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Difference in serum CRP levels between patients with FPIES and FPIP in Japan

Running title: Differential CRP levels between FPIES and FPIP

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Author contribution

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Abstract

Background: Some infants with food protein-induced enterocolitis syndrome (FPIES) showed an increase in the serum CRP level and fever in Japan. This study aimed to clarify the incidence of those findings by comparing a large number of patients with FPIES to patients with food protein-induced proctocolitis (FPIP). **Methods:** One hundred and sixteen infants with non-IgE-mediated gastrointestinal food allergies were enrolled in this study and classified into three phenotypes: FPIES presenting with vomiting and/or diarrhea (N=47), FPIP showing bloody stool alone (N=19), and the mixed phenotype (MP) showing bloody stool along with vomiting and/or diarrhea (N=50). **Results:** The serum level of CRP was increased in 55.3% of subjects in the FPIES group, which was comparable to that in the MP group (54.0%), and significantly higher than that of the FPIP group (15.8%, $p<0.01$). Fever was observed in 29.8% of subjects in the FPIES group, which was significantly higher than those in the MP group (8.0%, $p<0.01$) and FPIP group (0%, $p<0.05$). Patients with fever showed significantly higher serum CRP levels than patients without fever (median 12.8 vs. <0.2 mg/dL, $p<0.00001$).

Conclusions: The serum CRP level was shown to be significantly higher in the FPIES group than that in the FPIP group. This suggests that serum CRP level is a useful marker for the study of the pathogenesis of FPIES in comparison with FPIP. From the perspective of serum CRP levels, the pathology of the intestinal inflammation in MP subjects is suggested to be similar to that of FPIES.

Key words: food protein-induced enterocolitis syndrome, food protein-induced proctocolitis, CRP, fever, cow milk,

Introduction

It is well-known that, in addition to IgE-mediated immediate allergic reactions, food causes gastrointestinal symptoms via the cell-mediated hypersensitivity. This has been termed “non-IgE-mediated gastrointestinal food allergy” (GIA) (1). GIA comprises of food protein-induced enterocolitis syndrome (FPIES), which shows vomiting (V) and/or diarrhea (D), and food protein-induced proctocolitis (FPIP), showing bloody stool alone (B). The pathology of the intestinal lesion in FPIES and FPIP is thought to be different. Although these two conditions have been studied separately in western countries, they are usually treated as one ailment in Japan under the name of “neonatal and infantile gastrointestinal allergy” (NIGIA) (2). NIGIA contains another phenotype with a mix of symptomatic features of FPIES and FPIP, namely showing B in addition to V and/or D (3)(4).

While the difference in the symptoms may reflect the difference in the pathogenesis of those phenotypes, little is known about the pathogenesis of this disease. Laboratory examinations are often useful for studying the mechanism of the diseases. Powell observed an increase in the absolute neutrophil count (ANC) in patients with FPIES by using an oral food challenge test (OFC) (5). This may provide insight into the nature of the inflammation that causes FPIES and is consistent with the study that reports an increase in the production of tumor necrosis factor- α (6), a representative proinflammatory cytokine. However, the serum level of CRP, which is also a good indicator of inflammation caused by proinflammatory cytokines, was not examined. In Japan, many studies report on subjects exhibiting increased serum CRP levels (7)(8) and fever (9). Patients with both fever and highly increased serum CRP levels have been referred to as the sepsis-like phenotype of FPIES (9). Since fever and an increase in the serum CRP level can be reproduced by OFC in patients with FPIES (10), it is suggested that these findings are caused by FPIES itself, but not by complications such as infectious disorders.

Thus far, increased serum CRP levels and fever in FPIES patients has not yet been studied well. The present study attempts to clarify the incidence of these findings in infants with FPIES by using a large population of subjects and comparing these subjects with other phenotypes.

Materials and Methods

Subjects

One hundred and sixteen infants with NIGIA who were referred to our institute between January 1, 2001 and May 31, 2015, were enrolled in this study (Table 1). The causative food was cow milk (CM) in all cases. NIGIA was diagnosed according to the following criteria, which correspond to those of the Japanese Guidelines for Food Allergy 2014 (2): 1) development of gastrointestinal (GI) symptoms without symptoms typically observed in IgE-mediated immediate allergic diseases after ingestion of causative food, 2) disappearance of symptoms after discontinuation of causative food, 3) reproduction of symptoms on an OFC with cow milk (CM) formula, and 4) exclusion of other diseases such as infections, surgical problems, and so on. The reproduction of GI symptoms by an accidental re-exposure to CM formula was considered to be equivalent to a positive response at a planned OFC.

