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Non-immunoglobulin E-mediated gastrointestinal food allergies in children with Down syndrome: An epidemiological study

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ABSTRACT

Background: Non-immunoglobulin E-mediated gastrointestinal food allergies (non-IgE-GI-FAs) in children with Down syndrome (DS) tend to be more severe, with some children presenting with sepsis-like symptoms. However, the epidemiology of this condition remains unknown. This study aimed to investigate the prevalence rate and clinical characteristics of non-IgE-GI-FAs in children with DS.

Methods: This study included 115 children with non-IgE-GI-FAs diagnosed at 13 hospitals in Yamaguchi Prefecture, Japan, between January 1, 2011, and December 31, 2020. The children were classified into DS and non-DS groups, and their clinical characteristics were retrospectively compared.

Results: Among the 115 children with non-IgE-GI-FAs, 7 and 108 were included in the DS and non-DS groups, respectively. During the study period, 184 children with DS were born in Yamaguchi prefecture, and 7 developed non-IgE-GI-FAs. In this study, the prevalence rate of non-IgE-GI-FAs was 3.8% (7/184) in children with DS and 0.11% (108/98,989) in children without DS. No significant differences were observed in causative foods, age at onset, age at diagnosis, or age at confirmed clinical remission between the 2 groups. Most children in both groups experienced vomiting and diarrhea, but none had hypothermia. Sepsis-like symptoms, such as lethargy (71.4% vs. 24.1%, $P = 0.0150$), hypotension (42.9% vs. 0.9%, $P = 0.0006$), and fever (57.1% and 8.3%, $P = 0.0030$), were significantly more common in the DS group than in the non-DS group.

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Conclusions: The prevalence rate of non-IgE-GI-FAs was 3.8% in children with DS and 0.11% in children without DS. Non-IgE-GI-FAs in children with DS were significantly more severe than those in children without DS. Non-IgE-GI-FAs should be considered a differential diagnosis when sepsis-like symptoms are observed in children with DS.

Keywords: Down syndrome, Epidemiology, Food allergy, IgE, Sepsis-like

INTRODUCTION

Non-immunoglobulin E-mediated gastrointestinal food allergies (non-IgE-GI-FAs) primarily occur in infants and young children.[1,2] They include food protein-induced enterocolitis syndrome (FPIES), food protein-induced enteropathy (FPE), and food protein-induced allergic proctocolitis (FPIAP).[3] FPIES typically presents with repetitive vomiting and diarrhea; FPE presents with chronic, non-bloody stools with malabsorption, poor weight gain, and failure to thrive; and FPIAP presents with only bloody stools. In contrast to FPIES and FPE, most children with FPIAP remain clinically well, with no severe symptoms of vomiting and diarrhea and no significant growth failure.[3] In non-IgE-GI-FAs, associated gastrointestinal (GI) symptoms are usually delayed after exposure to foods and can present chronically.[4,5] Internationally recognized consensus guidelines define the diagnostic criteria for FPIES;[6] however, no such criteria exist for FPE and FPIAP. Although specific biomarkers remain lacking and intestinal biopsies are not routinely performed, FPIES and FPIAP are diagnosed based on clinical symptoms; however, FPE diagnosis requires histological confirmation.[7] Notably, non-IgE-GI-FAs comprise distinct clinical entities but may present with overlapping clinical symptoms.[3] The epidemiology of non-IgE-GI-FAs remains underexplored. Cohort data indicates 0.015%–0.70% and 0.16%–64.0% incidence of FPIES[8-11] and FPIAP,[5,12] respectively. Although the overall prevalence of FPE is unknown, reports suggest that it has been declining over the past few decades.[13]

The number of children with non-IgE-GI-FAs appears to be increasing rapidly worldwide, including in Japan in the last 10 years.[14] However, most children in Japan do not meet the diagnostic criteria for non-IgE-GI-FAs proposed in the United States.[15-17] They exhibit several symptoms, ranging from bloody stools alone to sepsis-like symptoms, such as fever and shock.[18-20] Considering this information, the 2017 Japanese Pediatric Guidelines for Food Allergy (JPGFA) classified all clinical presentations of GI symptoms caused by food allergens, especially during infancy, as "neonatal and infantile GI allergy" or "non-IgE-GI-FAs in neonates and infants."

Down syndrome (DS) is caused by a trisomy of human chromosome 21 and occurs in approximately 1 in 1000 newborns.[21-23] As the immune system in individuals with DS is altered, accompanied by signs of deficiency and dysregulation, the incidence and prevalence of autoimmune diseases is high among them.[24] Both FPIES and FPE have been reported in patients with DS, who may present with a protracted course.[25-31] Non-IgE-GI-FAs in children with DS tend to be more severe, with sepsis-like symptoms being observed in some. However, most of the published data on non-IgE-GI-FAs in children with DS are based on a single-center experience, and their epidemiological and clinical characteristics remain unclear.

In this study, we aimed to investigate the prevalence rate and the clinical characteristics of non-IgE-GI-FAs in children with DS in a prefecture of Japan, based on information collected from all pediatric hospitals throughout the prefecture.

METHODS

Participants

This study included children with non-IgE-GI-FAs diagnosed at 13 hospitals in Yamaguchi Prefecture, Japan, between January 1, 2011, and December 31, 2020. Japan is divided into 47 prefectures. Each prefecture has its own local government and is responsible for areas such as education, police, transportation, and medical care. No other hospitals are engaged in pediatric inpatient cases in Yamaguchi prefecture, which is located at the western edge of the main island, covering 6110.9 km^2 and with a population of 1,342,059.[32] All 13 hospitals are secondary and tertiary pediatric emergency hospitals in the prefecture, located evenly in the east, west, south, and north. Each hospital confirmed the medical records during the period 2011–2020. This study also included all children with DS born in the prefecture during the study period, to estimate the prevalence rate of non-IgE-GI-FAs in children with DS. Non-IgE-GI-FAs were diagnosed based on the following criteria proposed by the JPGFA, which is modified from the one proposed by Powell:[2] (1) development of GI symptoms after ingestion of causative foods, (2) disappearance of symptoms after discontinuation of causative foods, (3) exclusion of other disorders that could cause GI symptoms, and (4) recurrence of GI symptoms during oral food challenge (OFC) or reintroduction. Informed consent was obtained from each children's parents prior to OFC. Children meeting all the criteria were considered confirmed cases, and those meeting up to the third of the diagnostic criteria were considered suspected cases. The children who met only the first and second diagnostic criteria were excluded, as they might have had other diseases.

