Prognosis of infantile food protein-induced enterocolitis syndrome in Japan

Mitsuaki Kimura, Masaki Shimomura, Hideaki Morishita and Takaaki Meguro
Department of Allergy and Clinical Immunology, Shizuoka Children’s Hospital, Shizuoka, Japan

Abstract

Background: Although serum C-reactive protein (CRP) and the percentage of eosinophils in peripheral blood (Eo) are increased at onset in infants with food protein-induced enterocolitis syndrome (FPIES), the relationship of these laboratory findings to prognosis is presently unknown.

Methods: Correlation of serum CRP and Eo at onset with prognosis was analyzed in 32 patients with FPIES caused by cow’s milk (CM).

Results: The rate of tolerance acquisition was 18.8%, 56.3%, 87.5%, and 96.9% at the ages of 6, 12, 24, and 36 months, respectively. Serum CRP increased in 50% of subjects at onset (median, 0.21 mg/dL; range, <0.20–18.2 mg/dL) and Eo was elevated in 71.9% of subjects at onset (median, 7.1%; range, 1.0–50.5%). Age at tolerance acquisition was significantly positively correlated with serum CRP at onset ($r = 0.45$, $P < 0.01$), and significantly negatively correlated with Eo at onset ($r = -0.36$, $P < 0.05$). Although CM-specific immunoglobulin E antibody (sIgE) was positive in nine of 32 FPIES patients at onset (median, 0.93; range, 0.38–18.9 kU/L), it decreased thereafter. CM-sIgE at onset did not correlate significantly with prognosis ($r = 0.22$, $P > 0.05$).

Conclusions: Serum CRP is not only an indicator of the activity of intestinal inflammation, it is also a useful parameter of poor prognosis in FPIES. In contrast, eosinophilia at onset could be used as a marker of good prognosis, suggesting that it has some beneficial effects in the pathophysiology of FPIES.

Key words C-reactive protein, eosinophilia, food protein-induced enterocolitis syndrome, immunoglobulin E, prognosis.

Methods

Subjects

Thirty-seven patients with GIFA (FPIES, $n = 32$; food protein-induced allergic proctocolitis [FPIAP], $n = 5$) who were referred between 1 January 2001 and 31 January 2016, and completed the follow-up program until the acquisition of tolerance, were enrolled in this study (Table 1). FPIES patients presented with vomiting, and/or diarrhea. Patients with bloody stool in addition to vomiting and/or diarrhea were classified into FPIES. Those patients with bloody stool alone were classified as having FPIAP. Subjects with an extremely low birthweight (<1500 g) or any unsolved medical issues, such as cardiovascular, respiratory, gastrointestinal, or neuromuscular disorders, were not included.

Diagnostic criteria

Non-IgE-mediated gastrointestinal food allergy was diagnosed on the basis of following criteria defined by the Japanese Guidelines for Food Allergy 2014: (i) development of GI symptoms without symptoms typically observed in IgE-mediated food allergy; (ii) disappearance of symptoms after discontinuing intake of causative food; (iii) reproducibility of symptoms after OFC with
CM formula; and (iv) exclusion of other diseases including infection and surgical problems. The reproduction of GI symptoms by an accidental re-exposure to CM formula was considered equivalent to a positive response during a planned OFC.

Estimation of tolerance acquisition

The acquisition of tolerance to CM proteins was estimated using OFC, which was done every 6 months up to 2 years of age and once a year thereafter.\(^\text{10,11}\)

Laboratory tests

Serum CRP, white blood cell (WBC) count, percentage of neutrophils (Ne) and of eosinophils (Eo) in peripheral blood, ANC, and absolute eosinophil count (AEC) were measured. Serum CRP ≥ 0.20 mg/dL was defined as test positive. Eosinophilia was defined as Eo ≥5%.\(^\text{14,15}\)

The CM-sIgE level was measured using the ImmunoCAP system (Thermo Fisher Scientific, Tokyo, Japan), and ≥0.35 kU/L was regarded as positive. Allergen-specific lymphocyte stimulation test (ALST) was also performed using flow cytometry\(^\text{16}\), or radioisotopes.\(^\text{17}\)

Long-term follow-up of Eo and CM-sIgE

To investigate the chronological changes in Eo and CM-sIgE, they were re-estimated during the first (4–8 months of age) and second (1–2 years of age) follow-up stages.

