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REVIEW ARTICLE

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Gastrointestinal Food Allergy in Infants

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ABSTRACT

Food allergies are classified into three types, "IgE-mediated," "combined IgE- and cell-mediated" and "cell-mediated/non-IgE-mediated," depending on the involvement of IgE in their pathogenesis. Patients who develop predominantly cutaneous and/or respiratory symptoms belong to the IgE-mediated food allergy type. On the other hand, patients with gastrointestinal food allergy (GI allergy) usually develop gastrointestinal symptoms several hours after ingestion of offending foods; they belong to the cell-mediated/non-IgE-mediated or combined IgE- and cell-mediated food allergy types. GI allergies are also classified into a number of different clinical entities: food protein-induced enterocolitis syndrome (FPIES), food protein-induced proctocolitis (FPIP), food protein-induced enteropathy (Enteropathy) and eosinophilic gastrointestinal disorders (EGID). In the case of IgE-mediated food allergy, the diagnostic approaches and pathogenic mechanisms are well characterized. In contrast, the diagnostic approaches and pathogenic mechanisms of GI allergy remain mostly unclear.

In this review, we summarized each type of GI allergy in regard to its historical background and updated clinical features, offending foods, etiology, diagnosis, examinations, treatment and pathogenesis. There are still many problems, especially in regard to the diagnostic approaches for GI allergy, that are closely associated with the definition of each disease. In addition, there are a number of unresolved issues regarding the pathogenic mechanisms of GI allergy that need further study and elucidation. Therefore, we discussed some of the diagnostic and research issues for GI allergy that need further investigation.

KEY WORDS

eosinophil-associated gastrointestinal disorders (EGID), food protein-induced enterocolitis syndrome (FPIES), food protein-induced enteropathy (Enteropathy), food protein-induced proctocolitis (FPIP), non-IgE-mediated food allergy

INTRODUCTION

Food allergies continue to increase, especially in westernized countries,[1] and are now recognized as a worldwide problem. Food allergies are classified into three types: "IgE-mediated," "combined IgE- and cell-mediated" and "cell-mediated/non-IgE-mediated," depending on the involvement of IgE in their pathogenesis.[1-3]

Most food allergies that exhibit cutaneous and/or respiratory symptoms within 1 hour after ingestion of offending foods belong to IgE-mediated food allergies. The mechanisms and pathogenesis of IgE-mediated food allergies are well characterized. In brief, food-specific IgE antibodies are generated after initial exposure to food antigens and then bind to the surface of mast cells and basophils. Upon re-exposure to the offending foods, the food antigens bind to and cross-link the food-specific IgE antibodies bound to the mast cells and basophils, causing their activation and degranulation. Released mediators such as histamine and leukotrienes cause cutaneous and/or respiratory symptoms (Fig. 1).[4] These mechanisms were supported by the existence of serum IgE antibodies specific for offending foods and elevation of the serum histamine level after ingestion of offending

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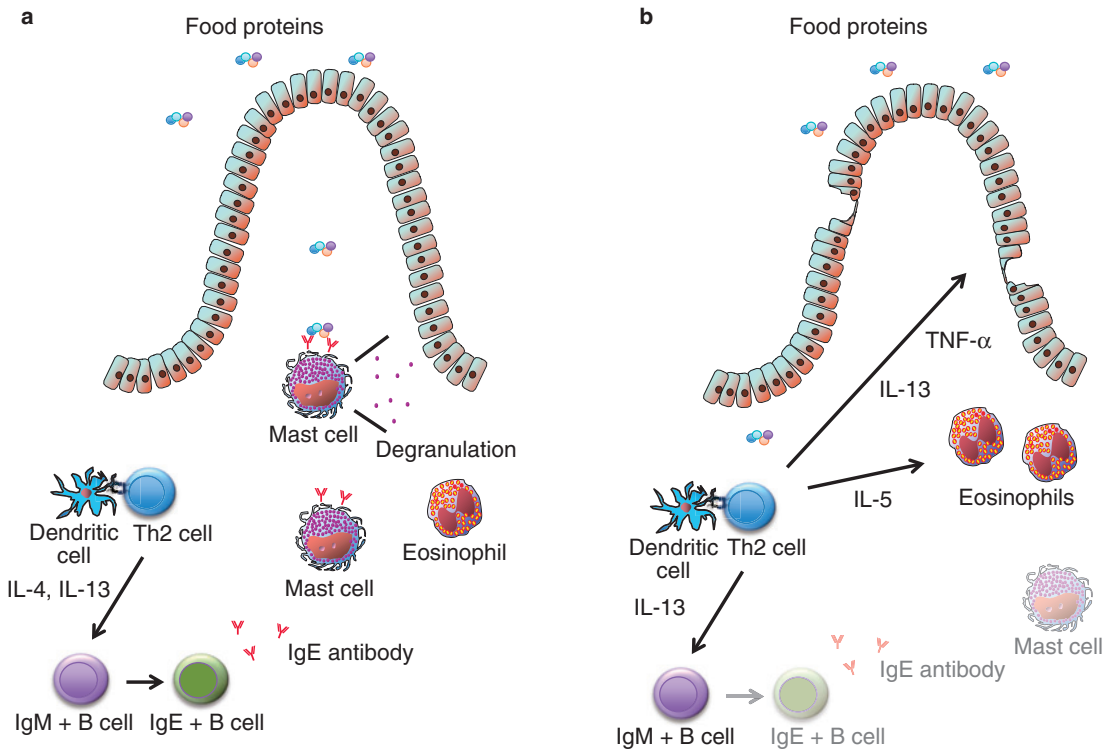