Children with DS underwent confirmatory tests via chromosomal examination. This multicenter, observational retrospective study was approved by the Institutional Review Board of Yamaguchi University Hospital (H2020-198). Subsequently, ethics committee approval was obtained from the 12 collaborating hospitals in Yamaguchi Prefecture. Data were collected from the children's medical records at all 13 hospitals in Yamaguchi Prefecture, Japan. As this was a retrospective study, we also applied an opt-out method using a poster on our hospital website to obtain consent for this study. The poster was approved by the Institutional Review Board of Yamaguchi University Hospital.

Outcome measurements

Children with non-IgE-GI-FAs were classified into DS and non-DS groups, and their clinical characteristics compared. The demographic characteristics included sex, gestational age, birth weight, comorbidities, surgical history, and serum antigen-specific IgE levels. Serum antigen-specific IgE levels were detected using ImmunoCAP (Thermo Fisher Scientific, Waltham, MA, USA) or the multiple antigen simultaneous test 33 (SRL Inc., Tokyo, Japan). The clinical characteristics of non-IgE-GI-FAs included age at onset, age at diagnosis, age at confirmed clinical remission, causative foods, OFC, clinical symptoms at diagnosis, and severity. In this study, cases with only GI symptoms were defined as mild; those accompanied by pallor were defined as moderate; and those accompanied by lethargy, hypotension, hypothermia, or fever were defined as severe.[6] Although fever is not a common symptom of non-IgE-GI-FAs in Western countries, it has been described in Japanese and Chinese studies as a phenotype specific to these regions.[18,20,33,34] GI symptoms included vomiting, diarrhea, and bloody stool. Hypotension was defined as <70 mmHg in age of <1 year, $<(70 + [2 \times \text{age}])$ mmHg in age of 1–10 years, and <90 mmHg in age of 11 years to adult.[14] Hypothermia was defined as a temperature of <36 °C. Fever was defined as a temperature of ≥ 37.5 °C. Clinical remission was defined as the absence of adverse reactions after the OFC or reintroduction at home.

In cases of multi-antigen-positive non-IgE-GI-FAs, the age at onset was defined as the age at the first episode of non-IgE-GI-FAs, and the age at confirmed clinical remission was defined as the age at which clinical remission was confirmed with all foods.

Statistical analyses

All statistical analyses were performed using JMP Pro version 18 (SAS Institute, Cary, NC, USA). Differences between the 2 groups were analyzed using the Mann–Whitney *U* test, chi-squared test, or Fisher's exact probability test. Continuous values were expressed as medians and range values or in raw values with percentages. The significance of gestational age, birth weight, serum antigen-specific IgE levels, age at onset, age at diagnosis, and age at clinical remission of non-IgE-GI-FAs was tested using the Mann–Whitney *U* test. The significance of sex, comorbidities, surgical history, causative foods, OFC, clinical symptoms at diagnosis, and severity was tested using the chi-square or Fisher's exact test. Statistical significance was set at $P < 0.05$.

RESULTS

Participant selection

A total of 129 children with non-IgE-GI-FAs were enrolled in this study. Notably, 14 of the 129 children were excluded from the analysis (Fig. 1). Four children were duplicate cases, and 10 children had insufficient data. Finally, statistical analyses were performed on 115 children.

During the study period, 233 children with DS were born in Yamaguchi Prefecture, Japan, and were diagnosed as DS at 13 hospitals. Notably, 49 children were duplicate cases and were excluded from the analysis. Finally, statistical analyses were performed on 184 children with DS to estimate the prevalence rate of non-IgE-GI-FAs in children with DS (Fig. 1).

Demographic characteristics of children with non-IgE-GI-FAs

Among the 115 children with non-IgE-GI-FAs, 7 had DS (Fig. 1). During the study period, 184 children with DS were born in 13 hospitals, 7 of whom developed non-IgE-GI-FAs (Fig. 1). Thus, in this study, the prevalence rate of non-IgE-GI-FAs in children with DS was 3.8%. During the 10-year study period, the total number of births in Yamaguchi Prefecture, Japan, was 99,173,[35] of which 184 children had DS. Moreover, the live birth incidence rate of children with DS in this study was 1.86 per 1000 live births. On the other hand, the prevalence rate of non-IgE-GI-FAs in children without DS was 0.11% (108/98,989).

In this study, sex and median birth years were similar in both groups (Table 1). The median gestational age and birth weight were significantly lower in the DS group than in the non-DS group ($P = 0.0039$ vs. $P = 0.0296$). Comorbidities, such as cardiac disease (71.4% vs. 3.7%, $P = <0.0001$), hematological disorders (42.9% vs. 1.9%, $P = 0.0014$), and surgical history (57.1% vs. 0%, $P = <0.0001$), were significantly more common in the DS group than in the non-DS group. However, GI diseases were similar in both groups. The median serum antigen-specific IgE levels detected using ImmunoCAP were lower

