

Prognosis of infantile food protein-induced enterocolitis syndrome to wheat: A case series

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To the Editor,

Food protein-induced enterocolitis syndrome (FPIES) is a type of non-IgE-mediated food allergy characterized by repetitive vomiting 1–4 h after ingestion of any food.¹ FPIES is commonly caused by foods such as cow's milk, soy, hen's egg, fish, rice, and oat, varying in prevalence by geographical region; however, wheat-induced FPIES (wheat-FPIES) is relatively rare.^{2–4} In Japan, the incidence of wheat-FPIES has been reported to be increasing, along with FPIES to cow's milk, egg, and soy.⁵ However, to our knowledge, no

study has reported the clinical features and tolerance acquisition of wheat-FPIES. Therefore, this study aimed to describe the clinical characteristics of wheat-FPIES and the prognosis at the age of 5 years.

We retrospectively reviewed children who visited our hospital from May 2012 to July 2018 with a suspected diagnosis of wheat-FPIES. The diagnostic criteria proposed by Nowak-Węgrzyn et al. were used in the study. Infants who either fulfilled the diagnostic criteria based on the history of symptoms or symptoms observed during oral food challenge (OFC) were defined as wheat-FPIES patients.¹ Those who were followed up to age 5 years were included in the study. Wheat- and ω -5-gliadin-specific immunoglobulin E (sIgE) levels were measured using ImmunoCAP (Thermo Fisher Scientific/Phadia, Uppsala, Sweden) at the first visit. Sensitization was defined as a sIgE level of ≥ 0.35 .

All the patients received OFCs with 52 or 390 mg of wheat protein in the form of boiled udon noodles for diagnosis or to confirm tolerance to the amount challenged. Patients who passed their initial OFC proceeded to confirm if they could tolerate 2,600 mg (equivalent to the amount of wheat protein in half a slice of bread) by receiving stepwise OFCs, by gradually increasing the amount consumed at home, or by a combination of the two. Stepwise OFCs were performed by sequentially increasing the dose from 52 mg to 390, 1300, and $\geq 2,600$ mg on separate days when the preceding OFC was negative. When a patient failed any OFC, it was repeated after 6–18 months. The children were considered to have achieved tolerance when they could consume 2,600 mg without any symptoms. All OFCs were performed in the hospital under the supervision of a physician. The challenge amount was administered in a single dose with monitoring for at least 5 hours. OFCs were determined to be positive when vomit was induced after >1 hour, and no IgE-mediated skin or respiratory symptoms were observed.

A total of 11 patients were suspected of having wheat-FPIES. Seven patients fulfilled the diagnostic criteria based on their history of symptoms, of which one patient was excluded because he had only been followed up to the age of 2 years. Of the remaining 4 patients, one presented with repetitive vomiting, lethargy, and pallor during OFC and therefore fulfilled the diagnostic criteria based on symptoms during the OFC. In total, 7 patients were included in the study (Figure 1).

Table 1 presents the characteristics of the 7 patients. The median age at the onset of symptoms was 7 (range: 6–9) months, and the median age at the first visit to our hospital was 13 (range: 8–17) months. The patients had experienced a median of 4 episodes of vomiting before their first visit. Data concerning wheat consumption before the first episode of symptoms was available for 5 patients, and they had all previously consumed wheat without any symptoms. Overall, 2 (29%) patients had comorbid atopic dermatitis, one had IgE-mediated egg allergy, and two had FPIES to a different food. All patients were not sensitized to ω -5-gliadin; however, one patient had a slightly elevated wheat-sIgE level of 0.42 kU_A/L.

Initial OFCs were performed at a median age of 18 (range: 8–45) months. The proportion of patients who became tolerant to wheat increased with age, and at the age of 5 years, 6 (86%) patients were confirmed to have achieved tolerance, and the remaining patient was able to consume 52 mg of wheat protein (Figure 2). The patient sensitized to wheat achieved tolerance at the age of four. The patient who was not confirmed to have achieved tolerance at the age of 5 years had a positive initial OFC to 52 mg at 45 months and underwent a repeat OFC with the same dose at 62 months, which was negative. Whether the patient could consume larger amounts was not examined at the time because he refused to eat during the following OFCs. Among the 6 patients who achieved tolerance, 2 patients gradually increased the amount consumed at home after a negative OFC with 390 mg, 2 patients received stepwise OFCs up to 1,300 mg and then gradually increased the amount consumed at home, and 2 patients received stepwise OFCs up to $\geq 2,600$ mg. The median age of the last reaction to wheat was 18 (range: 8–45) months, and the median time from the last reaction to when the patient was confirmed to have acquired tolerance was 24 (range: 5–32) months.

In this study, although the number of patients is limited, we found that most Japanese infants with wheat-FPIES achieved tolerance by 5 years. Patients with solid FPIES have been considered to acquire tolerance later than those with FPIES to cow's milk and soy.^{6–8} However, recent studies from the US have reported tolerance for FPIES to cow's milk at approximately 5 years of age.^{3,5} Patients with solid FPIES to grains

such as oat and rice have been reported to acquire tolerance at a median age of 4 and 4.7 years, respectively.³ In Spain, 75% of patients with FPIES to egg and fish have been reported to achieve tolerance by the age of 5 years.⁹ The rate of tolerance acquisition in Japanese children with wheat-FPIES in our study was comparable to these previous results, with 86% of the patients acquiring tolerance by the age of 5 years. These results suggest that although a subset of patients may have prolonged FPIES, most patients achieve tolerance before school age.

