



Unique features of non-IgE-mediated gastrointestinal food allergy during infancy in Japan

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Purpose of review

An increase in incidence of unique phenotypic non-IgE-mediated gastrointestinal food allergies (non-IgE GIFAs) has occurred in Japan ahead of Western countries. There are differences in clinical features of non-IgE GIFAs in Western and Japanese patients. As this phenotype has now come to be recognized internationally, we describe it in this review.

Recent findings

A large number of Japanese patients with non-IgE GIFAs present with vomiting accompanied by bloody stool, putting them between food protein-induced enterocolitis syndrome (FPIES) and food protein-induced allergic proctocolitis. Some neonates and early infants with non-IgE GIFAs who present with fever and elevated C-reactive protein have symptoms consistent with severe systemic bacterial infections (e.g., sepsis). Some of these cases have now been defined in international guidelines as chronic FPIES. Eosinophils might be involved in the inflammatory process observed. The incidence of FPIES and food protein-induced allergic proctocolitis is increasing in Western countries and likely worldwide, after it has increased in Japan.

Summary

The phenotype observed in Japan shows distinct clinical features compared with the classical phenotype, that is, increased levels of eosinophils, suggestive of 'eosinophilic shift' alongside symptomatic differences, making it difficult to categorize.

Keywords

eosinophilic gastrointestinal disorders, food protein-induced allergic proctocolitis and food protein-induced enteropathy, food protein-induced enterocolitis syndrome, non-IgE-mediated gastrointestinal food allergies

INTRODUCTION

Non-IgE-mediated gastrointestinal food allergies (non-IgE GIFAs), including food protein-induced enterocolitis syndrome (FPIES), food protein-induced allergic proctocolitis (FPIAP), and food protein-induced enteropathy (FPE) [1^{*}] have been well established concepts since the late 1960s [2]. However, non-IgE GIFAs have recently attracted more attention in Japan, as the number of patients with non-IgE GIFAs has been increasing since the 2000s [3,4]. In addition, the phenotype observed among Japanese patients is considered different from traditional phenotypes. Specifically, a number of Japanese patients with non-IgE GIFAs have eosinophilic inflammation in histopathology findings or laboratory findings suggestive of the association with eosinophil infiltration. This 'Japanese phenotype' has been internationally recognized up to a point and included in the international consensus

guidelines as a chronic type of FPIES [5]. This review briefly discusses the unique features of Japanese non-IgE GIFAs in infancy.

CLASSIFICATION OF GASTROINTESTINAL FOOD ALLERGIES BASED ON ALLERGEN-SPECIFIC IgE TYPES

Gastrointestinal allergies have been divided into three broad groups on the basis of detectability of

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Curr Opin Allergy Clin Immunol 2020, 20:000–000

DOI:10.1097/ACI.0000000000000642

KEY POINTS

- A different non-IgE-GIFA phenotype, including chronic FPIES, occurred in Japan before it occurred in Western countries.
- Non-IgE-GIFAs are associated with eosinophils, implying a histology overlap with eosinophilic gastrointestinal disorders.
- Laboratory tests for non-IgE-GIFAs such as C-reactive protein, allergen-specific lymphocyte stimulation tests, and fecal eosinophil-derived neurotoxin, which have been developed in Japan, might contribute to improvement in diagnostic accuracy.
- 'Eosinophilic shift' might be present in non-IgE-GIFAs as well as chronic rhinosinusitis.

allergen-specific IgE: IgE-mediated, non-IgE-mediated, and mixed type (Fig. 1) [1^{*},6]. Although digestive symptoms often present in IgE-mediated food allergy (or an IgE-mediated gastrointestinal allergy), a number of clinical entities falls within the non-IgE GIFAs category, namely, FPIES, FPIAP, and FPE. In addition, typical mixed type gastrointestinal

allergies are eosinophilic gastrointestinal disorders (EGIDs) [7^{*}]. These disease categories are not independent. Indeed, allergen-specific IgEs are detectable in approximately 30% of patients with non-IgE GIFAs [4,6,8]. As patients with non-IgE GIFAs do not always undergo endoscopic biopsy [9^{**}], standard histology remains unclear, at least, eosinophilic infiltration fulfilled the criteria of EGIDs are commonly presented in classical FPIAP [10] and recently also seen in a subtype of FPIES [11^{*},12].