**Table 1** Subject profile

|                  | FPIES Median (range) or % | FPIAP Median (range) or % |
|------------------|---------------------------|---------------------------|
| **n**            | 32                        | 5                         |
| Sex (M/F)        | 20/12                     | 3/2                       |
| Gestational age (weeks) | 38 (32–41)\(^\text{†,***}\) | 40 (38–41)                |
| Birthweight (g)  | 2,768 (1,808–4,400)       | 3,186 (2,519–2,702)       |
| Age at onset     | 7 days (0 days–3 months)  | 21 days (4 days–2 months) |
| GI symptoms      |                           |                           |
| Vomiting         | 71.9                      | 0.0                       |
| Diarrhea         | 56.3                      | 0.0                       |
| Bloody stool     | 50.0                      | 100.0                     |
| CM-sIgE (kU/L)   | <0.35 (<0.35–18.9)\(^\text{†,***}\) | <0.35 (<0.35–<0.35)      |
| CRP (mg/dL)      | 0.21 (<0.20–18.2)         | <0.2 (<0.2–<0.2)          |
| CRP positive     | 50.0                      | 0.0                       |
| WBC (/µL)        | 13,550 (7,300–30,700)     | 8,500 (7,100–17,500)      |
| Ne (%)           | 41.0 (14.9–70.0)          | 25.0 (17.5–38.0)          |
| ANC (/µL)        | 5,540 (1,237–18,205)      | 2,698 (2,125–5,233)       |
| Eo (%)           | 7.1 (1.0–50.5)            | 12.5 (3.0–29.8)           |
| Eosinophilia     | 71.9                      | 80.0                      |
| AEC (/µL)        | 1,049 (79–13,181)         | 1,143 (255–5,215)         |
| ALST positive    | 90.6                      | 80.0                      |

\(^{***}P < 0.001\) (\(^{†}\)significantly correlated with birthweight, \(r = 0.71\); \(^{‡}\)significantly correlated with Eo, \(r = 0.75\)); AEC, absolute eosinophil count; ALST, allergen-specific lymphocyte stimulation test; ANC, absolute neutrophil count; CM-sIgE, cow’s milk-specific IgE antibody; CRP, C-reactive protein; Eo, percentage of eosinophils in peripheral blood; FPIAP, food protein-induced allergic proctocolitis; FPIES, food protein-induced enterocolitis syndrome; GI, gastrointestinal; Ne, percentage of neutrophils in peripheral blood; WBC, white blood cell count.

Ethics

The Ethics Committee of Shizuoka Children’s Hospital approved this study. The parents provided informed consent before participating in the study. Data were collected from the medical records.

Statistical analysis

Mann–Whitney \(U\)-test was used to estimate the significance of the differences. The significance of the incidence was estimated using Fisher’s exact test and the significance of the correlation was calculated using Spearman’s rank correlation coefficient. The difference in diagnosis between the FPIES and FPIAP groups was investigated on Kaplan–Meier analysis. All statistical analysis was performed using STATA 13 (Light Stone, Tokyo, Japan).

**Results**

**Subject profile**

The 32 patients with FPIES consisted of 20 boys and 12 girls (Table 1). Median gestational age and birthweight were 38 weeks and 2768 g, respectively. Median age at onset was 7 days. Vomiting, diarrhea, and bloody stool were seen in 71.9%, 56.3% and 50.0% of subjects, respectively. Serum CRP was increased in 50.0% of the subjects at onset. Eosinophilia was seen in 71.9% of the subjects, and ALST was positive in 90.6% of the subjects.
The five patients with FPIAP consisted of three boys and two girls. Except for GI symptoms, the demographic and laboratory data of FPIAP patients at onset were not significantly different from the FPIES patients, although neither serum CRP nor CM-sIgE was increased in the FPIAP group at onset.

