



Neonates undergoing gastrointestinal surgery have a higher incidence of non-IgE-mediated gastrointestinal food allergies

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Abstract

Purpose We aimed at investigating the incidence and risk factors of non-IgE-mediated gastrointestinal food allergies (non-IgE-GI-FAs) in neonates and infants.

Methods A total of 126 infants who underwent neonatal gastrointestinal surgeries were grouped into those with ($n = 13$) and those without an onset of non-IgE-GI-FAs ($n = 113$). The characteristics of the two groups (e.g., birth weight, delivery type, small intestinal surgeries, and pre-/postoperative nutrition) were compared. Small intestinal surgeries were classified into those with and those without full-layer invasion of the small intestine. For the statistical analysis, postoperative nutrition was classified into breast milk only, formula milk, and elemental diet only.

Results Except for full-layer surgical invasion of the small intestine and the period of parenteral nutrition, no significant differences were found between the two groups. Surgery with full-layer invasion was a risk factor of non-IgE-GI-FAs (odds ratio (OR) 10.70, 95% confidence interval (95% CI) 2.11–54.20; $p = 0.004$). Formula milk after surgery was a risk factor of non-IgE-GI-FAs when compared to breast milk (OR 5.65, 95% CI 1.33–24.00; $p = 0.019$).

Conclusion Neonates undergoing gastrointestinal surgery have a higher incidence of non-IgE mediated gastrointestinal food allergies. We recommend that formula milk should not be administered to newborns who underwent neonatal gastrointestinal surgeries with full-layer invasion of the small intestine.

Keywords Non-IgE-mediated gastrointestinal food allergy · Intestinal surgery · Small intestine · Eosinophilia · Formula milk

Introduction

In contrast to IgE-mediated food allergies, non-IgE-mediated gastrointestinal food allergies (non-IgE-GI-FAs), which occur in newborns and infants who are introduced to milk protein, are T-cell mediated. The digestive symptoms of non-IgE-GI-FAs are abdominal distention, vomiting, diarrhea, constipation, and bloody stools; non-specific symptoms include poor weight gain, fever, and apnea [1, 2]. Serious complications of non-IgE-GI-FAs include necrotizing enterocolitis, massive bloody stools, and disseminated intravascular coagulation [3]. Some patients with non-IgE-GI-FAs

require surgical treatment as they develop intestinal perforation and necrotizing enterocolitis [4].

In Japan, about 0.21% of newborns at a neonatal intensive care unit (NICU) showed food-related symptoms suggestive of non-IgE-GI-FAs [5]. Reports from other countries estimated that approximately 0.34–0.50% of all infants develop non-IgE-GI-FAs [6, 7].

Neonatal gastrointestinal surgeries (e.g., surgeries on the esophagus, stomach, small intestine, and large intestine, as well as those for abdominal wall defects such as gastroschisis, omphalocele, and congenital diaphragmatic hernia) tend to increase the incidence of non-IgE-GI-FAs [1, 8, 9]. However, few studies investigated the incidence of non-IgE-GI-FAs according to the different parts of the gastrointestinal tract. Small intestinal surgery is a known risk factor of non-IgE-GI-FAs [1]; however, whether the small intestine is directly invaded or not during surgery might also affect the development of non-IgE-GI-FAs because the small intestine is the main organ responsible for food digestion

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and absorption. Uncovering the risk factors of non-IgE-GI-FAs may prevent this condition. In this study, we aimed at clarifying if full-layer surgical invasion of the small intestine and the type of pre/postoperative enteral nutrition affects the development of non-IgE-GI-FAs during the neonatal period or infancy.

Methods

Study setting and population

The data of all patients who were treated at the NICU of the Yachiyo Medical Center, Tokyo Women's Medical University, between December 2006 and May 2018 were retrospectively reviewed. We identified patients who underwent neonatal gastrointestinal surgeries through operation records at the Department of Pediatric Surgery. This retrospective study was approved by the ethics committee of the Tokyo Women's Medical University.

Enteral feeding

During the study period, most patients who underwent neonatal gastrointestinal surgeries were fed breast or formula milk after improved intestinal motility was confirmed. Some patients were fed breast or formula milk before surgery. Formula milk was used if the amount of breast milk was inadequate or if no breast milk was available. Starting in 2013, some patients were administered an elemental diet (Elental P; EA Pharma, Tokyo, Japan) to prevent the development of non-IgE-GI-FAs when the clinical features had been attributed to non-IgE-GI-FAs. Postoperative enteral feeding was classified into three groups for analysis: breast milk only, formula milk, elemental diet only.