Fig. 1 Pathogenic mechanisms of IgE-mediated food allergy and gastrointestinal food allergy. (**a**) IgE-mediated food allergy. Th2 cytokines such as IL-4 and IL-13, which are produced by T cells in response to specific food antigens, induce B cells to produce food-specific IgE antibodies. The food-specific IgE antibodies bind to the surface of mast cells. Upon re-exposure to the offending food, the food-specific IgE antibodies become cross-linked on the surface of the mast cells, triggering activation and degranulation of the cells. Released mediators, such as histamine and leukotrienes, cause cutaneous and/or respiratory symptoms. (**b**) Gastrointestinal food allergy. Unlike IgE-mediated food allergy, large amounts of inflammatory cytokines such as TNF-α are also produced antigen-specifically by T cells in GI allergies. TNF-α increases intestinal permeability, which facilitates the uptake of undigested food antigens. On the other hand, as in the case of IgE-mediated food allergy, Th2 cytokines such as IL-4, IL-5 and IL-13 are produced by T cells in response to specific food antigens. However, B cells do not produce food antigen-specific IgE antibodies in most patients with GI allergy. IL-13 induces intestinal epithelial damage through activation of the tumor necrosis factor-like weak inducer of apoptosis-fibroblast growth factor-inducible molecule 14 (TWEAK-Fn14) axis. IL-5 accumulates and activates eosinophils in gastrointestinal tissues.

foods.[5] Positive skin-prick tests and significant histamine release from peripheral blood basophils after stimulation with offending food proteins *in vitro* also support these concepts. In some patients, gastrointestinal symptoms such as vomiting and diarrhea are accompanied by cutaneous and/or respiratory symptoms. However, the gastrointestinal symptoms usually appear within 1 hour after ingestion of offending foods,[1] and they are also surmised to be induced by IgE-mediated immune responses.

Unlike IgE-mediated food allergy, some patients exhibit gastrointestinal symptoms such as vomiting, diarrhea and bloody stool several hours (at least 1 hour) after ingestion of offending foods, with only rare cutaneous or respiratory manifestations. Those patients are diagnosed as having a subtype of food allergy, called gastrointestinal food allergy (GI allergy).[6] Specific IgE antibodies to offending foods are rarely detected in sera from patients with GI allergy, especially infants. Therefore, GI allergy is thought to be "cell-mediated/non-IgE-mediated" or "combined IgE- and cell-mediated" disease. However, the precise mechanisms and pathogenesis of GI allergy remain unclear.

GI allergy has classically encompassed a number of different clinical entities: food protein-induced enterocolitis syndrome (FPIES), food protein-induced proctocolitis (FPIP), food protein-induced enteropathy and eosinophilic gastrointestinal disorders (EGID).[2] In the first three, most patients are infants and rarely have detectable food-specific IgE antibodies. Therefore, they have been classified as non-IgE-

mediated diseases. On the other hand, most patients with EGID are adults and young children, and often have detectable food-specific IgE antibodies. Therefore, EGID has been classified as combined IgE- and cell-mediated disease. However, these classifications evolved from different perspectives: the clinical manifestation for the first three entities, and the histological findings for the last. Therefore, there must be some overlap between these clinical entities.[7]

In this review, we trace the history of GI allergy in the literature and summarize the defining features of each disease. We have also tried to elucidate unresolved issues regarding each disease that require further investigation.

FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME (FPIES) (DIETARY PROTEIN-INDUCED ENTEROCOLITIS SYNDROME)

HISTORY

In 1967, Gryboski reported a series of 21 children who developed vomiting and/or diarrhea after ingestion of milk.[8] In 1986, Powell characterized the clinical features of such patients, established diagnostic criteria and coined the term "food protein-induced enterocolitis of infancy".[9] Subsequently, Sicherer *et al*. established the term "Food Protein-Induced Enterocolitis Syndrome (FPIES)".[10]

CLINICAL FEATURES

Patients with FPIES experience repetitive vomiting, starting one or two hours after ingestion of offending foods, followed by diarrhea.[9-16] However, these patients do not develop acute cutaneous or respiratory symptoms, which commonly accompany IgE-mediated food allergy.[9-13,15] Although most patients develop symptoms at least one hour after ingestion of offending foods, total nine patients who have developed symptoms within one hour after ingestion of offending foods were reported.[10,17]

FPIES is sometimes accompanied by systemic symptoms such as hypotension,[9-12,14,17,18] lethargy,[9,11-13,17] pallor,[13] hypothermia,[13] bloody stool,[12,17-19] ileus,[19,20] methemoglobinemia[10,13,14,21] and thrombocytosis.[13,22] Some FPIES patients also develop a high fever, with neutrophilia. Therefore, these patients are sometimes initially mistakenly diagnosed as sepsis or surgical abdominal emergency, etc.[13,22-24]

Although comparatively acute onset after ingestion of offending foods is a characteristic feature of FPIES compared with other GI allergy entities, as stated above, some patients with FPIES exhibit a chronic clinical course.[13,25] The reason for this remains unclear.

OFFENDING FOODS

The most common causal foods of FPIES are cow's milk and soy-based formulas. However, solid foods such as rice,[13,16,17,26-29] oats,[13,17] eggs,[16,30,31] barley,[17] sweet potato,[13,17] chicken,[10,13,17,29,32,33] turkey,[10,17,32] peas,[10,17,32] bananas,[13] fish,[13,16,17,29] lamb,[13] corn,[16,34] and orange juice[35] have also been reported as causal foods. Breast feeding was previously thought to be a protective factor, but recent reports documented five patients with FPIES who reacted to cow's milk or soy protein passed through the breast milk.[25,36,37]

ETIOLOGY

A prospective population-based study in Israel reported that the incidence of milk-induced FPIES was 0.34%.[38] Age at onset of typical FPIES caused by cow's milk or soy-based formula was reported to be less than 9 months of age. However, some patients develop FPIES later than 9 months.[10-12] In addition, the mean age at onset of FPIES caused by solid foods tends to be higher than that of FPIES caused by cow's milk or soy-based formula. A recent report indicates that even adults may develop FPIES caused by solid foods.[39]

DIAGNOSIS

Powell initially defined FPIES based on four criteria.[9] (1) Disappearance of the symptoms of vomiting and diarrhea, and of blood and leukocytes in the stool, after all antigens are removed from the diet. (2) No other cause for the colitis is demonstrable. (3) Symptoms do not recur and weight gain is normal for one month on a low-antigen formula. (4) Challenge with milk or soy formula, or other offending food antigens, reproduces symptoms. Powell also proposed a detailed method for oral food challenge (OFC) as a diagnostic test and criteria for positive responses. Briefly, when more than three of the following five criteria are positive, the challenge is considered positive[9]: (1) vomiting and/or diarrhea symptoms, (2) blood in the stool, (3) leukocytes in the stool, (4) eosinophils in the stool and (5) a change in the blood polymorphonuclear neutrophil count. Although OFC is the most conclusive diagnostic method, it has been associated with a risk of systemic reactions.[9-12,14,17,18,21] Therefore, OFC for diagnostic confirmation can be omitted when the clinical course is typical.[15] In recent years, the diagnostic criteria described by Sicherer have been more commonly used.[10] They are: (1) younger than 9 months of age at initial diagnosis, (2) repeated exposure to the incriminated food elicited diarrhea and/or repetitive vomiting within 24 hours without any other plausible cause for the symptoms, (3) there were no symptoms other than gastrointestinal symptoms elicited by the incriminated food and (4) removal of the offending protein from the diet resulted in resolution of the symptoms, and/or a standardized food challenge elicited diarrhea and/or vomiting within 24 hours after administration of the food.

