Early diagnosis and intervention induce early tolerance in egg yolk-associated FPIES.

YUKA OKURA[1], Masaki Shimomura[1], Yutaka Takahashi[1], and Ichiro Kobayashi[1]

[1]KKR Sapporo Medical Center

January 18, 2022

To the Editor,

Food protein-induced enterocolitis syndrome (FPIES) is a non-immunoglobulin E (IgE) mediated food allergy that predominantly affects infants and is characterized by repetitive vomiting that occurs 1–4 h after the ingestion of causative food. The etiology and underlying mechanisms of FPIES are not well understood. Recently, egg yolk (EY) has been recognized as a major causative food of FPIES.[1,2] Most FPIES patients achieve tolerance with age;[3] however, the practice management of EY-associated FPIES (EY-FPIES) has yet to be established. In a preliminary analysis of EY-FPIES, we found that the patients who acquired tolerance to EY had been diagnosed at a significantly younger age than non-tolerated patients despite no difference in the age of onset between both patients. This suggested that the early diagnosis and intervention is beneficial for tolerance acquisition in EY-FPIES. To investigate this further, we compared clinical outcomes between the early and late diagnosis of EY-FPIES.

The present study enrolled 21 patients with EY-FPIES (1) diagnosed by positive oral food challenge (OFC) tests at our hospital between April 2018 and April 2021 who (2) subsequently underwent OFC to evaluate tolerance acquisition (re-OFC) at least once. The open OFC was performed by ingestion of a single dose once or three divided doses every 30 minutes. OFC was considered positive for FPIES based on delayed abdominal reactions without immediate skin or respiratory reactions. After confirmation by OFC, we instructed all patients to continue complete elimination of EY, regardless of threshold doses of OFC. We retrospectively collected data from electronic medical records on sex, age of first ingestion of EY, disease onset, first visit to our hospital, diagnosis, specific IgE (sIgE) to EY measured by ImmunoCAP test at diagnosis, asymptomatic histories of EY consumption before onset, the number of symptomatic episodes before diagnosis, the period between the first ingestion of EY and diagnosis of EY-FPIES, and age of tolerance acquisition. Tolerance acquisition was defined by (1) negative OFC and (2) the ability of daily EY consumption without FPIES reactions for three months at home. We divided the patients into the following two groups according to their age at the time of diagnosis: the early diagnosis (ED) group (<12 months) and the late diagnosis (LD) group ([?]12 months), and compared the clinical features between both groups. A sIgE value higher than 0.35 U_A/ml was defined as positive. Statistical analyses were performed using GraphPad Prism 9. The Mann-Whitney U test was used to compare nonparametric independent samples between the groups. Tolerance acquisition during follow-up was analyzed using a Kaplan–Meier survival curve and the log-rank test. P-value <0.05 was considered statistically significant. This study was approved by the Institutional Review Board of the KKR Sapporo Medical Center (2021-06).

Patients' characteristics are shown in Table 1. The ED group consisted of 12 patients (57.1%), 10 (83.3%) of whom acquired tolerance to EY, and the LD group consisted of nine patients (42.9%), three (33.3%) of whom acquired tolerance to EY. Among 21 patients with EY-associated FPIES, a total of 35 re-OFCs were performed, with a median interval of seven months (interquartile range [IQR], 6–11 months) (Figure 1). The median ages that re-OFC proved negative in ED and LD groups were 16 and 26 months, respectively (p =

0.014) (Table 1). The time to tolerance acquisition was significantly longer in the LD group than that in the ED group, as shown in the Kaplan–Meier analysis (log-rank, p = 0.0015) (Figure 2). The median ages of onset and first visit to our hospital were significantly younger in the ED group than those in the LD group (Table 1). All patients had a history of three episodes (IQR 2–6) of asymptomatic consumption before onset. Although the median age of the first introduction of EY in the ED group was younger than that in the LD group (six months vs. eight months, p = 0.004), there was no significant difference in the median number of asymptomatic consumptions before onset and the period between the first introduction and onset between the groups. The period between the first introduction of EY and FPIES diagnosis was shorter in the ED group than that in the LD group (2.5 months vs. 7 months, p = 0.0002).

We demonstrated that the ED group achieved tolerance at a higher rate than the LD group, suggesting that early diagnosis and intervention predict favorable prognosis in EY-FPIES. Consistent with a previous report,[4] all patients with EY-FPIES had histories of asymptomatic consumption before disease onset. Involvement of both innate and adaptive immunities with resultant proinflammatory cytokine production has been suggested in the pathology of acute FPIES.[5] Our results suggest that the development of EY-FPIES requires sensitization of the adaptive immune system. T helper (Th)2 and Th17 cells are considered as key players of the immune response in FPIES,[6] which is reflected by local infiltration of eosinophils and neutrophils, respectively. Adaptive immunity of infants shows dynamic changes with a rapid decline of regulatory T cells and maturation of Th17, while Th2 dominance is preserved.[7] Additionally, the intestinal barrier function immaturity was also observed, resulting in a higher permeability of antigens across the intestines.[8] Thus, early infants may be predisposed to FPIES because of immunological as well as anatomical immaturity. Although both ED and LD groups shared a similar interval between the first introduction of EY and onset, the period between the onset and diagnosis in the ED group was significantly shorter than that in the LD group. Our results suggest that an earlier elimination of EY after onset prevents the complete development of EY-FPIES.