Diagnosis of non-IgE-mediated gastrointestinal food allergies

The diagnostic criteria of non-IgE-GI-FAs included the following three components [3]: (1) the appearance of symptoms suggesting non-IgE-GI-FAs such as abdominal distention, vomiting, diarrhea, bloody stools, and poor weight gain after the introduction of milk; (2) the disappearance of these symptoms after the elimination of milk; and (3) no recurrence of the symptoms after the introduction of therapeutic milk such as extensively hydrolyzed formula (New MA-1; Morinaga, Tokyo, Japan) or an elemental diet (Elental P or Elemental Formula; Meiji, Tokyo, Japan). For allergy tests, peripheral eosinophil counts, C-reactive protein (CRP), fecal eosinophils, and the allergen-specific lymphocyte stimulation test (ALST) were used to diagnose non-IgE-GI-FAs as a reference. Eosinophilia in neonates is defined as a peripheral

eosinophil count ≥ 700 cells/mm³ [10–12]; the highest eosinophil count at the onset of symptoms was used.

Neonatal gastrointestinal surgeries

We classified neonatal gastrointestinal surgeries into esophageal, gastric, small intestinal, and large intestinal surgeries. Small intestinal surgeries included those of the duodenum, jejunum, and ileum. Surgeries for congenital diaphragmatic hernia and abdominal wall defects included those for gastroschisis and omphalocele and were classified as small intestinal surgeries. We further classified small intestinal surgeries into surgeries with and those without full-layer invasion of the small intestine. For example, gastroschisis and congenital diaphragmatic hernia surgeries without complications were not considered full-layer surgical invasion of the small intestine, whereas the same procedures with complications such as the resection of the intestine were considered full-layer surgical invasion.

Before surgery, antibiotic treatment was administered patients with elevated CRP levels. After the gastrointestinal surgeries, antibiotics treatment was administered to prevent surgical site infection. The period of administration was defined as the day of the surgery to the day of the appearance of clinical features attributed to non-IgE-GI-FAs. If the clinical features appeared after the end of the administration of the antibiotics, the period of administration was defined as the day of the surgery to the day of the end of antibiotics administration.

Statistical analyses

Continuous variables are expressed as medians (ranges). The Mann–Whitney *U* test and Fisher's exact test were used to analyze continuous and nominal variables (including sex and chromosome abnormalities), respectively.

A stepwise logistic regression analysis was used to test the association between full-layer surgical invasion of the small intestine/postoperative enteral feeding and the development of non-IgE-GI-FAs. Because there were three categories for postoperative enteral feeding, we created the three dummy variables breast milk dummy, formula milk dummy, and elemental diet dummy. The formula and elemental diet dummies were used in the analysis with reference to breast milk.

All *p* values were two sided, and *p* values ≤ 0.05 were considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [13], a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

Results

During the study period, a total of 2756 newborns were treated at the NICU; of these, 126 (4.6%) underwent neonatal gastrointestinal surgeries. Of the total of 2756 newborns, 18 (0.65%) were diagnosed with non-IgE-GI-FAs. Of the 2630 newborns who did not undergo neonatal gastrointestinal surgeries, 5 (0.19%) developed non-IgE-GI-FAs, whereas of the 126 who did undergo these surgeries, 13 (10.3%) developed non-IgE-GI-FAs. Children undergoing neonatal gastrointestinal surgeries had a higher incidence of non-IgE-GI-FAs than children who did not undergo these surgeries ($p < 0.001$).

We grouped the 126 infants who had undergone neonatal gastrointestinal surgeries into those with an onset of non-IgE-GI-FAs ($n = 13$) and those without an onset of non-IgE-GI-FAs ($n = 113$) and compared the characteristics between the two groups (Table 1). No significant differences were found between the groups for any of the characteristics except for full-layer surgical invasion of the small intestine ($p = 0.008$) and the period of parenteral nutrition ($p = 0.04$). The period of *non per os* after surgery tended to be longer in the group of newborns who developed non-IgE-GI-FAs than in the group who did not ($p = 0.12$). For preoperative enteral feeding, patients with *non per os* tended to develop non-IgE-GI-FAs ($p = 0.06$).

Figure 1 shows the incidence of non-IgE-GI-FAs by the type of postoperative enteral feeding. In our study, the incidence rates of non-IgE-GI-FAs were 6.0% (3/50) for breast milk only, 25.0% (3/12) for formula milk only, 14.3% (6/42) for breast milk and formula milk, 6.3% (1/16) for an elemental diet only, and 0% (0/6) for breast milk and an elemental diet (Fig. 1). Patients fed formula milk tended to develop non-IgE-GI-FAs ($p = 0.07$, Table 1).