EXAMINATIONS

The skin-prick test (SPT)[13,17] and specific IgE antibodies[13] for offending foods in the serum are negative in the majority of patients with FPIES at the time of diagnosis. However, some patients have detectable IgE[10,17,36,38] and positive SPT reactions[16,38,40] to offending foods. The symptoms in these patients tend to persist,[10,15] and those patients often develop IgE-mediated food allergy.[16,38,40,41] However, the role of such specific IgE antibodies in the pathogenesis of FPIES remains unclear.

The antigen-specific lymphocyte stimulation test (ALST) is a well-known method for investigating antigen-specific T-cell responses and theoretically should be suitable for diagnosis of FPIES that is thought to be cell-mediated. However, the usefulness of ALST for diagnosis of FPIES has been controversial.[42-45] We recently found that certain amounts of lipopolysaccharide (LPS) that contaminated commercially available cow's milk proteins used in previous reports are able to induce proliferative responses that are antigen-non-specific. In addition, the lymphoproliferative response to LPS was higher in neonates than in young children.[46] Therefore, ALST could be a helpful tool for diagnosis of FPIES if LPS-depleted cow's milk protein preparations are used.

Fogg reported the usefulness of the atopy patch test (APT) for initial diagnosis of FPIES, with 100% sensitivity, 71% specificity, 75% positive predictive value and 100% negative predictive value.[47] However, a more recent report found that APT does not predict outgrowing of FPIES (11.8% sensitivity, 85.7% specificity, 40% positive predictive value and 54.5% negative predictive value).[48] Further studies are needed to elucidate the usefulness of APT for initial diagnosis and prediction of outgrowing FPIES.

TREATMENT

The primary therapy for FPIES is to avoid the causal food antigens, just as for IgE-mediated food allergies. In infantile cases of FPIES caused by cow's milk, breastfeeding tends to be protective. Therefore, 1) exclusive breastfeeding is recommended when possible. However, a small number patients with FPIES react to cow's milk or soy protein passed through the breast milk.[25,36,37] Thus, some account should be taken of this possibility. 2) If exclusive breastfeeding is impossible, cow's milk should be replaced with other nutrition, such as a hydrolysate-based formula, soy-based formula or amino acid formula. Among those formulas, hydrolysate-based formula is preferable to soy-based formula, because it was reported that about half of FPIES patients are sensitive to both milk and soy.[10,17,47,49,50] However, recent reports indicate that the rates of coexisting milk and soy sensitivity are much lower than formerly thought.[13,38] 3) On the other hand, some patients tend to react even to hydrolysate-based formula.[51-53] For them, an amino acid formula is needed.

PATHOGENESIS

The histological findings of patients with FPIES have been reported to be uncharacteristic inflammation: edema, villous atrophy and cellular infiltration in the duodenum and jejunum.[54,55] However, TNF-α expression in the epithelial cells and mononuclear cells in the lamina propria was markedly increased in FPIES patients, especially those having villous atrophy.[55] In addition, TNF-α was highly secreted, antigen-specifically, by PBMC from patients with FPIES[46,56,57] and was also increased in the stool after milk challenge of patients with gastrointestinal milk allergy.[58,59] TNF-α is known to increase intestinal permeability.[57,60] Therefore, TNF-α could be involved in the pathogenesis of FPIES through alteration of intestinal permeability.

Thrombocytosis and leukocytosis after ingestion of offending foods are sometimes observed in patients with FPIES.[13,22] In addition, C-reactive protein (CRP) is often elevated in the sera from patients with GI allergy.[36,61,62] Both reactive thrombocytosis and elevation of CRP are known to be induced by IL-6. We recently found that IL-6 was highly produced, antigen-specifically, by PBMC from patients with GI allergy.[46] Thus, in addition to TNF-α, IL-6 may play some role in the pathogenesis of FPIES.

FOOD PROTEIN-INDUCED PROCTOCOLITIS (FPIP) (DIETARY PROTEIN-INDUCED COLITIS)

HISTORY

Cases of infants with rectal bleeding in the first few months of life have been reported since the 1950s.[63-67] However, in most cases no direct cause for rectal bleeding was able to be identified. In 1982, Lake *et al.* first suggested cow's milk protein passed through breast milk as a possible cause of rectal bleeding, which they experienced in a series of 6 infants who developed bloody diarrhea in the first month of life while being exclusively breast fed.[68] All 6 patients improved after being switched to hydrolyzed milk or soy-based formula, and the bloody diarrhea relapsed in all after being switched back to breast milk. In addition, elimination of cow's milk protein from the maternal diet led to tolerance of breast milk in 2 of 5 patients. Therefore, Lake *et al.* named those cases "dietary protein-induced colitis," meaning "food antigen-specific".[68] Sampson subsequently termed it "food protein-induced proctocolitis" (FPIP).[69]