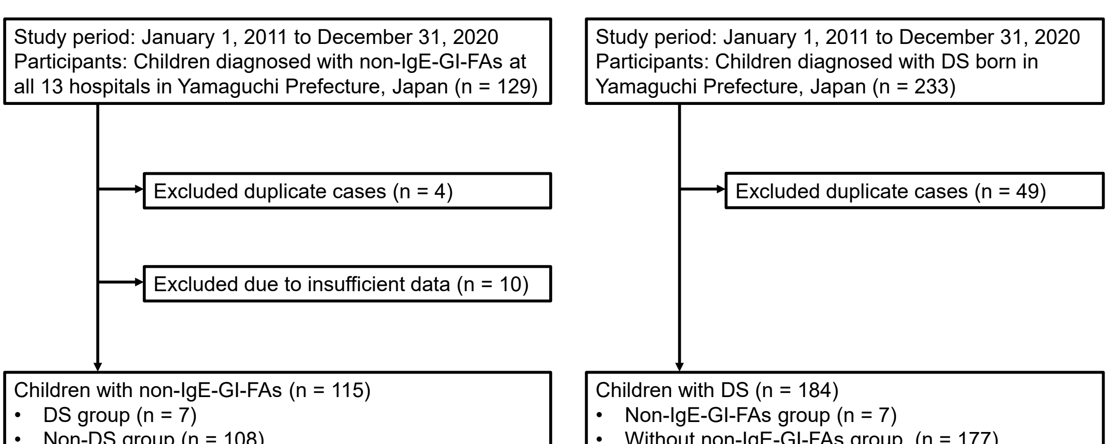

Fig. 1 Flow diagram of the participant selection process. One hundred and twenty-nine children with non-IgE-GI-FAs were enrolled in this study. Of these, 14 children were excluded from the analysis: 4 with duplicate cases and 10 with insufficient data. Finally, statistical analyses were performed on 115 children. Among the 115 children with non-IgE-GI-FAs, 7 had DS. During the study period, 233 children with DS were born in Yamaguchi Prefecture, Japan, and were diagnosed with DS at 13 hospitals. Furthermore, 49 children were duplicate cases and were excluded from the analysis. Finally, statistical analyses were performed on 184 children with DS to estimate the prevalence rate of non-IgE-GI-FAs in children with DS. Among the 184 children with DS, 7 (3.8%) developed non-IgE-GI-FAs. DS, Down syndrome; IgE, immunoglobulin E; non-IgE-GI-FAs, non-immunoglobulin E-mediated gastrointestinal food allergies; FPIAP, food protein-induced allergic proctocolitis.

	Children with non-IgE-GI-FAs (n = 115)		*P*-value
	DS (n = 7)	Non-DS (n = 108)	
Male (n [%])	4 (57.1)	56 (51.9)	1.0000[a]
Median birth years (year [range])	2017 (2012–2019)	2016 (2011–2020)	0.8969[b]
Median gestational age (weeks [range])	37 (31–38)	39 (28–41)	0.0039[b,c]
Median birth weight (g [range])	2574 (1714–2890)	2909 (1307-4061)	0.0296[b,c]
Comorbidities			
Cardiac disease (n [%])	5 (71.4)	4 (3.7)	<0.0001[a,c]
Gastrointestinal disease (n [%])	2 (28.6)	5 (4.7)	0.0588[a]
Hematological disorder (n [%])	3 (42.9)	2 (1.9)	0.0014[a,c]
Surgical history (n [%])	4 (57.1)	0 (0)	<0.0001[a,c]
Median age at surgery (months [range])	1.5 (0–2)	N/A	N/A
Median age at IgE test (months [range])	2 (1–12)	7 (0–78)	0.5492[b]
Serum antigen-specific IgE			
ImmunoCAP (n [%])	7 (100)	102 (94.4)	1.0000[a]
MAST33 (LC) (n [%])	0 (0)	6 (5.6)	1.0000[a]
ImmunoCAP (UA/mL [range])	<0.35 (<0.35–0.47)	<0.35 (<0.35–8.15)	0.3468[b]
MAST33 (LC) (UA/mL [range])	N/A	0.45 (0.05–7.95)	N/A

Table 1. Demographic characteristics of children with non-IgE-GI-FAs. *DS, Down syndrome; IgE, immunoglobulin E; MAST33, multiple antigen simultaneous test 33; N/A, not applicable; non-IgE-GI-FAs, non-immunoglobulin E-mediated gastrointestinal food allergies.* [a]*Fisher's exact test.* [b]*Mann–Whitney U test.* [c]*Significant at P < 0.05.*

than the detection limit (<0.35 kU_A/L) in both groups, with no significant difference between the 2 groups.

Clinical characteristics of children with non-IgE-GI-FAs

The causative foods are summarized in Table 2 and Fig. 2. Considering all cases in this study, cow's milk (CM) formula was the most common food (64.3%), followed by hen's egg yolk (15.7%), soy (7.8%), wheat (3.5%), and hen's egg white (2.6%). Reactions to rice were less common, despite its frequent consumption from early weaning in Japan. Most children had reactions to a single food. Four (3.5%) children exhibited reactions to 2 or more foods, who all were in the non-DS group (Table 2 and Fig. 2). In this study, the number of non-IgE-GI-FAs cases due to hen's egg yolk dramatically increased, particularly since 2019, accounting for almost half of all the non-IgE-GI-FAs cases in 2020 (Fig. 3). In contrast, the numbers of non-IgE-GI-FAs cases due to CM, soy, and wheat remained unchanged (Fig. 3). In this study, no significant differences were observed in causative foods, age at onset, age at diagnosis, or age at confirmed clinical remission between the 2 groups (Table 2). One child (14.3%) in the DS group and 29 children (26.9%) in the non-DS group were classified as having FPIAP. Six children (85.7%) in the DS group and 79 children (73.1%) in the non-DS group were classified as having FPIES. No one was diagnosed with FPE in either group. Four children (57.1%) in the DS group and 73 (67.6%) in the non-DS group were the confirmed diagnosis cases, and no significant difference between the 2 groups was observed (Table 2). Non-IgE-GI-FAs due to CM formula occurred in approximately 70% of the children in both groups (Table 2). No significant differences were observed in the choice of therapeutic milk between the 2 groups. Amino acid, extensively hydrolyzed, and hydrolyzed formula were mainly used in both groups ($P = 0.3370$, $P = 1.0000$, and $P = 0.4452$, respectively) (Table 2), whereas breast milk and soy formulae were used only in the non-DS group ($P = 1.0000$ and $P = 1.0000$,

