of egg white specific IgE, (kUA/L)	5.87 (2.47 – 10.55)
Ovomucoid, n (%)	5 (35.7)
Titer of ovomucoid specific IgE, (kUA/L)	0.46 (0.13 – 1.60)
SI of egg yolk ALST	5.31 (2.97 - 5.42) ^{† ‡}

145

146

SI, Stimulation index; ALST, allergen-specific lymphocyte stimulation test

147

[‡] Offending foods are fish, wheat, and both milk and fish in each patients (not

148 validated as FPIES based on an OFC). †, Values are shown as median (interquartile
149 range); ¶, This date was shown as percentage per 13 patients; ‡ The date from 10
150 patients is shown

151 **Figure legend**

152 Figure 1. Flow chart for evaluating the patients with egg yolk-FPIES.

153

Journal Pre-proof

Online Repository

Oral food challenge

OFCs were performed openly under the physicians' supervision at Sendai Medical Center. The administered dose of well-boiled egg yolk was approximately 5 g (ranging from 0.5 to 15 g, where a whole egg yolk was defined as 15g) for each patient. The food was administered at once or divided into 3 portion (1/10, 3/10, and the rest) with 30-minute' intervals. After the diagnosis of egg yolk-FPIES, the patients continued complete elimination of egg yolk, and 5 of them underwent egg white OFCs before tolerance acquisition of egg yolk. Several months after diagnosis or the most recent reaction, tolerance acquisition of egg yolk was evaluated based on OFCs. OFCs were considered positive for FPIES if delayed abdominal reactions were observed. If immediate reactions occurred, the results of the OFCs were regarded as positive for a conventional IgE-dependent food allergy. If no reaction was observed, the amounts of hen's egg were gradually increased at home. The definition of tolerance acquisition of egg yolk was the ability to consume a whole boiled egg yolk in this study.

Measurement of serum-specific IgE, and the allergen-specific lymphocyte

stimulation test

Each serum-specific IgE (sIgE) level of egg yolk, egg white, and ovomucoid was measured using the ImmunoCAP assay system (Thermo Fisher Scientific, Uppsala, Sweden) and defined as positive for sIgE levels higher than 0.35 kUA/L. The allergen-specific lymphocyte stimulation test (ALST) was conducted, and the results of which were commercially measured by SRL Inc. (Tokyo, Japan) using crude boiled egg yolk extract. The stimulation index (SI) was measured and presented as a ratio of scintillation counts of egg yolk-stimulated mononuclear cells to those of non-stimulated cells.

Title of Table E1: Comparison of early and non-early tolerance acquisition groups.

	ET group (n=9)	non-ET group (n=5)	P value
Median age undergoing 1 st OFC for tolerance evaluation, month	18	24	0.364 [†]
Median duration [§] of elimination diet to 1 st OFC for tolerance evaluation, month	7	8	0.282 [†]
Male, n	5	0	0.038 [‡]
Onset, month	9	8	0.059 [†]
Diagnosis, month	10	14	0.502 [†]
Family history of AD, n	2	2	0.481 [‡]
Past history			
AD, n	5	3	0.872 [‡]
Food allergy, n	0	0	NA
FPIES with multiple trigger, n	1	2	0.207 [‡]
Eosinophils, counts [¶]	170	300	0.384 [†]
Platelet, counts [¶]	35.4	32.5	0.589 [†]
Total IgE, IU/ml	25	9	0.386 [†]
Positive with Egg yolk specific IgE at diagnosis, n	4	1	0.360 [‡]
Median SI of egg yolk ALST	3.07	7.00	0.053 [†]

ET group, early tolerance acquisition group; non-ET group, non-early tolerance acquisition group; OFC, oral food challenge; AD, atopic dermatitis; FPIES, food protein induced enterocolitis syndrome; SI, stimulation index; ALST, allergen-specific lymphocyte stimulation test ; NA, not applicable

§ duration from diagnosis or the most recent reaction to 1st OFC for evaluating tolerance; ¶ per microliter of blood; † Mann-Whitney U test; ‡ Chi-square test; ¶ n=7 (ET group), n=3 (non-ET group)

Title of Table E2: Introduction of egg white in the patients with egg yolk-FPIES

Patients [¶]	Age undergoing egg white OFC (month)	Titer of egg white specific IgE (kUA/L) ^Ψ	Administered dose of boiled egg white (g)	Immediate reaction	FPIES reaction
Group 1 (n=5)					
#1	24	<0.35	2	(-)	(-)
#2	24	<0.35	2	(-)	(-)
#3	32	3.26	2	rash, abdominal pain	(-)
#4	36	7.09	2	(-)	(-)
#5	57	99.7	0.5	cough, wheezing	(-)
Group 2 (n=9)					
#6	16	11.7	2	(-)	(-)
#7	16	<0.35	2	(-)	(-)
#8	16	<0.35	2	(-)	(-)
#9	18	4.64	1	urticaria	(-)
#10	21	15.8	2	(-)	(-)
#11	21	<0.35	2	(-)	(-)
#12	28	<0.35	2	(-)	(-)
#13	40	<0.35	2	(-)	(-)
#14	70	<0.35	Not measured [§]	(-)	(-)

¶ Each patients in Group 1 don't include those in Group 2. Ψ The titer which was measured most recently in the egg white OFC was shown. § In this patient, egg white was introduced at home.