We then evaluated the association between full-layer surgical invasion of the small intestine/type of postoperative enteral feeding and the development of non-IgE-GI-FAs using logistic regression analysis. Full-layer surgical invasion of the small intestine was significantly associated with the development of non-IgE-GI-FAs (odds ratio (OR) 10.70, 95% confidence interval (CI) 2.11–54.20; $p = 0.004$). Being fed formula milk was significantly associated with the development of non-IgE-GI-FAs when compared to being fed human breast milk (OR 5.65, 95% CI 1.33–24.00; $p = 0.019$). In contrast, we found no significant difference between breast milk and an elemental diet (OR 0.87, 95% CI 0.081–9.19; $p = 0.91$).

Table 2 shows the detailed characteristics of the 13 patients who developed non-IgE-GI-FAs. They had gastroschisis, strangulated ileus, duodenal atresia, intestinal atresia, immaturity of ganglia, congenital diaphragmatic hernia, milk curd syndrome, Hirschsprung's disease,

omphalocele, and anorectal malformation. Because patient 1 developed an adhesive small bowel obstruction after a surgery for gastroschisis, his small intestine was partially resected. Patient 9 required an incision of the small intestine to eliminate milk curds. Eleven patients experienced full-layer surgical invasion of the small intestine and ten had eosinophilia. Three patients underwent an examination of fecal eosinophils; ALST was only conducted in one patient. After radical surgery for intestinal atresia, patient 6 developed non-IgE-GI-FA that caused necrotizing enterocolitis. The median period between the age at surgery and the age at the onset of non-IgE-GI-FAs was 41 days (range 8–123 days). The periods of postoperative antibiotics, *non per os* after surgery, and parenteral nutrition were not associated with the onset of non-IgE-GI-FAs.

Different types of preoperative antibiotics [e.g., ampicillin (ABPC), gentamicin (GM), arbekacin (ABK), cefmetazole (CMZ), meropenem (MEPM), and vancomycin (VCM)] were administered to some patients undergoing neonatal gastrointestinal surgeries. Between 2006 and 2011, various postoperative antibiotics [e.g., cefazolin (CEZ), cefotaxime (CTX), and CMZ] were administered to patients with esophageal atresia, duodenal atresia, intestinal atresia, anorectal malformation, abdominal wall defect, or congenital diaphragmatic hernia. In contrast, between 2012 and 2018, almost all patients with these diseases received sulbactam/ABPC (SBT/ABPC). Patients with intestinal perforation were administered various types of antibiotics, most often MEPM and VCM (data not shown). Although the trend of antibiotics use changed in the last decade, the type of pre/postoperative antibiotics did not affect the development of non-IgE-GI-FAs.

Discussion

Since the 1990s, reports of non-IgE-GI-FAs have been increasing in Japan [3]. An incidence of non-IgE-GI-FAs of 0.21–0.50% in neonates hospitalized in the NICU has been reported previously [5–7]. Our study revealed an incidence of non-IgE-GI-FAs of 0.47% among all newborns treated at the NICU of our hospital.

El Hassani et al. [8] reported that neonatal gastrointestinal surgery increased the incidence of non-IgE-GI-FAs to 4.3%. Another study reported that the incidence of non-IgE-GI-FAs among newborns undergoing neonatal gastrointestinal surgery was approximately four times higher than that of all newborns and infants at the NICU [9]. Similarly, we showed that patients who underwent neonatal gastrointestinal surgery had a higher incidence of non-IgE-GI-FAs than those who did not. Moreover, we made two important clinical observations. First, full-layer surgical invasion of the small intestine (including the duodenum, jejunum, and ileum) was

Table 1 Characteristics of patients who did or did not develop non-IgE-mediated gastrointestinal food allergies after neonatal gastrointestinal surgery