CLINICAL FEATURES

Patients with FPIP typically develop grossly blood-streaked stool with mucus in the first few months of life. In contrast to FPIES, almost all patients with

FPIP develop no systemic symptoms and seem to be well except for the bloody stool. They have no growth delay or poor weight gain.[68,70-72] Mild anemia is seen in rare cases.[70,72-74] Many patients with FPIP are breast-fed, and the cause is thought to be mainly cow's milk protein passed through the breast milk.[68,71,73,75] Cow's milk and soy-based formulas are the major causative foods in the remaining cases.[74,76] Recently, FPIP have also been seen to manifest in childhood.[77] However, it remains unclear whether FPIP in childhood has the same pathogenesis as that in infants.

DIAGNOSIS

In 1982, Lake *et al*. observed a series of six infants who developed bloody diarrhea caused by cow's milk protein passed through breast milk and confirmed the antigen-specificity using both the antigen elimination test and OFC.[68] Subsequently, there were many reports of infants who developed bloody stool in the first few months of life and showed resolution of the symptoms after being switched to a hydrolyzed milk or soy-based formula.[73,74,76,78] Based on those reports, subsequent papers have assigned a clinical diagnosis of FPIP without OFC to apparently healthy infants with bloody stool and whose symptoms disappear on an elimination diet.

However, recent studies have questioned the accuracy of the elimination diet in diagnosis of the antigen-specificity of FPIP.[79-81] To elucidate the effect of a cow's milk elimination diet on the duration and severity of rectal bleeding in infants, Arvola *et al*.[79] randomly assigned infants with bloody stool to start a cow's milk elimination diet or to continue their current diet. As a result, the cow's milk elimination diet did not affect the duration or severity of rectal bleeding between the two groups. In addition, only 2 of 19 patients who started the cow's milk elimination diet experienced recurrence of gastrointestinal symptoms after reintroduction of cow's milk protein.[79] Jang *et al*. reported that 10 of 16 patients with a chief complaint of rectal bleeding showed resolution of symptoms without any dietary change, while the remaining 6 cases responded to a cow's milk elimination diet. However, only 2 of those 6 responders developed symptoms after OFC.[81]

These findings indicate that infants with bloody stool might include a small percentage of patients with FPIP that is actually caused in an antigen-specific manner. In support of this notion, Ohtsuka *et al*. reported 2 infants who had bloody stool on the first day of life, before initial feeding, but subsequently never developed bloody stool even with breast milk without maternal diet modification.[82] These facts suggest that there are some special enteral environments in early infancy that may result in antigen-nonspecific hemorrhage in the colon.

In that sense, patients with bloody stool whose antigen specificity was confirmed by both an elimination diet and OFC should be referred to as "true" FPIP. However, in this review we are going to treat patients with bloody stool as having FPIP even if they were diagnosed only by an elimination diet, without OFC. Thus, a certain proportion of FPIP patients may have antigen-nonspecific bloody stool, but in order to discuss FPIP, we must include these patients because only little studies other than Lake *et al*.'s confirmed antigen specificity in their subjects by OFC.

EXAMINATIONS

The endoscopic findings for FPIP are lymphonodular hyperplasia (LNH), with an oozing and edematous mucosal surface. The common histological features are LNH[70,71,78,83-86] and numerous eosinophils in the lamina propria.[70,71,73,74,76,78,83,86,87] Accordingly, apparently healthy infants with bloody stool and LNH and/or numerous eosinophils in the lamina propria were histologically diagnosed as FPIP and also called "allergic colitis".[73,74,76,78,83]

LNH in the colon has been reported to be associated with food allergy.[88-90] LNH can also be observed in other diseases, not just in FPIP.[88,89,91] In addition, Xanthakos reported several patients with LNH who had spontaneous resolution of rectal bleeding without any dietary change.[80] These findings suggest that LNH may be a self-limiting, age-related change, regardless of the antigen specificity.

A histological finding of eosinophil infiltration (6 cells/high power field (HPF)) in the lamina propria was thought to be a useful threshold for diagnosis of FPIP.[75,83] However, DeBrosse *et al*. recently described that eosinophils (mean 16-20 cells/HPF) were normally observed in the gastrointestinal tract of control children, especially in the colon.[92] In addition, Jang *et al*. reported that only 2 of 10 patients who exhibited marked eosinophil infiltration of the lamina propria (more than 6 cells/HPF) developed symptoms after OFC.[81]

Therefore, diagnosis of FPIP based on elimination tests, the endoscopic findings and the histological findings presents a risk of over-diagnosis. In this context, for accurate diagnosis of FPIP, OFC after an elimination diet should be recommended for apparently healthy patients with bloody stool.