**Age at tolerance acquisition**

Of 32 patients with FPIES, 18.8%, 56.3%, 78.1%, 87.5%, and 96.9% of patients acquired tolerance at 6, 12, 18, 24, and 36 months of age, respectively (Fig. 1). In contrast, all subjects with FPIAP acquired tolerance by 12 months of age. Age at tolerance acquisition was significantly lower in the FPIAP than in the FPIES group (mean age, 9.6 vs 16.3 months; \( P < 0.05 \), Kaplan–Meier analysis).

**Serum CRP at onset and FPIES prognosis**

There was a significant positive correlation between serum CRP at onset and age at tolerance acquisition in FPIES \( (r = 0.45, P < 0.01; \text{Fig. 2a}) \).

In the FPIES group, there was a significant difference in the age at tolerance acquisition between those with high serum CRP (≥1 mg/dL) and those with low serum CRP at onset (<1 mg/dL; median, 21 vs 12 months, \( P < 0.01 \); Table 2). No patient with high serum CRP acquired tolerance before 12 months of age, while all four patients who acquired tolerance at ≥36 months of age had high serum CRP at onset (Fig. 2a).

**Eosinophilia and FPIES prognosis**

The Eo at onset had a significant negative correlation with age at tolerance acquisition in the FPIES group \( (r = -0.36, P < 0.05; \text{Fig. 2b}) \). Age at tolerance acquisition in FPIES patients with eosinophilia was significantly lower than that in those without eosinophilia at onset (median, 12 vs 18 months, \( P < 0.01 \); Table 2). No patients without eosinophilia acquired tolerance before 12 months of age (Fig. 2b).

**CM-sIgE, ANC and FPIES prognosis**

The CM-sIgE at onset did not show any significant correlation with FPIES prognosis \( (r = 0.22, P > 0.05; \text{Fig. 2c}) \). No patients, however, with positive CM-sIgE at onset acquired tolerance before 12 months of age.

Neither ANC nor Ne at onset correlated significantly with age at tolerance acquisition in the FPIES group (data not shown).

**Change in Eo with growth**

To further study the relationship between eosinophilia and the prognosis, long-term change in Eo was studied. Although
eosinophilia was seen in as many as 71.9% of the FPIES subjects at onset, the incidence of eosinophilia drastically decreased to 21.9% at the first follow-up stage (4–8 months) and did not increase again at the second follow-up stage (1–2 years; 13.0%; Table 3). Median Eo decreased from 7.1% at onset to 3% and 2.9% in the first and second follow-up stages, respectively.

The FPIAP subjects had a similar change in Eo with growth to the FPIES subjects (data not shown).

Change in CM-sIgE with growth

The CM-sIgE was detected in 28.1% (9/32) of patients with FPIES at onset (Table 3). Median and range of CM-sIgE in those nine subjects with positive CM-sIgE were 0.93 and 0.38–18.9 kU/L, respectively. Maximum CM-sIgE decreased from 18.9 kU/L at onset to 1.27 kU/L at the first follow-up stage, and to 1.20 kU/L at the second follow-up stage. The rates of positive CM-sIgE at the first and second follow-up stages were 18.8% and 26.1%, respectively, which were not higher than that at onset.

Other allergic disorders complicated with FPIES

One subject had FPIES as a complication following ingestion of soybean formula concurrently with CM formula at onset (Table 4). Another subject developed FPIES due to rice during weaning. Atopic dermatitis (AD) developed secondarily in seven subjects, and bronchial asthma (BA) appeared later in one subject. Mild eosinophilia was seen only in those subjects with secondary complications of AD and/or BA during the second follow-up stage. None later developed IgE-mediated food allergy.