The original diagnostic criteria for FPIES were proposed by Powell (11), modified by Sicherer (12), and then further modified by Caubet in a recent large-scale study (13). The criteria applied in this study are consistent to those of Caubet.

Subjects were divided into three groups according to GI symptoms: FPIES includes those subjects with V and/or D, FPIP comprises patients with B alone, and mixed phenotype (MP), which includes patients with B as well as V and/or D.

Data were collected from the medical records. Informed consent was obtained from the parents before the study, which was approved by the ethics committee of Shizuoka Children's Hospital.

OFC

A planned OFC was performed using CM formula at the volume usually ingested by the patient. From 2008, a planned OFC was performed daily according to a stepwise incremental protocol with an initial volume of 1mL/Kg, which then increased to the volume usually ingested by the patient in order to reduce the incidence of severe reactions (10).

Laboratory examinations

Serum levels of total IgE and CM-specific IgE (sIgE) were measured using the ImmunoCAP system (Thermo Fisher Scientific Inc., Tokyo, Japan). An allergen-specific lymphocyte stimulation test (ALST) was performed with flow cytometry (3) or radioisotopes (14). A positive result depended on the upper limit of the normal range set by each method.

Statistical analysis

Mann–Whitney *U*-test was used to estimate the significance of differences, while the significance of the incidence was estimated using Fisher's exact test. The accuracy for discriminating subjects with fever was analyzed by the receiver operating characteristics (ROC) curve and expressed as the area under the curve (AUC). All analyses were performed using STATA 13 statistical software (Light Stone Corp., Tokyo, Japan).

Results

Subjects' profiles

One hundred and sixteen patients were enrolled in this study (Table 1). There were no significant differences in the sex ratio. The median age at onset was 8 days. CM-sIgE was negative in 97 (83.6%) patients. Fever and increased CRP levels at onset were seen in 18 (15.5%) and 56 (48.3%) subjects respectively. ALST was positive in 98 (84.5%) subjects. With regard to the disease type, 47, 19, and 50 subjects were included in the group of FPIES, FPIP, and MP, respectively (Table 2). The age at onset was significantly earlier in patients with MP (median 6.5 days) than in those with FPIES (median 20 days, $p<0.0002$) or FPIP (median 21 days, $p<0.05$).

Comparison of CRP levels between FPIES and FPIP

The serum level of CRP was significantly higher in the FPIES group than in the FPIP group (median 0.41 vs. <0.2 mg/dL, $p<0.005$) (Table 2). The percentage of patients with increased CRP levels (≥ 0.2 mg/dL) was also significantly higher in the FPIES group than that in the FPIP group (55.3% vs. 15.8%, $p<0.01$).

Serum CRP levels in the FPIES group were highest in patients with both V and D (median 2.12 mg/dL). This was significantly higher than serum CRP levels in patients with V alone which was lowest in the FPIES group (median <0.2 mg/dL, $p<0.02$) (Fig.1).

Comparison of CRP levels between FPIES and MP

There were no significant differences between the FPIES and the MP group with regard to the serum CRP level (median 0.41 vs. 0.2 mg/dL) or the percentage of patients with increased CRP levels (≥ 0.2 mg/dL) (55.3% vs. 54.0%) (Table 2). However, the percentage of patients with considerably increased CRP levels (≥ 3 mg/dL) was significantly higher in the FPIES group than in the MP group (31.9% vs. 10.0%, $p<0.02$) (Table 2).

Comparison of CRP levels between FPIP and MP

The serum level of CRP (median 0.2 vs. <0.2mg/dL, $p<0.01$) and the percentage patients with increased serum CRP levels (54.0% vs. 15.8%, $p<0.01$) were significantly higher in the MP group than in the FPIP group.

Characteristics of patients with fever

Fever developed in 18 patients, but was absent in 98 patients. The serum CRP levels were significantly higher in patients with fever than in those without fever (median 12.8 vs. <0.2 mg/dL, $p<0.00001$) (Table 3). The incidence of patients who were systemically administered antibiotics was also significantly higher in those with fever than in those without fever (100% vs 4.1%, $p<0.00001$). White blood cell (WBC) count was significantly higher in febrile patients than in afebrile patients (17,765 vs 13,800 / μ l, $p<0.005$). There were no significant differences in sex ratio, age at onset, the level of CM-sIgE, or the result of an ALST between febrile and afebrile subjects.