TREATMENT

As in the case of other food allergies, elimination of causal food antigens is the gold-standard treatment for FPIP. Many patients with FPIP are breast-fed infants. Therefore, elimination of cow's milk from the maternal diet would be the first choice and an effective method.[71] However, some patients still react to breast milk even after the mother has strictly eliminated cow's milk from her diet.[68,78,93] For such patients, the infant's nutrition should be changed to a hydrolyzed milk or soy-based formula. However,

some patients respond even to hydrolyzed milk.[51,78,80] For them, an amino acid formula is needed.

PATHOGENESIS

Based on the endoscopic and pathological findings, activation of eosinophils and lymphocytes associated with LNH is thought to play an important role in the pathogenesis of FPIP. In support of this notion, Ohtsuka *et al*. recently showed that CCL11 (eotaxin-1) mRNA and CXCL13 mRNA were highly expressed in the large-intestine mucosa of infants with FPIP compared with control subjects.[94] However, the pathogenic mechanisms underlying induction of eosinophilic inflammation in the colon remain unclear.

INTESTINAL MICROBIOTA

Several investigator groups have reported an interesting finding that delayed maturation of the intestinal flora possibly causes rectal bleeding in infants.[79,95,96] In normal newborn babies, there is transient intestinal colonization by facultative anaerobes immediately after birth. Thereafter, obligate anaerobes such as *Bifidobacterium*, *Bacteroides*, *Clostridium* and *Lactobacillus* species increase and establish colonization, with reduction of facultative anaerobe counts. However, the counts of obligate anaerobes, especially *Bifidobacterium*,[79,95] *Lactobacillus*,[79] *Clostridium leptum* group (*C. leptum) and Clostridium coccoides* group (*C. coccoides*),[96] were significantly lower in the feces of patients with FPIP than in healthy breast-fed infants. These findings suggest that there is delayed maturation of the intestinal flora in patients with FPIP.

In addition, Atarashi *et al*. revealed that a mixture of 46 strains of *Clostridium spp*., including *C. leptum* and *C. coccoides*, promote regulatory T cell (Treg cells) accumulation and also affect their function in the colon of mice.[97] The fact that there are lower counts of *C. leptum* and *C. coccoides* in the feces of patients with FPIP suggests that impaired induction of Treg cells in the colon may be involved in the pathogenesis of FPIP. In support of this, Cseh *et al*. found that the ratio of Treg cells in PBMC was lower in patients with FPIP than in control subjects.[98] Moreover, *C. leptum* and *C. coccoides* also promote accumulation of IgA-positive cells in the colon[99] and induce IgA production through induction of Treg cells that produce TGF-β.[100] In support of this, secretory IgA concentrations in the feces tend to be lower in patients with FPIP than in control subjects.[96] These findings suggest that impaired induction of Treg cells and IgA (which contribute to homeostasis in the intestine) due to delayed maturation of the intestinal flora may be a cause of FPIP. In fact, children who outgrew their GI allergy had higher frequencies of circulating Treg cells after OFC compared with children with persistent GI allergy.[101]

However, it remains totally unknown how antigen-specific immune responses link to delayed maturation of the intestinal microbiota. Further investigation is needed to elucidate whether the underlying mechanisms are the same between patients with FPIP who really respond to food antigens specifically and those who do not.

FOOD PROTEIN-INDUCED ENTEROPATHY (ENTEROPATHY)

HISTORY

Patients with food protein-induced enteropathy (Enteropathy) were initially described by several investigators in the 1960s as malabsorption syndromes caused by cow's milk protein.[102-105] Subsequently, in the late 1970s, such patients were described as having "enteropathy induced by cow's milk".[106,107]

CLINICAL FEATURES

Patients with Enteropathy typically develop chronic diarrhea and show poor weight gain in the first several months of life.[108] Mild to moderate anemia and hypoproteinemia were seen in some patients with Enteropathy.[108] The clinical features of Enteropathy are similar to those of celiac disease that is associated with sensitivity to wheat protein. However, celiac disease is not included in this entity.