Discussion

Although the prognosis of FPIES due to CM is thought to be good, there is considerable variation between studies concerning the timing of tolerance acquisition. Sicherer et al. reported that 60% of subjects acquire tolerance by 30 months of age, whereas Hwang reported that all FPIES patients acquire tolerance by 2 years of age. Age at tolerance acquisition reported by Katz et al. and Sopo et al. is similar to that reported by Hwang et al., while the Ruffner et al. result is similar to that of Sicherer et al. In contrast, Caubet et al. noted the poorest prognosis for FPIES due to CM, in which only approximately 30% of subjects were tolerant to CM at 3 year of age. According to the present study, >90% of subjects in Japan acquire tolerance by 3 years of age. Thus, worldwide, Japanese patients seem to be included in the group with the best prognosis.

In contrast to FPIES, little is known about the prognosis of FPIAP. This may be because of the lack of diagnostic criteria for FPIAP. In Japan, FPIAP is diagnosed by the same criteria as FPIES. In this study, we compared the prognosis of FPIAP with that of FPIES, and found that the duration of FPIAP symptoms was significantly shorter than that of FPIES. This is consistent with a previous study on the prognosis of FPIAP due to breast milk.

In this study, we explored the relationship between the laboratory findings at onset and FPIES prognosis. Powell reported an increase in ANC after OFC. In the present study, however, no significant correlation was found between ANC at onset and age at tolerance acquisition (data not shown). In contrast, serum CRP at onset was significantly correlated with FPIES prognosis (Fig. 2a). This suggests that immunological abnormalities that cause an increase in serum CRP at onset last for

| Table 3 Change in Eo and CM-sIgE with growth |
|----------------------------------------------|
| Onset                                       | Follow-up stage |
| Eosinophil                                  |                |
| Eo (%) median (range)                       | 7.1 (1.0–50.5) | 3.0 (0.0–8.9) |
| Eosinophilia (%)                            | 71.9           | 21.9          |
| IgE antibody                                |                |
| CM-sIgE (kU/L) median (range)               | <0.35 (<0.35–18.9) | <0.35 (<0.35–1.27) |
| Positive rate (%)                           | 28.1           | 18.8          |

1 n = 23. CM-sIgE, cow milk-specific IgE antibody; Eo, percentage of eosinophil in peripheral blood; FPIES, food protein-induced enterocolitis syndrome.

| Table 4 Other allergic disorder complications in FPEIS patients |
|-------------------------------------------------------------|
| Disorders                   | n  | Remark                        |
|-----------------------------|----|-------------------------------|
| Contemporary FPIES          | 2  | Soy bean 1, rice 1            |
| Secondary AD                | 7  | Mild persistent eosinophilia (3) |
| BA                          | 1  | Together with AD              |

AD, atopic dermatitis, BA, bronchial asthma; FPIES, food protein-induced enterocolitis syndrome.

With regard to the FPIAP group, one subject later developed AD.

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a long time and affect the prognosis of the disease. Indeed, an increase in serum CRP was observed after OFC even in subjects older than 1 year of age.\textsuperscript{10} This suggests that pro-inflammatory cytokines play a critical role in the pathophysiology of FPIES in infants.\textsuperscript{19} This is also consistent with an observation made by Chung \textit{et al.},\textsuperscript{20} who reported an increase in expression of TNF-\textgreek{a}, a representative pro-inflammatory cytokine, in the intestine of infants with FPIES.

We previously demonstrated significant eosinophilia in infants with FPIES.\textsuperscript{12} Eosinophils are well-known effector cells of allergic inflammation,\textsuperscript{21} and eosinophilia in the peripheral blood is often linked to tissue eosinophilia.\textsuperscript{22} Given that the incidence of vomiting and bloody stool is higher in infants with FPIES with marked eosinophilia (Eo \textgreek{g} \geq 15\%), it is suggested that eosinophilia may facilitate the development of these symptoms.\textsuperscript{12} In the present study, however, Eo at onset was negatively correlated with age at tolerance acquisition (Fig. 2b). Consequently, FPIES patients with eosinophilia acquire tolerance earlier than those patients without eosinophilia (Table 2). This raises a question about the role of eosinophilia in the pathogenesis of FPIES in infants.