The incidence of patients with fever was significantly higher in the FPIES group (29.8%) than in the FPIP group (0%, $p<0.02$) and in the MP group (8.0%, $p<0.01$) (Table 2). There was no significant difference in the incidence of febrile patients between the FPIP and the MP group.

Discrimination of patients with fever by the serum CRP level

Patients with fever were distinguished from those without fever by the serum CRP level with high precision. The AUC of the ROC curve was 0.983 (Fig.2). The odds ratio was highest at the serum CRP level of 3mg/dL: the sensitivity and the specificity at this level were 85.0% (17/20) and 99.0% (95/96), respectively. WBC count also showed some usefulness in distinguishing patients with fever (AUC=0.717).

Discussion

Pathology of FPIES has been shown to include the inflammation of GI system (15)(16). However, although the cell-mediated hypersensitivity is assumed to play a critical role (3)(17)(18), much remains to be elucidated about the mechanism of the inflammation. An abnormal laboratory finding associated with FPIES patients may be a useful tool for the study of the pathogenesis of FPIES. Neutrophilia was noted as a characteristic of FPIES (5), while eosinophilia is often described in FPIP (1). In addition to these findings, an increase in the serum CRP level and fever in patients with NIGIA has also been demonstrated (7-9). As fever and an increase in the serum CRP level can be reproduced by OFC in patients with FPIES (10), it is suggested to be the phenomenon derived from FPIES itself, but not from other complicated disease such as infections. However, further studies are needed to clarify the exact mechanisms involved. The increase in the serum CRP levels at OFC was closely correlated with those at onset (10). This suggests that serum CRP levels at onset may reflect the intensity of the intestinal inflammation in FPIES patients. In order to further clarify the significance of the increased serum CRP levels and fever, we analyzed the incidence and degree of these findings at onset in a large population of Japanese infants with FPIES and compared them with other phenotypes of the disease.

This study has demonstrated a clear increase in the serum CRP level in FPIES patients at onset. Increased serum CRP levels have not yet been reported from western countries in either early studies (5)(12) or recent studies including a large number of subjects (13)(19-23). However, an increase in the serum CRP level might not be unexpected as the increased production of a representative proinflammatory cytokine TNF- α was noted in patients with FPIES (6). Although the regulation of inflammation is very complex, increased TNF- α production may be caused by IFN- γ , which is produced by type 1 helper T cells (Th1) (1). IFN- γ activates monocytes and induces the production of

proinflammatory cytokines such as TNF- α , IL-6 and IL-1 β . These cytokines have been shown to play a critical role in inducing neutrophilia, as well as increasing the serum CRP level (24)(25). In fact, neutrophilia is often accompanied with an increase in serum CRP level in patients with various inflammatory disorders.

We also reported the development of fever in patients with FPIES with considerably increased CRP levels ($\geq 3\text{mg/dL}$), which could be reproduced by OFC (10). In this study, we reconfirmed a close correlation between fever and the serum CRP level. Fever was eventually limited to patients with FPIES with considerably increased CRP levels ($\geq 3\text{mg/dL}$), who have been called the sepsis-like phenotype of FPIES in Japan (9). Clinically, this provides an important suggestion about the management of patients with FPIES in the acute phase. If physicians see neonates or young infants with fever and markedly increased serum CRP levels, they must assume severe systemic bacterial infections such as sepsis or meningitis. This can sometimes lead to serious outcomes such as death or severe sequelae. Multiple examinations including invasive procedures like spinal taps, and systemic administration of antibiotics are needed for the management of those infants.

In fact, all patients with the sepsis-like phenotype of FPIES received systemic antibiotics in this study. This should be indispensable as an empiric countermeasure to severe systemic bacterial infections in neonates and young infants with fever and high serum CRP levels. However, as indicated by the results of this study, physicians must be mindful of the fact that some patients with FPIES could show similar findings. If the systemic administration of antibiotics is ineffective, FPIES should then be considered as a possible cause. Judgment could easily be made as symptoms and abnormal laboratory findings would improve soon after discontinuation of CM formula and be completely resolved within a few days in case of FPIES.