	Children with non-IgE-GI-FAs (n = 115)		*P*-value
	DS (n = 7)	Non-DS (n = 108)	
Median age at onset (months [range])	2 (1-12)	5 (0-27)	0.9283[b]
Median age at diagnosis (months [range])	2 (1-12)	6 (0-27)	0.9386[b]
Disease types (n [%])			
FPIAP	1 (14.3)	29 (26.9)	0.6743[a]
FPIES	6 (85.7)	79 (73.1)	0.6743[a]
FPE	0 (0)	0 (0)	1.0000[a]
Diagnosis (n [%])			
Confirmed diagnosis cases	4 (57.1)	73 (67.6)	0.6830[a]
Suspected cases	3 (42.9)	35 (32.4)	0.6830[a]
Causative foods (n [%])			
CM	5 (71.4)	69 (63.9)	1.0000[a]
Hen's egg yolk	1 (14.3)	17 (15.7)	1.0000[a]
Soy	0 (0)	9 (8.3)	1.0000[a]
Wheat	1 (14.3)	3 (2.8)	0.2285[a]
Hen's egg white	0 (0)	3 (2.8)	1.0000[a]
Others (rice, peach)	0 (0)	3 (2.8)	1.0000[a]
Multiple foods[c]	0 (0)	4 (3.7)	1.0000[a]
Therapeutic milk (n [%])			
Breast milk	0 (0)	8 (7.4)	1.0000[a]
Soy formula	0 (0)	3 (2.8)	1.0000[a]
Hydrolyzed formula	1 (14.3)	7 (6.5)	0.4452[a]
Extensively hydrolyzed formula	2 (28.6)	13 (12.0)	1.0000[a]
Amino acid formula	2 (28.6)	24 (22.2)	0.3370[a]
Unknown	0 (0)	14 (13.0)	0.5762[a]
Clinical symptoms at diagnosis (n [%])			
Vomiting	6 (85.7)	59 (54.6)	0.1360[a]
Diarrhea	5 (71.4)	46 (42.6)	0.2385[a]
Bloody stools	3 (42.9)	50 (46.3)	1.0000[a]
Pallor	2 (28.6)	16 (14.8)	0.3008[a]
Lethargy	5 (71.4)	26 (24.1)	0.0150[a,d]
Hypotension	3 (42.9)	1 (0.9)	0.0093[a,d]
Hypothermia	0 (0)	0 (0)	1.0000[a]
Fever	4 (57.1)	9 (8.3)	0.0030[a,d]
Poor weight gain	3 (42.9)	22 (20.4)	0.1733[a]
Severity (n [%])			
Mild-to-moderate	2 (28.6)	81 (75.0)	0.0174[a,d]
Severe	5 (71.4)	27 (25.0)	0.0174[a,d]
OFC (n [%])	5 (71.4)	68 (63.0)	1.0000[a]
To confirm a definite diagnosis (n [%])	0 (0)	14 (13.0)	0.5950[a]
To confirm clinical remission (n [%])	5 (71.4)	54 (50.0)	0.5950[a]
OFC-Positive (n [%])	2 (28.6)	18 (26.5)	0.6101[a]
OFC-Negative (n [%])	3 (42.9)	50 (73.5)	0.6101[a]
Median age at OFC (months [range])	30 (18-35)	15 (0-101)	0.0056[b,d]

(continued)

	Children with non-IgE-GI-FAs (n = 115)		*P*-value
	DS (n = 7)	Non-DS (n = 108)	
Confirmed clinical remission (n [%])	3 (42.9)	69 (63.9)	0.4219[a]
Median age at remission (months [range])	26 (18–49)	18 (0–104)	0.1173[b]

Table 2. (Continued) Clinical characteristics of children with non-IgE-GI-FAs. *CM, cow's milk; DS, Down syndrome; FPE, food protein-induced enteropathy; FPIAP, food protein-induced allergic proctocolitis; FPIES, food protein-induced enterocolitis syndrome; non-IgE-GI-FAs, non-immunoglobulin E-mediated gastrointestinal food allergies; OFC, oral food challenge. [a]Fisher's exact test. [b]Mann-Whitney U test. [c]CM + wheat + banana, CM + wheat, CM + rice, or hen's egg yolk + corn. [d]Significant at P < 0.05.*

respectively) (Table 2). Regarding the clinical symptoms at diagnosis, vomiting was observed within 4 h after ingestion the causative food in all the cases who had vomiting at the diagnosis. No significant differences were observed in vomiting, diarrhea, bloody stools, and pallor between the 2 groups ($P = 0.1360$, $P = 0.2385$, $P = 1.0000$, and $P = 0.3008$, respectively) (Table 2). However, lethargy (71.4% vs. 24.1%, $P = 0.0150$), hypotension (42.9% vs. 0.9%, $P = 0.0006$), and fever (57.1% and 8.3%, $P = 0.0030$) were significantly more common in the DS group than in the non-DS group (Table 2). None of the patients in either group had hypothermia. Moreover, non-IgE-GI-FAs in the DS group were significantly more severe than that in those in the non-DS group (71.4% vs. 25.0%, $P = 0.0174$) (Table 2).

OFC was performed in 5 (71.4%) children in the DS group and 68 (63.0%) in the non-DS group. Furthermore, all 5 (71.4%) children in the DS group and 54 (50.0%) in the non-DS group underwent OFC to confirm clinical remission (Table 2). Among the positive cases of OFC, detailed OFC records including blood test data were obtained from 7 patients, 2 of whom were children with DS. Blood test included white blood cell (WBC), absolute neutrophil count (ANC), absolute eosinophil count (AEC), and C-reactive protein (CRP). Each data was collected before OFC, 6 h after OFC, and 24 h