INTERNATIONAL CONSENSUS GUIDELINES-BASED CLASSIFICATION OF FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME ASSOCIATED WITH THE JAPANESE PHENOTYPE

FPIES is the most controversial type of non-IgE GIFAs, which can be severe and persistent. It has been known since the late 1960s [2], but it is not well recognized among pediatricians. Recently, the first international consensus guidelines on FPIES have been published [5], including criteria that differ from the well known Powell's criteria and challenge protocol [13] for FPIES due to cow's milk. In

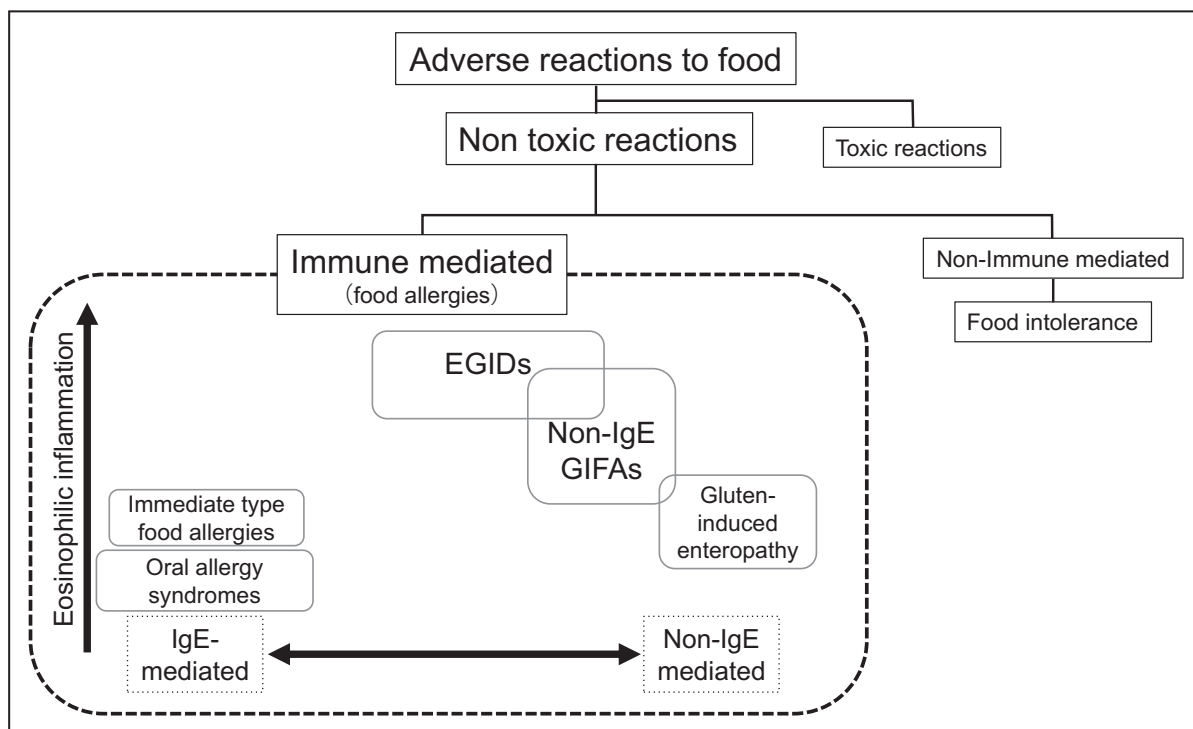


FIGURE 1. Classification of adverse reactions to food. Allergic adverse reactions to food (food allergies) are caused through antigen-specific immunological mechanisms after exposure to offending foods. There is an overlapping between non-IgE mediated gastrointestinal food allergies including food protein-induced enterocolitis syndrome, food protein-induced allergic proctocolitis and food protein-induced enteropathy and eosinophil gastrointestinal disorders. Longitudinal and horizontal axes are the strength of involvement in eosinophil and the detectability of allergen-specific IgE, respectively. EGIDs, Eosinophil gastrointestinal disorders; non-IgE-GIFAs: non-IgE mediated gastrointestinal food allergies.