FPIP is also included into GIA, as is FPIES (1). In addition to the difference in the symptoms, eosinophilia is noted specifically in patients with FPIP, suggesting that a Th2 cytokine such as IL-5 participates in the development of FPIP (1). Since Th2-skewed immune responses are thought to be incompatible with Th1-skewed immune responses, in which proinflammatory cytokines play a pivotal roles (26)(27), it is expected that the serum CRP level does not increase in patients with FPIP. In this study, the serum level of CRP between the FPIES and FPIP group was directly compared. As a result, it was confirmed that the serum CRP levels of the FPIP group were significantly lower than that of the FPIES group. No patients with FPIP showed considerably increased CRP levels ($\geq 3\text{mg/dL}$). Correspondingly, no patients with FPIP had fever. Thus, the supposition of the difference in the pathogenesis between FPIES and FPIP is again supported by the results of this study.

In Japan, about one-third of patients with NIGIA are classified into the MP group (3)(4). According to symptoms, FPIES and FPIP seem to coexist in patients with MP. However, the immunopathology assumed for FPIES and FPIP are thought to be incompatible. It is important for the improved understanding of the disease to clarify the major mechanism in patients with MP. The results of this study showed that the serum CRP level in the MP group is comparable to that of the FPIES group, but not to that of the FPIP group. Fever was also observed in patients with MP, although the incidence was lower than that in the FPIES group. This suggests that proinflammatory cytokines play an important role in the development of the intestinal inflammation in MP patients in a similar way to that observed in FPIES. It remains to be clarified how FPIP-like symptoms, namely B, develop in those patients. Since the age at onset is younger in the MP group than in other disease types (Table 2)(3)(4), the relative immaturity of the immune system might allow the transient coexistence of Th1- and Th2-skewed immunopathology which, ordinarily, are incompatible.

There is no clear definition about whether patients with both B and D should be separated from patients with FPIP, which show B alone. In this study, symptoms of FPIP were limited to B alone. Patients with both B and D were considered as part of the MP group. This is reasonable because patients with both B and D showed increased serum CRP levels similar to those with D only. This is a sharp contrast to the FPIP group. This may suggest that the pathogenesis of patients with both B and D more closely resembles that of FPIES as opposed to that of FPIP. Thus, from the perspective of CRP levels, patients with both B and D should be categorized into the MP group separately from those patients with B alone, who belong to the FPIP group.

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Tables and Figures

Table 1. Profile of subjects

Data are presented as mean and range for age, CM-sIgE, WBC, and serum CRP levels.

d, day; m, month; V, vomiting; D, diarrhea; B, bloody stool; CM, cow milk; sIgE, specific IgE antibody; CRP, C-reactive protein; ALST, allergen-specific lymphocyte stimulation test; WBC, white blood cell.

Table 2. Serum CRP levels and fever in each disease type

N, number of subjects; FPIES, food protein-induced enterocolitis syndrome; FPIP, food protein-induced allergic proctocolitis; MP, mixed phenotype; V, vomiting; D, diarrhea; B, bloody stool; d, day; m, month; CRP, C-reactive protein.

Compared to FPIP: ***, <0.005; **, p<0.01; *, p<0.02.

Compare to MP: ##, p<0.01; #, p<0.02.

\$. vs FPIES, p<0.0002; vs FPIP, p<0.05

Table 3. Characteristics of patients with fever

CRP, C-reactive protein; WBC, white blood cell; CM, cow milk; sIgE, specific IgE antibody; ALST, allergen-specific lymphocyte stimulation test.

Fig. 1. Distribution of serum CRP levels in each disease type

Serum CRP levels in each disease type were blotted according to symptoms.

V, vomiting; D, diarrhea; B, bloody stool; FPIES, food protein-induced enterocolitis syndrome; FPIP, food protein-induced allergic proctocolitis; MP, mixed phenotype;.

Fig. 2. ROC curves for serum CRP levels and WBC to distinguish patients with fever

AUC, area under the curve; CRP, C-reactive protein; WBC, white blood cell.