The median age at onset in the 21 patients with EY-FPIES was 8 months (IQR, 7–9 months), which is comparable to previous reports.[9] Similar to another report,[9] 13 patients (65.0%) achieved tolerance at the median age of 16 months. This is earlier than the median age reported in a European series that demonstrates a 50% cumulative probability of resolution at the age of 41 months.[10]Notably, the median age of diagnosis is older (12 months) in that study compared with that in our series. Thus, the different clinical courses may attribute to differences in age of diagnosis. Otherwise, the clinical course may depend on ethnicity. In 2017, the Japanese Society of Pediatric Allergy and Clinical Immunology recommended the early introduction of EY to infants with a high risk for IgE-mediated egg allergy. This might have increased the number of early-onset EY-FPIES in Japan. Our results suggest that a first re-OFC seven months after the diagnosis is reasonable for preventing unnecessary food avoidance in EY-FPIES.

Our study is limited by a retrospective review of a small number of patients from a single institute. Additionally, accidental exposures after diagnosis occurred in one patient in the LD group, influencing the scheduling of re-OFC. Moreover, we evaluated solely patients with a confirmational diagnosis by OFC, which might be insufficient to reflect the whole heterogeneity of EY-FPIES.

Conclusively, the ED group achieved tolerance in EY-FPIES earlier compared with the LD group. Early diagnosis and complete elimination of EY may be beneficial for EY-FPIES.

Keywords

food protein-induced enterocolitis syndrome; FPIES; egg yolk; tolerance acquisition; food hypersensitivity; early diagnosis.

Signature

Yuka Okura, M.D., Ph.D.

Masaki Shimomura, M.D.

Yutaka Takahashi, M.D., Ph.D.

Ichiro Kobayashi, M.D., Ph.D.

Department of Pediatrics, KKR Sapporo Medical Center,

Sapporo, Japan

Acknowledgments

We thank all patients who participated in this study. We would like to thank Enago (www.enago.jp) for the English language review.

References

1. Yamamoto-Hanada K, Pak K, Saito-Abe M, et al. Allergy and immunology in young children of Japan: The JECS cohort. *World Allergy Organ J* 2020;13:100479.

2. Lee E, Barnes EH, Mehr S, Campbell DE. An exploration of factors associated with food protein-induced enterocolitis syndrome: Birth, infant feeding and food triggers. *Pediatr Allergy Immunol*2021;32:742-749.

3. Katz Y, Goldberg MR. Natural history of food protein-induced enterocolitis syndrome. *Curr Opin Allergy Clin Immunol*2014;14:229-239.

4. Nishino M, Sato S, Nagakura KI, et al. Food protein-induced enterocolitis syndrome triggered by egg yolk and egg white.*Pediatr Allergy Immunol* 2021;32:618-621.

5. Hoffmann NV, Ahmed A, Fortunato JE. Food protein-induced enterocolitis syndrome: Dynamic relationship among gastrointestinal symptoms, immune response, and the autonomic nervous system. *Ann Allergy Asthma Immunol* 2021;126:498-505.

6. Su KW, Shreffler WG, Yuan Q. Gastrointestinal immunopathology of food protein-induced enterocolitis syndrome and other non-immunoglobulin E-mediated food allergic diseases. *Ann Allergy Asthma Immunol*2021;126:516-523.

7. Kollmann TR, Levy O, Montgomery RR, Goriely S. Innate immune function by Toll-like receptors: distinct responses in newborns and the elderly.*Immunity* 2012;37:771-783.

8. Westrom B, Arevalo Sureda E, Pierzynowska K, Pierzynowski SG, Perez-Cano FJ. The Immature Gut Barrier and Its Importance in Establishing Immunity in Newborn Mammals. *Front Immunol*2020;11:1153.

9. 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.

10. Vazquez-Ortiz M, Machinena A, Dominguez O, et al. Food protein-induced enterocolitis syndrome to fish and egg usually resolves by age 5 years in Spanish children. *J Allergy Clin Immunol Pract*2017;5:512-515.e1.

Figure Legends

Figure 1

Oral food challenge flow diagram showing a cascade of negative and positive results.

ED, early diagnosis; LD, late diagnosis

Figure 2

Kaplan–Meier analysis showing tolerance acquisition over time.

ED, early diagnosis; LD, late diagnosis

Hosted file

`Table 1.xlsx` available at https://authorea.com/users/423043/articles/553105-early-diagnosis-and-intervention-induce-early-tolerance-in-egg-yolk-associated-fpies

Hosted file

`Figure 1.pptx` available at https://authorea.com/users/423043/articles/553105-early-diagnosis-and-intervention-induce-early-tolerance-in-egg-yolk-associated-fpies

Hosted file

`Figure 2.pptx` available at https://authorea.com/users/423043/articles/553105-early-diagnosis-and-intervention-induce-early-tolerance-in-egg-yolk-associated-fpies