addition, the new criteria remove the age limit for FPIES onset and emphasize repetitive vomiting as a symptom. In addition to its acute form, chronic FPIES has been introduced as a separate subtype, which occurs worldwide [14²²,15], however, it tends to be more common in Japan and Korea [4,16,17]. The associated symptoms include intermittent emesis, chronic diarrhea, poor weight gain, and/or failure to thrive due to daily ingestion of offending foods. Symptoms usually resolve within days after exclusion of the offending foods and reoccur as an acute FPIES when the offending foods are reintroduced. However, literature regarding chronic FPIES is limited [14²²,15]. Indeed, some cases different from the classical FPIES suggestive of chronic FPIES might present with clinical course different than the symptoms listed in the new guidelines [16].

THE CHARACTERISTICS OF NON-IgE-MEDIATED GASTROINTESTINAL FOOD ALLERGIES IN JAPAN

The number of infants with non-IgE-mediated food allergy has been increasing rapidly in Japan since the late 1990s. The estimated incidence of non-IgE GIFAs at neonatal care units in Japan was 0.21% from 2004 to 2005 (the incidence of non-IgE GIFAs was estimated to be 0.13% after excluding patients suspected of FPIAP) [3]. In contrast, pediatric FPIES incidence in the United States was 0.023% (peaking at 6 months of age) from 2005 to 2009, before its recent increase to 0.42%, (cumulative incidence: 0.14%) [18²²]. Differences in clinical features of non-IgE GIFAs between Western and Japanese patients have been observed [3,4,8,19–21]. Classically, non-IgE GIFAs in patients with bloody stool as a prominent symptom are classified as FPIAP [9²²,22,23²⁴,25²²]. Patients with FPIAP present with bloody stool but are otherwise healthy; such cases are associated with good prognosis. In contrast, classical FPIES is characterized by repetitive projectile vomiting and subsequent diarrhea, which rarely contains blood [26,27]. However, nearly half of patient with the Japanese type of non-IgE GIFAs presented with vomiting accompanied by bloody stool, which classifies them in-between the FPIES and FPIAP categories [4,20]. According to recent studies, the incidence of FPIAP and FPIES is increasing in the United States [22,23²⁴,25²²]. Clinical features such as fever and elevated C-reactive protein (CRP) levels in neonates or early infants represent a mixed phenotype, reminiscent of severe systemic bacterial infections such as sepsis or meningitis [19,20]. Symptoms of greater severity in patients with mixed phenotypes indicate FPIES rather than FPIAP [20]. Indeed, this phenotype

should be included in the international consensus guidelines as a subtype of chronic FPIES [5]. As these three types of non-IgE GIFAs are usually treated as a single entity in Japan, to accurately classify Japanese patients with non-IgE GIFAs, a cluster analysis was performed using data from patients registered in a national database of clinical parameters [4]. The analysis authors identified four clusters based on the presence or absence of vomiting and bloody stool, consistent with the clinical phenotype described above. Classical FPIES and FPIAP were categorized as cluster 2 and cluster 4, respectively. Cluster 1 was the previously described mixed phenotype. Based on symptoms, FPE should be included in cluster 3, although pathological findings required for diagnosis were not included in the analysis [28]. In this cluster analysis, all clusters had abnormally high percentage of peripheral blood eosinophils, whereas fecal eosinophils were observed in more than half of all included patients, except for patients in cluster 3. Furthermore, cluster 4 seemed to present with symptoms severer than those of classical FPIAP. Finally, approximately 10% of patients developed severe complications. Moreover, levels of eosinophil granule protein and eosinophil-derived neurotoxin (EDN) were greater in patients with FPIES [29] and FPE [30], implying eosinophil infiltration. These findings were partly corroborated by gastrointestinal eosinophilia confirmed in histological analysis [11¹²]. In addition, studies have shown that, in Japan, neonates undergoing gastrointestinal surgery have a higher incidence of non-IgE GIFAs [31]. To improve their recognition, guidelines on diagnosis and management of non-IgE GIFAs in Japanese patients (available only in Japanese) were released in 2018 [32,33]. The characteristic statements are presented in Table 1. It is a common understanding that better recognition of non-IgE-GIFAs as a whole is important. Therefore, practice guidelines have also published in various countries [9²²,34].