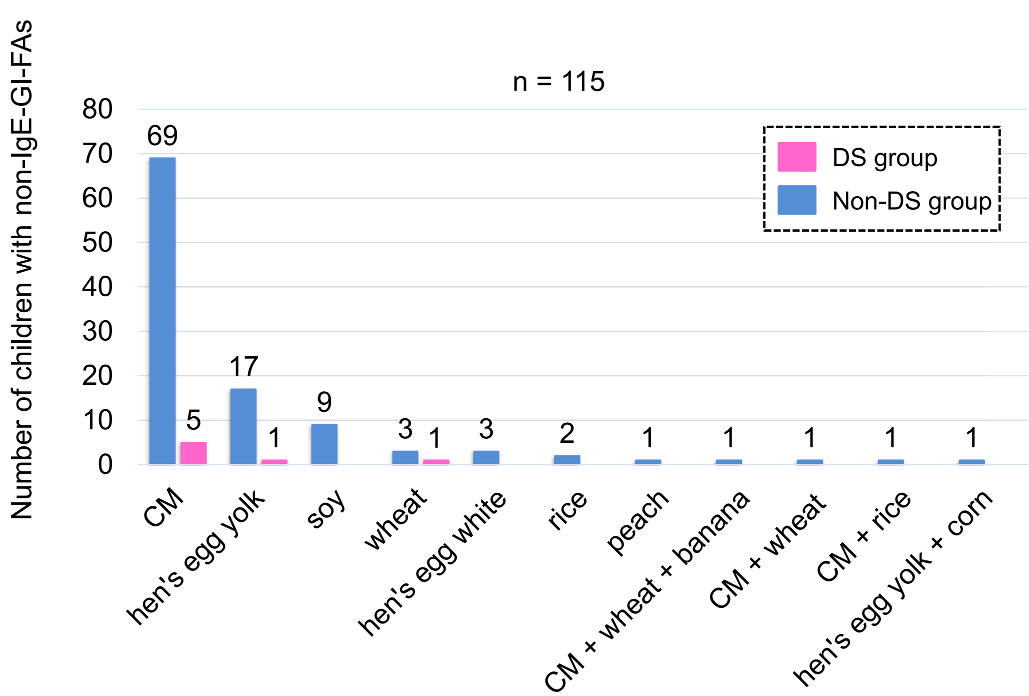

Fig. 2 Identification of causative foods in children with non-IgE-GI-FAs. CM, cow's milk; non-IgE-GI-FAs, non-immunoglobulin E-mediated gastrointestinal food allergies.

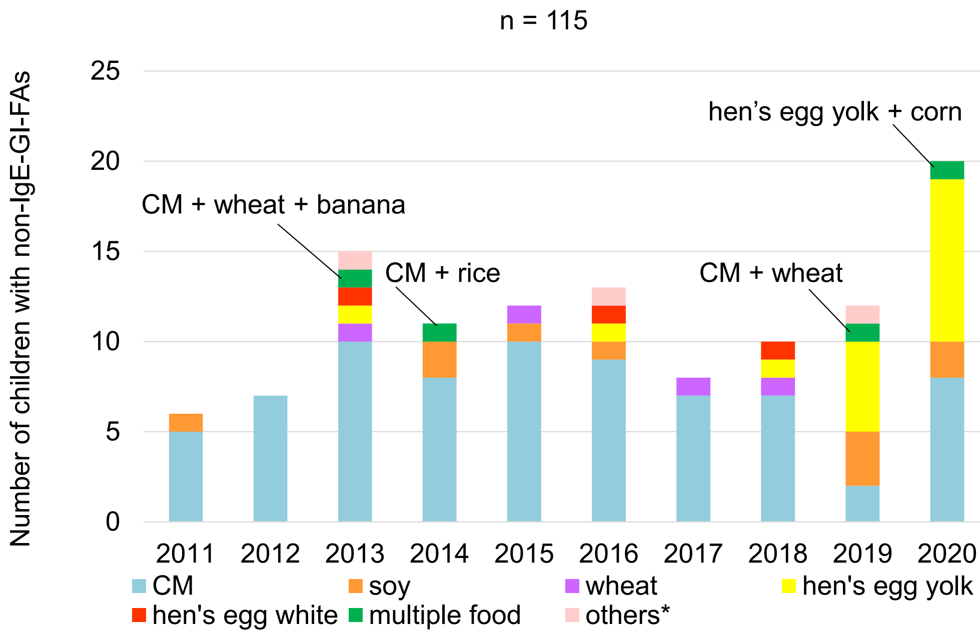

Fig. 3 Changes in causative foods in children with non-IgE-GI-FAs. CM, cow's milk; non-IgE-GI-FAs, non-immunoglobulin E-mediated gastrointestinal food allergies. *The other causative foods were rice for 2 children and peach for 1 child.

after OFC. OFC results are shown in Table 3. The causative foods were hen's egg yolk and wheat in DS group, and hen's egg yolk, wheat, and soy in non-DS group. Vomiting was observed within 4 h in all children, while fever was observed 7 h after in 2 children with DS. On the other hand, fever was not observed in children without DS. In all cases, ANC increased by more than 1500/μl from the baseline 6 h after OFC, while the AEC decreased compared to the baseline. CRP levels increased 24 h after OFC in all cases, particularly prominent in children with DS. In the non-DS group, there was no significant difference in the WBC count before and after OFC. ANC significantly increased 6 h after OFC compared to that before OFC ($P = 0.0283$), and significantly decreased 24 h after OFC compared to that 6 h after OFC ($P = 0.0472$). In contrast, there was no significant difference in ANC 24 h after OFC compared to that before OFC ($P = 1.0000$). On the other hand, AEC significantly decreased 6 h after OFC compared to that before OFC ($P = 0.0090$), and significantly increased 24 h after OFC compared to that 6 h after OFC ($P = 0.0090$). In contrast, there was no significant difference in AEC 24 h after OFC compared to that before OFC ($P = 0.2506$). CRP levels significantly elevated 24 h after OFC compared to that before OFC and 6 h after OFC ($P = 0.0088$ and $P = 0.0088$, respectively), while there was no significant difference in CRP levels 6 h after OFC compared to that before OFC ($P = 0.7511$).