Table 1 Profile of subjects

	Data
Number	116
Sex	m:f=62:54
Age at onset	8d (0d–6m)
Symptoms	V 64 (55.2%)
	D 53 (45.7%)
	B 69 (59.5%)
	fever 18 (15.5%)
Systemic antibiotics	22 (19.0%)
CM-sIgE (UA/ml)	<0.35 (<0.35–18.9)
Undetectable CM-sIgE	97 (83.6%)
WBC (/μl)	14,260 (6,500–64,540)
CRP (mg/dL)	<0.2 (<0.2–28.2)
Increased CRP (≥0.2mg/dL)	56 (48.3%)
Positivity in ALST	98 (84.5%)

Table 2 Serum CRP levels and fever in each disease type

		N	Onset age	CRP			Fever
				Median (Range)	Positivity rate		
					≥0.2mg/dL	≥3mg/dL	
FPIES	V-D	10	16d 6d–2m	2.12 <0.2–28.2	9 (90.0%)	5 (50.0%)	5 (50.0%)
	V	18	7.5d 1d–3m	<0.2 <0.2–13.8	7 (38.9%)	4 (22.2%)	4 (22.2%)
	D	19	28d 0d–6m	0.34 <0.2–19.2	10 (52.6%)	6 (31.6%)	5 (26.3%)
	Whole	47	20d 0d–6m	0.41*** <0.2–28.2	26 (55.3%)**	15 (31.9%)*##	14 (29.8%)*##
FPIP	B	19	21d 1d–6m	<0.2 <0.2–1.0	3 (15.8%)	0 (0%)	0 (0%)
MP	V-D-B	11	7d 0d–1m	0.2 <0.2–14.3	6 (54.5%)	2 (18.2%)	2 (18.2%)
	Vo-B	25	6d 0d–1m	0.2 <0.2–13.7	15 (60.0%)	1 (4.0%)	1 (4.0%)
	D-B	14	7.5d 0d–6m	<0.2 <0.2–10.2	6 (42.9%)	2 (14.3%)	1 (7.1%)
	Whole	50	6.5d ⁵ 0d–6m	0.2** <0.2–14.3	27 (54.0%)**	5 (10.0%)	4 (8.0%)

Table 3. Characteristics of patients with fever

	Fever	Without fever	p
Number	18	98	
Sex (male : female)	12:6	50:48	NS
CRP (mg/dL)	12.8 (1.24–28.2)	<0.2 (<0.2–11.0)	p<0.00001
definitely increased CRP (≥3mg/dL)	17 (94.4%)	3 (3.1%)	p<0.00001
WBC (/μl)	17,765 (6,500–65,540)	13,800 (6,500–32,900)	p<0.005
Age at onset	7.5d (1d–2m)	8d (0d–6m)	NS
Systemic antibiotics	18 (100%)	4 (4.1%)	p<0.00001
CM-sIgE	<0.35 (<0.35–8.33)	<0.35 (0.35–18.9)	NS
Positivity in ALST	18 (100%)	80 (81.6%)	NS

Fig. 1 Distribution of serum CRP levels in each disease type

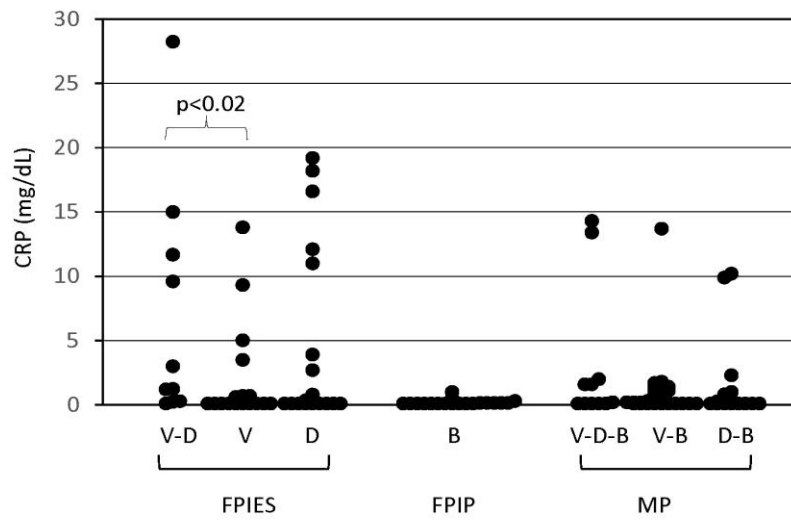


Fig. 2 ROC curve for distinguishing patients with fever