THE RELATIONSHIPS BETWEEN EOSINOPHILIC GASTROINTESTINAL DISORDERS AND NONIMMUNOGLOBULIN E-MEDIATED GASTROINTESTINAL FOOD ALLERGIES

EGIDs have attracted attention due to rapid progress in research on eosinophilic esophagitis (EoE). EGIDs include EoE, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, and eosinophilic colitis [7¹⁰]. EGIDs are primarily allergic disorders, involving mechanisms that fall between IgE-mediated and cellular (Th2) responses. Allergic/eosinophilic inflammation is a common pathophysiological

Table 1. Characteristic statements contained in Japanese non-IgE mediated gastrointestinal food allergies guidelines

Characteristic statements	
1	ALST is not specific to non-IgE allergies but confirms antigen specificity
2	Elimination test are strongly recommended. Challenge tests should be carefully considered
3	The association with eosinophils is not necessary for the diagnosis
4	Histological findings may support a definitive diagnosis in some cases
5	Not moderately but highly hydrolyzed milk is recommended for treatment
6	Steroids are not recommended as maintenance therapy
7	Leukotriene receptor antagonists are occasionally effective when presentation overlaps with EGIDs
8	If a challenge test is positive, repeat every 6 months to 1 year until negative
9	Non-IgE-GIFAs have a favorable prognosis

ALST, allergen-specific lymphocyte stimulation tests; EGIDs, eosinophilic gastrointestinal disorders; non-IgE GIFAs, non-IgE mediated gastrointestinal food allergies.

feature of allergic disorders and consists of three temporal phases: early-phase and late-phase reactions, and chronic inflammation (delayed reaction). Eosinophil accumulation is observed in late and delayed reaction phase, resulting in persistent inflammation [35]. This common mechanism applies to EGIDs to some extent. Unlike EoE, little new evidence has emerged on other EGIDs. Within EGIDs, pathological diagnosis of FPIAP among non-IgE GIFAs tends to be eosinophilic colitis. Eosinophilic colitis shows a bimodal age distribution, with peaks in infancy, and adolescence and early adulthood [10]. The infantile form tends to be diagnosed at a mean age of 2 months; FPIAP is considered an early form of eosinophilic colitis. In contrast to FPIAP, reports of involvement of eosinophils, such as peripheral blood and/or tissue eosinophils, and fecal eosinophils have been limited in publications about FPIES and FPE [26]. However, eosinophils associated with non-IgE GIFAs might also be present in FPIES cases in Japan [4,21] and elsewhere [15,17]. Although the level of peripheral eosinophils should decrease during an acute FPIES-related reaction [36], these can be marked increase subsequently [21] and besides, activated in both blood and gastrointestinal tract in FPIES [37]. Moreover, serum levels of Th2 cytokines, such as IL-4, IL-5, and IL-13 were elevated in patients with FPIES who presented with bloody stool compared with patients who presented without bloody stool [38]. In fact, the Minister of Health, Labour, and Welfare of Japan has designated severe non-IgE-GIFAs as an EGIDs-associated intractable disease [33]. In contrast, recent research, in which the severity of non-IgE GIFAs was graded according to the presence of extra-gastrointestinal symptoms, has shown that mild to moderate cases presented with eosinophilic inflammation, whereas infiltration of inflammatory cells (other than eosinophils) was a feature of the most severe cases [11[¶]]. In addition, the presence of eosinophilia at diagnosis correlated with sooner acquisition of tolerance [39].

The pathogenesis of non-IgE GIFAs remains poorly understood as endoscopy and biopsies are not routinely performed. These procedures require general anesthesia at this age and are unlikely to change clinical practice regarding non-IgE GIFAs, except for supporting differential diagnosis [9^{¶¶}]. Further research is required to determine whether non-IgE GIFAs share disease pathogenesis and clinical features with EGIDs.