Clinical characteristics of children with non-IgE-GI-FAs in the DS group

In the DS group, the causative food was CM formula in 5 cases, wheat in 1 case, and hen's egg yolk in 1 case (Table 4). Five children had cardiac comorbidities: 2 with tetralogy of Fallot (TOF), 2 with atrial septal defect (ASD), and 1 with atrioventricular septal defect (AVSD). Two children had GI comorbidities: 1 with rectovaginal fistula and the other with imperforate anus. Three children had hematological comorbidities, all with transient abnormal myelopoiesis (TAM). Surgical history was observed in 4 children: 2 with pulmonary artery (PA) banding for TOF and 2 with colostomy for rectovaginal fistula and imperforate anus. The median age at onset of non-IgE-GI-FAs was 2 months. An OFC was performed to confirm remission in 5 children. Three (42.9%) children whose causative food was CM formula showed clinical remission during the study period, whereas 2 children whose causative food was solid food did not show clinical remission. The median age at confirmed clinical

OFC No	Category	Age at OFC (months)	Causative foods	Clinical symptoms	Time until vomiting (h)	Time after OFC (h)	WBC (/μl)	ANC (/μl)	AEC (/μl)	CRP (mg/dl)
1	DS	35	Hen's egg yolk	V, D, B, P, L, F	2	0 6 24	5060 7990 12,940	2110 7420 10,546	90 50 0	0.02 0.08 8.47
2	DS	32	Wheat	V, D, P, L, F	3	0 6 24	5550 5940 6460	1831 5019 4392	111 0 0	0.02 0.04 4.27
3	Non-DS	23	Hen's egg yolk	V, P, L	3	0 6 24	5680 6360 3370	852 3529 202	170 0 84	0.06 0.06 0.24
4	Non-DS	11	Hen's egg yolk	V, D	2	0 6 24	9710 12,260 10,800	1747 9624 2700	388 61 108	0.01 0.02 1.03
5	Non-DS	8	Hen's egg yolk	V	3	0 6 24	15,680 17,220 14,420	3990 12,400 4030	530 60 470	0.01 0.04 1.44
6	Non-DS	24	Wheat	V, D, B, P, L	2	0 6 24	5930 6770 4140	1541 4434 414	237 67 82	0.03 0.04 2.55
7	Non-DS	7	Soy	V, B, P, L	2	0 6 24	12,340 8050 10,910	1789 3864 3763	345 40 381	0.07 0.03 0.96

Table 3. Positive OFC results in children with non-IgE-GI-FAs. *AEC, absolute eosinophil count; ANC, absolute neutrophil count; B, bloody stool; CM, cow's milk formula; CRP, C-reactive protein; D, diarrhea; DS, Down syndrome; F, fever; L, lethargy; No, number; non-IgE-GI-FAs, non-immunoglobulin E-mediated gastrointestinal food allergies; OFC, oral food challenge; P, pallor; V, vomiting, WBC, white blood cell.*

Non-IgE-GI-FAs in children with DS[a]	1	2	3[25]	4[25,29]	5[29]	6[29]	7
Sex	Female	Male	Male	Female	Female	Male	Male
Diagnosis	Confirmed case	Confirmed case	Suspected case	Suspected case	Suspected case	Confirmed case	Confirmed case
Causative foods	CM	CM	CM	CM	CM	Wheat	Hen's egg yolk
Comorbidities	TAM	TOF, TAM	TOF	ASD/ rectovaginal fistula	AVSD/ imperforate anus	TAM	ASD
Surgical history	N/A	PA banding	PA banding	Colostomy	Colostomy	None	None
Age at surgery (months)	N/A	2	1	2	0	N/A	N/A
Age at onset (months)	1	2	2	2	3	10	12
Age at OFC (months)	Not implemented	Not implemented	26	30	18	32	35
Result of OFC	N/A	N/A	Negative	Negative	Negative	Positive	Positive
Age at remission (months)	Not in remission	Not in remission	26	49	18	Not in remission	Not in remission
Clinical symptoms at diagnosis							
Vomiting	+	-	+	+	+	+	+
Diarrhea	-	-	+	+	+	+	+
Bloody stools	-	+	+	+	-	-	-
Pallor	-	-	+	+	+	-	+
Lethargy	-	-	+	+	+	+	+
Hypotension	-	-	-	+	+	-	+
Fever	-	-	+	+	+	+	-
Poor weight gain	-	-	+	+	+	-	-
Severity[6]	Mild	Mild	Severe	Severe	Severe	Severe	Severe

Table 4. Clinical characteristics of non-IgE-GI-FAs in children with DS. *ASD, atrial septal defect; AVSD, atrioventricular septal defect; CM, cow's milk formula; DS, Down syndrome; N/A, not applicable; OFC, oral food challenge; PA, pulmonary artery; TAM, transient abnormal myelopoiesis; TOF, tetralogy of Fallot; non-IgE-GI-FAs, non-immunoglobulin E-mediated gastrointestinal food allergies.* [a]*Cases 3, 4, 5, and 6 have been previously reported.*[25,29]

remission was 26 months. Vomiting was observed in 6 (85.7%) patients, diarrhea in 5 (71.4%), and bloody stool in 3 (42.9%). Pallor was observed in 3 (42.9%) patients, lethargy in 5 (71.4%), hypotension in 3 (42.9%), and fever in 4 (57.1%). Poor weight gain was observed in 3 (42.9%) patients, whose causative food was CM formula. None of the patients had hypothermia. Five (71.4%) of the 7 patients were diagnosed with severe disease.