DIAGNOSIS

The diagnostic procedure for Enteropathy relies heavily on elimination tests and OFC. Jejunal biopsy is often helpful for diagnosis and follow-up.[108]

PATHOPHYSIOLOGY

The histological findings of patients with Enteropathy were well characterized in the 1970s to 1980s. In brief, jejunal biopsy specimens from patients with Enteropathy showed various degrees of villous atrophy with crypt hyperplasia,[109-111] increased numbers of intraepithelial lymphocytes,[108,112] and increased numbers of lymphocytes, plasma cells and eosinophils in the lamina propria.[113]

Chung *et al*. reported that extracellular deposition of major basic protein (MBP), which is an eosinophil granule protein, in the lamina propria was significantly higher in patients with Enteropathy than in control subjects. In addition, extracellular deposition of MBP correlated significantly with the severity of mucosal villous atrophy.[114] These findings suggest that MBP released by eosinophils plays an important role in the pathogenesis of Enteropathy by inducing mucosal damage that leads to the villous atrophy.

However, patients with Enteropathy have rarely been reported since 2000.[115]

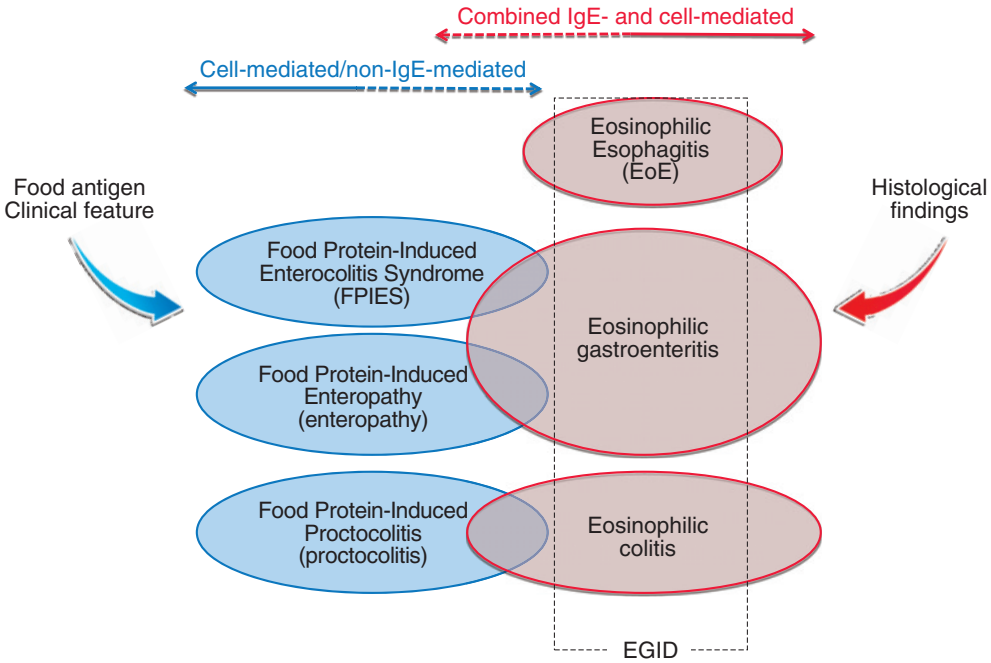

Fig. 2 Clinical and histological characterization of GI allergies. From the standpoint of an allergist, GI allergies (FPIES, FPIP and Enterocolitis) are diseases characterized by antigen-specific immune responses (left-hand side). On the other hand, from the standpoint of a gastroenterologist, gastrointestinal diseases with eosinophil infiltration are called eosinophilic esophagitis, gastroenteritis and colitis (right-hand side). The disease pathogenesis, especially how much these entities may overlap, warrants further investigation.

CURRENT TOPICS AND FUTURE PERSPECTIVES

FOUR DISTINCT CLINICAL SUBTYPES IN NON-IgE-MEDIATED FOOD ALLERGIES IN INFANTS

We recently tried to classify infants with gastrointestinal symptoms by using cluster analysis of their clinical and laboratory findings.[36] We found that these patients can be classified into 4 distinct subtypes according to the presence or absence of vomiting and bloody stool. In brief, patients who had vomiting with or without bloody stool were likely to be diagnosed as having FPIES. Patients who had only bloody stool were likely to be diagnosed as having proctocolitis. Patients who had neither vomiting nor bloody stool were likely to be diagnosed as having enteropathy. In all four clusters, oral food challenge tests showed remarkably high reproducibility of the symptoms found at the initial presentation, even though the oral challenge tests were performed several months after the initial presentation. This observation suggests that the upper or lower gastrointestinal tract-specific hypersensitivity and perhaps the responsible immune cells remain in the same part of the gastrointestinal tract even after several months' remission.