LABORATORY EXAMINATIONS FOR NON-IgE-MEDIATED GASTROINTESTINAL FOOD ALLERGIES MAINLY ESTABLISHED IN JAPAN

A diagnosis of a food allergy is based on the observation of *allergic symptoms* following the intake of suspected foods, performed as an oral food challenge test in clinical practice, and concurrent presence of *allergen-specific* immune reactions [40]. In contrast to IgE-mediated allergic reactions, only approximately 30% of patients with non-IgE GIFAs have antigen-specific IgE [3,4,39] and therefore require other laboratory tests to determine antigen specificity. Atopy patch tests for foods are an example of such alternative tests; it seems to be promising but standardization on the procedures may be an issue for the test [41–44]. In Japan, a large number of patients undergoes allergen-specific lymphocyte stimulation tests (ALST), which is considered a reliable diagnostic method [8,44,45]. As a result, the Japanese national guidelines alert physicians that ALST can be used to verify antigen specificity but not to confirm a diagnosis of non-IgE GIFAs [32]. The instant peripheral blood allergen stimulation test (iPAST), which requires a small amount of blood and is time-efficient compared with ALST, has been developed as a surrogate test [46[¶]].

Nevertheless, increased CRP levels accompanied by fever are sometimes observed in non-IgE

GIFAs, which are symptoms reminiscent of sepsis or meningitis in a neonate [20]. CRP should be routinely tested in cases of suspected non-IgE GIFAs in Japan. Increased CRP levels that occur simultaneously with fever are sometimes observed during oral food challenge in patients with FPIES, in which they might indicate intestinal inflammation [19]. Increased CRP levels might be indicators of poor prognosis in FPIES [39]. Recent studies have documented significant increases in CRP levels in patients based in Europe [47]. In addition to CRP, another study from Japan reported a transient increase in serum levels of thymus and activation-regulated chemokine that is a severity and treatment marker for atopic dermatitis [48], in the patients with FPIES after ingesting the offending foods [49].

In theory, fecal matter tests might better reflect colonic inflammation. Stool eosinophils might be a useful supplementary test; the level of eosinophil granule protein or EDN could reflect gastrointestinal eosinophilic inflammation [50]. Indeed, elevation in fecal EDN was observed in patients with FPIES [29] and FPE [30] as well as FPIAP [51], in which it is known as allergic (eosinophilic) colitis, reflecting histological findings. A separate report proposed abdominal Doppler ultrasonography and small intestinal vessel density at symptomatic state as parameters that support diagnosis and evaluation of non-IgE GIFAs [52].

Altogether, while there has been a growing interest in ALST (including iPAST), CRP, fecal eosinophils, and EDN, the risks and benefits of these tests on the interpretative significance should be carefully considered.

CONCLUSION

The incidence of non-IgE GIFAs in Japan and Western countries has increased; this phenotype might become more common worldwide [4,14¹¹]. Its clinical features in Japanese patients include coexistence of repetitive vomiting and bloody diarrhea alongside eosinophilic/type 2 inflammation (consistent with EGIDs), which are distinct from the classical phenotypes [20]. This phenotype is now partly recognized as a chronic type of FPIES, however, it remains poorly understood, whereby some patients develop the disease in the absence of regular/repeated ingestion of triggering foods [8] and even before ingestion of milk [53]. The cause of this difference remains unclear, but it might be associated with 'eosinophilic shift,' comparable with mechanism present in chronic rhinosinusitis [54]; increase of EoE could be another example of it. Determining if an 'eosinophilic shift' occurs in

non-IgE-GIFAs might help elucidate the cause and pathophysiology of the emerging non-IgE-GIFA phenotype.

Acknowledgements

The author is also thankful to Mses. Kyoko Iwasaki and Ryoko Murata for their excellent technical and office work.

Financial support and sponsorship

The work was supported by Research on Intractable Diseases, Health and Labour Sciences research grants from the Ministry of Health, Labour and Welfare of Japan (H22-Nanchi-Ippan-066 and 070, H24-Nanchi-Ippan-044 and H26-Nanchi-Ippan-048 to Y.Y.) and by a Grant-in-Aid for Scientific Research C from the Ministry of Education, Culture, Sports, Science and Technology of Japan (24592702 and 16K11358 to Y.Y.).

Conflicts of interest

There are no conflicts of interest.

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