Case 1 had TAM as a comorbidity and no surgical history. She developed non-IgE-GI-FAs at 1 month of age with only vomiting at the onset. She was a recent case, and clinical remission could not be confirmed within the study period. Case 2 had TOF and TAM as a comorbidity. PA banding was performed for pulmonary hypertension with TOF at 2 months of age. The postoperative nutrition was CM formula, and he developed non-IgE-GI-FAs at 2 months of age with only bloody stools at the onset. He was also a recent case, and clinical remission could not be confirmed within the study period. Case 3[25] had TOF as a comorbidity, and PA banding was performed for pulmonary hypertension with TOF at 1 month of age. The postoperative nutrition was CM formula, and the brand of formula milk was changed 34 days after the surgery, and vomiting, diarrhea, bloody stools, pallor, extreme lethargy, fever, and metabolic acidosis appeared. In Case 3, intracardiac repair was performed at 12 months of age, and clinical remission was confirmed at 26 months of age. Case 4[25,29] had ASD and rectovaginal fistula as a comorbidity. She did not require surgery for ASD, and a colostomy was performed at 2 months of age for a rectovaginal fistula. Shortly after surgery, the ingestion of CM formula caused severe symptoms, including vomiting, diarrhea, bloody stools, pallor, extreme lethargy, hypotension, fever, and metabolic acidosis. Colostomy closure was performed at 23 months of age. OFC result was negative at 30 months of age and feeding was gradually increased; finally, clinical remission was confirmed at 49 months of age. Case 5[29] had an AVSD and imperforate anus as a comorbidity. A colostomy was performed 1 day after birth for an imperforate anus. CM formula was resumed after surgery, and repetitive vomiting and diarrhea were observed after 3 months. Subsequently, 7 months after the surgery, watery diarrhea appeared following the administration of antibacterial agents after cardiac catheterization, which resulted in shock. Simultaneously, she also had pallor, extreme lethargy, fever, and metabolic acidosis. Colostomy closure was performed at 16 months of age, and clinical remission was confirmed at 18 months. The intracardiac repair was performed at 19 months of age for the AVSD. Case 6[29] had TAM as a comorbidity and no surgical history. Multiple episodes of repetitive vomiting, diarrhea, and extreme lethargy were reported after ingestion of wheat food, such as "udon" noodles and pancakes, at 10 months of age. Vomiting was observed after 3 h from ingestion of wheat food. Therefore, he avoided the wheat intake thereafter. OFC was performed at 32 months of age, but the result was positive. The clinical remission was not confirmed within the study period. Case 7 had ASD as a comorbidity but did not require surgery for ASD. A single episode of repetitive vomiting and diarrhea was reported after ingestion of the hen's egg yolk at 12 months of age. Vomiting was observed after 2 h from ingestion of hen's egg yolk. Therefore, he avoided the hen's egg yolk intake thereafter. An OFC for hen's egg yolk was performed to confirm clinical remission at 24 months of age, and the result was negative. Thus, he resumed hen's egg yolk intake at home. However, after ingestion of hen's egg yolk for a second time at home, repetitive vomiting and extreme lethargy appeared, and he was transferred to the emergency department, where he had pallor, extreme lethargy, and hypotension. An OFC was performed again at 35 months of age; however, the result was positive, and clinical remission was not confirmed during the study period. In the children with DS group, there were no cases of accidental ingestion at home after diagnosis.

DISCUSSION

In this study, the prevalence rate of non-IgE-GI-FAs was 3.8% (7/184) in children with DS and 0.11% (108/98,989) in children without DS. The incidence rate of DS was 1.86 per 1000 live births. Recent studies in Japan have reported the incidence rate of DS as 1.36–2.20 per 1000 live births,[36,37] which is consistent with our results. Sepsis-like symptoms, such as lethargy, hypotension, and fever, were significantly more common in the DS group than in the non-DS group. None of the patients in either group had hypothermia. Five (71.4%) of the 7 children with non-IgE-GI-FAs in children with DS were diagnosed as severe and required aggressive infusion. Differentiating non-IgE-GI-FAs that develop postoperatively from sepsis is challenging. Therefore, non-IgE-GI-FAs should be considered a differential diagnosis when sepsis-like symptoms, in addition to vomiting and diarrhea, are observed in children with DS.

In the DS group, Case 1 was a mild case whose causative food was CM formula. She experienced episode of vomiting at the onset, but did not strictly meet the diagnostic criteria for FPIES.[6] Case 2 was also a mild case whose causative food was CM formula. He only had bloody stools and had been diagnosed with FPIAP. Cases 3, 4, and 5 were severe, whose causative food was CM formula, and almost met the diagnostic criteria for FPIES.[6] However, performing OFC or reintroduction for a definitive diagnosis was difficult. Therefore, they were diagnosed as suspected cases of FPIES. Cases 6 and 7 were also severe cases whose causative food was wheat and hen's egg yolk, respectively, and they met the diagnostic criteria for FPIES.[6] In the present study, in non-IgE-GI-FAs in children with DS, 1 of the 7 (14.3%) patients was diagnosed with FPIAP, and 6 (85.7%) were considered to have FPIES.

Our findings revealed that the number of non-IgE-GI-FAs cases due to hen's egg yolk has dramatically increased, particularly since 2019, accounting for almost half of all the non-IgE-GI-FAs cases in 2020. In contrast, the numbers of non-IgE-GI-FAs cases due to CM, soy, and wheat remained unchanged. In a recent large epidemiological report of allergic disease in young children from Japan, the most common trigger food of GI food allergies was hen's eggs (34.5%), followed by CM (21.7%).[38] Furthermore, a recent report from Japan identified hen's egg yolk as an emerging trigger of non-IgE-GI-FAs and reported that the number of cases due to hen's egg yolk has dramatically increased, specifically in 2018–2019.[39] Our epidemiological study also found an increase in the number of cases due to hen's egg yolk after 2019, aligning with previous reports. The Japanese Society of Pediatric Allergy and Clinical Immunology recommended early introduction of hen's egg yolk from 6 months of age only to high-risk infants with eczema in 2017.[40] This apparent increase in case numbers due to hen's egg yolk in the past decade coincides with early introduction guidelines, suggesting that changing feeding practices may have implications for non-IgE-GI-FA epidemiology.

In the DS group, surgical history was observed in 4 (57.1%) children, and causative food for all was CM formula. Surgical history was significantly more common in the DS group than in the non-DS group. In a previous single-center study,[29] no significant differences were reported in cardiac or GI comorbidities or total surgical history between the 2 groups of children with DS who developed FPIES and those who did not. However, in that study, the surgical history of colostomy was significantly higher in the FPIES group than in the non-FPIES group. GI surgery is associated with a higher incidence rate (10.3%) of non-IgE-GI-FAs in neonates and infants.[41] Furthermore, surgery with full-layer invasion was a risk factor for non-IgE-GI-FAs, and CM formula after surgery was a risk factor for non-IgE-GI-FAs compared with breast milk.[41] In the present study, 2 children with DS developed FPIES due to CM formula after GI surgery with full-layer invasion, similar to a previous report. Although reports of FPIES due to CM formula after cardiac surgery are unavailable, PA banding in children with DS might be associated with the development of FPIES due to CM formula.