In contrast to bronchial tissue, the gut contains many eosinophils, even in healthy individuals.\textsuperscript{23} Thus, the pathological significance of eosinophilia in the gut of infants should be considered carefully because it may have both harmful and beneficial effects.\textsuperscript{24} The significant negative correlation of Eo with age at tolerance acquisition suggests that the increased number of eosinophils in the gut of young infants has some beneficial effect. Vomiting associated with eosinophilia might also relieve the gut from noxious influences of CM proteins by discharging CM formula quickly. Further studies are needed to elucidate both noxious and beneficial influences of eosinophils in the pathophysiology of FPIES in young infants.

Eosinophilia at onset is a remarkable laboratory finding in neonates and young infants with FPIES. Eosinophilia is also a representative hematological abnormality of eosinophilic gastrointestinal diseases (EGID).\textsuperscript{25,26} Given that both FPIES and EGID involve GI symptoms and eosinophilia, they could be assumed to be similar disorders, but there is a distinct difference in the clinical course between FPIES and EGID. EGID is a chronic disorder, and eosinophilia persists for a long time until the disease resolves. In contrast, in the present study, eosinophilia in neonatal FPIES was a self-limited phenomenon and persisted for no longer than a few months after birth (Table 3), suggesting that eosinophilia is not essential for the development of GI symptoms in infants with FPIES. Thus, FPIES in neonates and young infants seems to be a different disease from EGID, although eosinophilia is a common feature.

Cow’s milk-sIgE has been detected in some patients with FPIES.\textsuperscript{4} Although its significance has not yet been elucidated, Caubet \textit{et al.}\textsuperscript{9} reported on the significant influence of CM-sIgE on the prognosis of FPIES. They noted that the age at tolerance acquisition in patients with FPIES who are positive for CM-sIgE was extremely late compared with those negative for CM-sIgE. In contrast, we did not observe any significant difference in prognosis between FPIES patients with increased CM-sIgE and those patients negative for CM-sIgE (Fig. 2c). Although the cause of this discrepancy remains to be explained, it might be due to a remarkable difference in the level of CM-sIgE and the age at onset.

The CM-sIgE level in the CM-sIgE-positive patients in the Caubet \textit{et al.} study was much higher than in the present study (median, 5.14 vs 0.93 kU/L). Age at onset was much later in the Caubet \textit{et al.} study than in the present study (median, 5 months vs 7 days). Consequently, 41\% of patients with FPIES positive for CM-IgE developed an immediate CM allergy, while no patients developed immediate food allergy in the present study. This situation may be the cause of the delay in tolerance acquisition in the Caubet \textit{et al.} subjects. They also found that patients with FPIES who acquired tolerance by 3 years of age had early onset age (median, 0.8 months) and no positive results on CM-sIgE test. These features resemble those of the present FPIES patients.

Some investigators separate CM-sIgE-positive from -negative FPIES patients.\textsuperscript{4,16} In the present study, however, FPIES patients positive for CM-sIgE at onset were not separated from those negative for CM-sIgE. This is because some patients with FPIES with increased CM-sIgE at onset had increased serum CRP (5/9), which might be a useful marker of intestinal inflammation and prognosis. Thus, if FPIES patients positive for CM-sIgE at onset do not have an immediate CM allergy, they should not be separated from those negative for CM-sIgE. But they do manifest symptoms of immediate CM allergy, they should be separated, because the management and the prognosis of immediate food allergy are different from those of non-IgE-mediated FPIES.\textsuperscript{27}

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Disclosure

The authors declare no conflict of interest.

Author contributions

M.K. designed the study and wrote the manuscript; M.S., H.M., and T.M. collected data. All authors read and approved the final manuscript.

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