ROLE OF IgE ANTIBODIES IN GI ALLERGY

Some patients with non-IgE-mediated GI allergies have detectable levels of food-specific IgE antibodies.[10,17,38] In the abovementioned study,[36] a positive milk-specific IgE antibody titer was observed in 37% of the patients, with no statistically significant differences among any of the 4 subtypes. Interestingly, almost all symptoms at initial presentation as well as in OFC began to manifest at more than two hours after ingestion of the offending food, but no patients developed typical IgE-mediated symptoms such as urticaria or wheeze. These results strongly suggest that the presence of milk-specific IgE antibody neither fully explains the gastrointestinal symptoms nor rules out a diagnosis of non-IgE-mediated GI allergy in infants.

In contrast, EGID was classified as a combined IgE- and cell-mediated disease because many patients with EGID have detectable food-specific IgE antibodies.[7] However, the roles of IgE antibodies in the pathogenesis of EGID remain unclear.

The precise roles of IgE antibodies in GI allergy and EGID warrant further investigation.

CYTOKINE SECRETION PROFILES IN GI ALLERGY

We recently determined—for the first time—the

antigen-specific cytokine secretion profiles of PBMC from infants with non-IgE-mediated GI allergy using extensively LPS-depleted milk antigens and 89 blood samples originating from all over Japan through the Japanese Research Group for Neonatal, Infantile Allergic Disorders.[46] We found significantly high concentrations of TH2 cytokines, but not TH1 or TH17 cytokines, in the culture supernatants of those PBMC. The pathogenesis of non-IgE-mediated gastrointestinal allergy had been thought to be "non-TH 2" cell-mediated because IgE antibody is usually undetectable. However, our results strongly indicate that the pathogenesis is, in fact, "TH2" cell-mediated. In particular, high levels of IL-13 and TNF-α may play critical roles in intestinal epithelial cell damage and eosinophil infiltration, presumably through activation of the tumor necrosis factor-like weak inducer of apoptosis-fibroblast growth factor-inducible molecule 14 (TWEAK-Fn14) axis.[116] However, it remains unclear why these patients do not produce antigen-specific IgE antibodies. It may be due to reduced expression of the IL-4 receptor alpha chain and reduced IL-4-induced signaling in neonatal B cells. Further studies are needed to elucidate this issue.[117]

DISEASE ENTITIES OF GI ALLERGY AND EGID

The definitions and diagnostic criteria for GI allergy and EGID were drawn up from different perspectives. Non-IgE mediated diseases such as FPIES, FPIP and Enteropathy are diagnosed mainly on the basis of the clinical manifestation, as described earlier. On the other hand, combined IgE- and cell-mediated diseases such as EGID including eosinophilic gastroenteritis, eosinophilic colitis and eosinophilic esophagitis (EoE) are diagnosed mainly on the basis of a single histological finding, that is, inappropriate accumulation of eosinophils in the gastrointestinal tract.[118] However, many investigators reported that such accumulation is often observed even in patients with non-IgE-mediated GI allergy. Therefore, there must be some overlap and similar pathogenic mechanisms between non-IgE-mediated GI allergy and EGID.[7] In support of this, we recently found that—along with such inflammatory cytokines as TNF-α and IL-6—Th2 cytokines, including IL-3, IL-5 and IL-13, but not Th1 cytokine or Th17 cytokine, were significantly produced *in vitro* by milk protein-stimulated PBMCs from infant patients with GI allergy compared with control subjects.[46] These findings suggest that antigen-specific Th2-type immune responses underlie the pathogenesis of non-IgE-mediated GI-allergy (Fig. 1).

The incidence of each GI allergy is relatively low in comparison to that of IgE-mediated food allergy.[38,62] Therefore, the diagnostic and classification criteria depend heavily on small numbers of cases experienced by various investigators and were drawn up from their different standpoints, for example, as a pediatrician, an allergist, a neonatologist and a gastroenterologist. The low prevalence and the different standpoints may have strongly impacted on the different diagnostic criteria for GI allergy and EGID (Fig. 2). To resolve this matter and to obtain a complete view of GI allergy, we need to conduct a multicenter study with cooperation among pediatricians, allergists, neonatologists and gastroenterologists.

Fortunately, we have constructed a nation-wide database using an internet online system and have obtained data for over 500 patients with GI allergy, thanks to the cooperation of doctors all over Japan. That database has started to generate valuable results, step by step.[36,46] We hope to carry out further investigations that will fully elucidate the pathogenesis of GI allergy.

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