In a previous single center study on FPIES with DS, 22.5% were diagnosed with DS among a subgroup of patients affected by FPIES due to CM (total of 40 patients).[42] In our multicenter study, children with DS accounted for 9.1% (4/44) of FPIES due to CM formula.

The guidelines published in 2017 on FPIES describe elevated WBC with neutrophilia, thrombocytosis, metabolic acidosis, and methemoglobinemia and stool positive for leukocytes, eosinophils, or increased carbohydrate content during a severe acute FPIES reaction.[6] Increased CRP has also been highlighted during acute reactions in some published studies.[16,43,44] In our study, similar to that reported in a previous study,[42] in children with DS who had FPIES with positive result in OFC, ANC increased by more than 1500/μl from the baseline 6 h after OFC. CRP levels also increased 24 h after OFC in all cases, particularly prominently in children with DS.

Immune abnormalities in DS may be associated with higher incidence and severity of non-IgE-GI-FAs. $CD4^{+}$ $CD25^{+}$ $Foxp3^{+}$ regulatory T (Treg) cells have 2 subsets: natural Treg (nTreg) cells, which originate in the thymus, and induced Treg (iTreg) cells, which originate from peripheral naïve T cells.[45] Treg cells comprise almost 10% of peripheral $CD4^{+}$ T cells and are essential for the balance between pro- and anti-inflammatory responses at the mucosal surfaces.[45] The thymus in individuals with DS exhibits profound anatomical and architectural abnormalities,[46] which may alter the maturation process of nTreg cells.[47] Individuals with DS manifest with an overexpressed peripheral nTreg population with a defective inhibitory activity, partially explaining the increased frequency of autoimmune diseases.[47] Recently, antigen-specific nTreg cells have been identified to induce tolerance in children with non-IgE-GI-FAs to CM, suggesting that mucosal induction of tolerance against dietary antigens is associated with the development of nTreg cells.[48] In that study, children outgrowing non-IgE-GI-FAs to CM were compared with children with active non-IgE-GI-FAs to CM. Children outgrowing non-IgE-GI-FAs to CM had higher circulating nTreg cells specific for CM protein compared with that in children without clinical remission. The study also suggested that the suppressive action of CM-specific nTreg cells was exerted partly by direct cell–cell contact and partly by the production of tumor growth factor (TGF)-β. Similarly, interleukin (IL)-10 production by peripheral blood mononuclear cells tends to increase in tolerant children.[48] Under steady-state conditions, TGF-β and IL-10 maintain peripheral and gut tolerance.[49] TGF-β is a pleiotropic cytokine best known for its regulatory activity and induction of peripheral tolerance.[49] IL-10 is a key regulator of the immune system that acts by limiting the inflammatory response, which can otherwise cause tissue damage and is essential for the homeostasis of the immune system, specifically in the GI tract.[49] In the absence of effector cytokines and in the presence of high TGF-β concentrations, naïve $CD4^{+}$ T cells are converted into iTreg cells that produce TGF-β and IL-10. Considering this information, individuals with DS, who have deficient nTreg inhibitory activity and reduced inhibitory activity of effector cytokines, may be more likely to develop non-IgE-GI-FAs with more severity.

This study has notable strengths. First, this was a multicenter study. Second, all children with non-IgE-GI-FAs were diagnosed by pediatricians. Furthermore, all infants with DS born in Yamaguchi Prefecture, Japan, were followed up at one of the collaborating hospitals in this study, allowing us to accurately calculate the epidemiology of non-IgE-GI-FAs in children with DS. This study revealed that severe sepsis-like symptoms were common in cases of non-IgE-GI-FAs in children with DS.

Nevertheless, this study also has some limitations. First, because of the retrospective nature of the study, the mild cases may have been overlooked, specifically in the non-DS group. Second, performing OFC or reintroduction for definitive diagnosis on all cases was difficult, and some suspected cases were included in this study. Third, a diagnostic bias may exist, as diagnosis was first established in several different pediatric departments. Lastly, detailed cytokine profiles were insufficiently examined in this study. Larger prospective multinational cohort studies are required to better understand the actual prevalence and clinical characteristics of non-IgE-GI-FAs in children with DS.

In conclusion, the prevalence rate of non-IgE-GI-FAs was 3.8% (7/184) in children with DS and 0.11% (108/98,989) in children without DS. Sepsis-like symptoms, such as lethargy, hypotension, and fever, were significantly more common in the DS group than in the non-DS group. In addition, non-IgE-GI-FAs in children with DS were significantly more severe than in children without DS. Non-IgE-GI-FAs should be considered a differential diagnosis when sepsis-like symptoms, in addition to vomiting and diarrhea, are observed in children with DS. This may prevent unnecessary tests and invasive treatments and allow better and more appropriate clinical management of such patients.

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Availability of data and materials
We have not made the data publicly available.

Authors' contributions
FO and HW designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. All authors except for MS, TT, and SH contributed to data collection. FO and MS performed the statistical analysis and interpretation of the result. TT supervised the study design. SH supervised the study and critically reviewed the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
This study was approved by the Institutional Review Board of Yamaguchi University Hospital (H2020-198). Subsequently, ethics committee approval was obtained from the 12 collaborating hospitals. As this was a retrospective study, we also applied an opt-out method using a poster on our hospital website to obtain consent for this study. The poster was approved by the Institutional Review Board of Yamaguchi University Hospital.

Consent for publication
All authors have reviewed this manuscript and consent to its publication.

Impact statement
The prevalence of FPIES in children with DS was 3.8%, and sepsis-like symptoms, such as lethargy, hypotension, and fever, were significantly more common in children with DS than in those without DS. The results indicate that FPIES should be considered a differential diagnosis when sepsis-like symptoms, in addition to vomiting and diarrhea, are observed in children with DS. This may prevent unnecessary tests and invasive treatments.

Declaration of competing interest
All authors have no conflicts to disclose.

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