Caubet et al. have reported that for patients with FPIES to cow's milk, sensitization to milk was a factor that predicted poor outcomes.³ However, the patient sensitized to wheat in our study achieved tolerance at the age of 4 years.

A study limitation is that owing to the retrospective nature, the age at initial OFCs, the intervals between stepwise OFCs, and the rate at which the dose consumed at home was increased varied across patients. In addition, when OFCs were positive, they were repeated after a period of 6–18 months. Only after repeated OFCs were confirmed to be negative, did the patients receive the proceeding stepwise OFCs and/or increase the amount consumed at home to confirm tolerance. Thus, it took a median of 24 months from the last reaction caused by wheat to the time tolerance was confirmed. Therefore, some of the patients assumably achieved tolerance earlier than it is described in our study.

In conclusion, most Japanese infants with wheat-FPIES in our study acquired tolerance by the age of 5 years. OFCs must be repeated to assess tolerance, given that most patients outgrow their wheat-FPIES before school age. Further prospective studies are warranted with routine OFCs to determine a more accurate prognosis.

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Author Contributions

Makoto Nishino: Conceptualization (lead); formal analysis (lead); writing – original draft (lead). Noriyuki Yanagida: Methodology (equal); writing – original draft (supporting); writing – review and editing (lead). Sakura Sato: Methodology (equal); writing – original draft (supporting); writing – review and editing (lead). Kyohei Takahashi: writing – review and editing (equal). Nagakura: writing – review and editing (equal). Kiyotake Ogura: writing – review and editing (equal). Motohiro Ebisawa: Methodology (equal); writing – review and editing (lead).

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Key Message

The rate of tolerance acquisition in infants with food protein-induced enterocolitis syndrome caused by wheat increased with age and resolved in most patients by the age of 5 years. Oral food challenges should be repeated regularly to assess for tolerance acquisition.

Ethical Approval

Written informed consent was obtained from the guardian of the patient before each oral food challenge. The study was approved by the Ethical Committee Board of Sagamihara National Hospital.

Data Sharing and Data Accessibility

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Table 1 . Characteristics of the seven patients with wheat-induced food protein-induced enterocolitis syndrome

Patient	1	2	3	4	5	6	7
Sex	Female	Male	Male	Female	Male	Male	Male
Age of onset (months)	7	9	9	6	7	6	7
Age at first visit (months)	9	13	17	16	17	11	8
Fulfilled diagnostic criteria based on history	-	+	+	+	+	+	+

Patient	1	2	3	4	5	6	7
Fulfilled diagnostic criteria based on OFC	+	-	-	-	-	-	-
History of symptoms owing to wheat consumption							
Vomiting 2–4 hours after eating a food containing wheat	+	+	+	+	+	+	+
Two or more episodes of repetitive vomiting after eating the same food	+	+	+	+	+	+	+
Episodes of repetitive vomiting 1–4 hours after eating 2 or more different foods	+	+	-	+	+	+	+
Number of vomiting episodes before first visit	6	4	3	4	4	2	3
Extreme lethargy with a suspected reaction	-	-	-	-	-	-	+
Marked pallor with any suspected reaction	-	-	+	-	+	+	-

Patient	1	2	3	4	5	6	7
Visit to emergency department due to a suspected reaction	-	-	-	-	-	+	-
Requirement of intravenous fluid due to a suspected reaction	-	-	-	-	-	+	-
Diarrhea (within 24 hours)	-	+	+	+	+	+	+
Hypotension	-	-	-	-	-	+	-
Hypothermia	-	-	-	-	-	-	-
IgE-mediated skin and/or respiratory symptoms	-	-	-	-	-	-	-
Total IgE (IU/mL)	13.2	11.1	<5.0	19.2	7.1	129	12.2
Wheat-sIgE (kU _A /L)	<0.35	<0.35	<0.35	0.42	<0.35	<0.35	<0.35
ω-5-gliadin sIgE (kU _A /L)	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35
Current complications							
Atopic dermatitis	-	+	+	-	-	-	-
Recurrent wheezing	-	-	-	-	-	-	-
IgE-mediated food allergy	-	-	-	-	-	+	-
FPIES (other than wheat)	+	-	-	-	+	-	-

Patient	1	2	3	4	5	6	7
Age at last reaction to wheat (months)	28	14	10	18	19	45	8
Age at which tolerance was confirmed (months)	44	34	42	48	47	NA	13

Diagnostic criteria refer to those proposed in the international consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome. Patients who either met the diagnosis criteria based on their history of symptoms or symptoms exhibited during OFC were defined as wheat-FPIES patients.

Abbreviations: OFC, oral food challenge; FPIES, food protein-induced enterocolitis syndrome; sIgE, specific immunoglobulin E; NA, not applicable

Figure Legends

Figure 1. Selection of patients with wheat-FPIES included in the study. Seven patients fulfilled the diagnostic criteria based on the history of symptoms, of which one patient was excluded because they were not followed up to the age of five. One patient presented with repetitive vomiting, lethargy, and pallor during OFC and therefore fulfilled the diagnostic criteria based on symptoms during OFC.

Abbreviations: FPIES, food protein-induced enterocolitis syndrome; OFC, oral food challenge

Figure 2. Tolerance acquisition rate of the seven patients who were followed up to the age of 5 years. Patients were defined to be tolerant to wheat when they could consume 2,600 mg of wheat protein (equivalent to the amount of wheat protein in half a slice of bread,).

The patient who was not confirmed to have achieved tolerance at the age of 5 years was capable of consuming 52 mg but whether he could consume larger amounts could not be determined because of refusal of eating during the following OFCs.

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