	Non-IgE-GI-FA (+) (<i>n</i> = 13)	Non-IgE-GI-FA (–) (<i>n</i> = 113)	Univariate analysis <i>p</i> value	Multivariate analysis	
				OR (95% CI)	<i>p</i> value
Male, <i>n</i> (%)	8 (61.5)	65 (57.5)	1.0		
Birth weight (g)	1827 (895–3222)	2504 (502–3718)	0.25		
Gestational age (weeks)	36.0 (26–41)	37.0 (23–41)	0.18		
Cesarean section, <i>n</i> (%)	9 (69.2)	52 (46.0)	0.15		
Chromosome abnormalities, <i>n</i> (%) ^a	0 (0)	13 (11.5)	0.36		
Age at surgery (days)	3 (0–24)	4 (0–30)	0.61		
Disease	Surgery	Non-IgE-GI-FA (+) (<i>n</i> = 13)	Non-IgE-GI-FA (–) (<i>n</i> = 113)	Univariate analysis <i>p</i> value	Multivariate analysis OR (95% CI) <i>p</i> value
Esophageal atresia, <i>n</i> (%) ^b	End-to-end anastomosis	0 (0)	11 (9.7)		
Duodenal atresia, <i>n</i> (%)	Gastrostomy	0 (0)	5 (4.4)		
	Diamond-shaped anastomosis	2 (15.4)	12 (10.6)		
Intestinal atresia, <i>n</i> (%)	End-to-back anastomosis	2 (15.4)	6 (5.3)		
Hirschsprung’s disease, <i>n</i> (%)	Ileostomy	1 (7.7)	6 (5.3)		
Gastroschisis, <i>n</i> (%)	Gastroschisis repair	1 (7.7)	4 (3.5)		
	Gastroschisis repair small bowel resection	1 (7.7)	0 (0)		
Congenital diaphragmatic hernia, <i>n</i> (%)	Diaphragm plication	1 (7.7)	13 (11.5)		
	Diaphragm plication small bowel resection	0 (0)	3 (2.7)		
Others, <i>n</i> (%)		5 (38.4)	55 (48.7)		
	Full-layer surgical invasion of the small intestine, <i>n</i> (%)	11 (84.6)	51 (45.1)	0.008	10.70 (2.11–54.20) 0.004
Period of postoperative antibiotics (days)		5 (0–30)	5 (0–71)	0.78	
Postoperative probiotics use, <i>n</i> (%)		8 (61.5)	59 (52.2)	0.57	

Table 1 (continued)

Disease	Surgery	Non-IgE-GI-FA (+) (<i>n</i> = 13)	Non-IgE-GI-FA (–) (<i>n</i> = 113)	Univariate analysis <i>p</i> value	Multivariate analysis	
					OR (95% CI)	<i>p</i> value
Period of parenteral nutrition (days)		27 (4–3830)	12 (3–3500)	0.04		
Period of <i>non per os</i> after surgery (days)		4 (2–32)	3 (0–39)	0.12		
Preoperative enteral feeding						
<i>Non per os</i> , <i>n</i> (%)		12 (92.3)	73 (64.6)	0.06		
Breast milk, <i>n</i> (%)		0 (0)	18 (15.9)	0.21		
Formula milk, <i>n</i> (%)		1 (7.7)	22 (19.5)	0.46		
Postoperative enteral feeding						
Breast milk, <i>n</i> (%)		3 (23.1)	53 (46.9)	0.14	–	Reference
Formula milk, <i>n</i> (%)		9 (69.2)	45 (39.8)	0.07	5.65 (1.33–24.00)	0.019
Elemental diet, <i>n</i> (%)		1 (7.7)	15 (13.3)	1.0	0.87 (0.081–9.19)	0.91

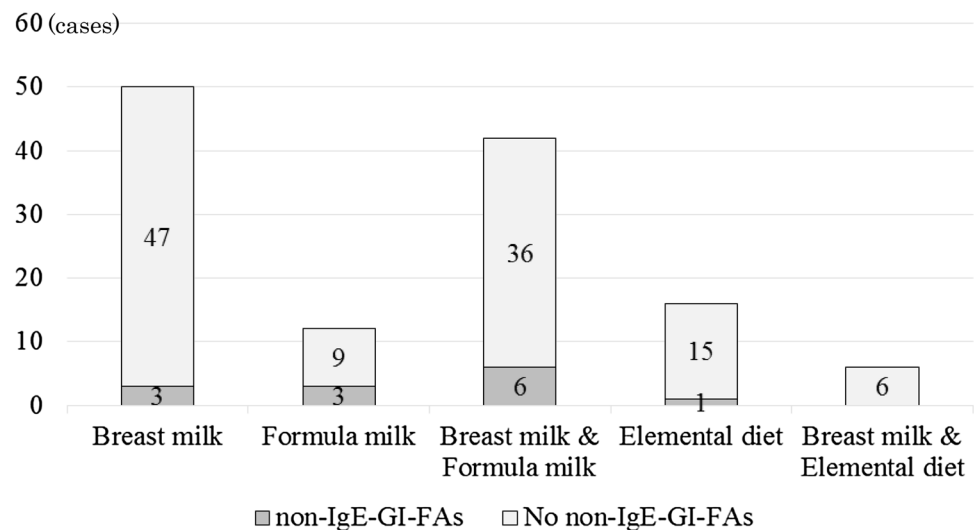
Data are shown as *n* (%) or median (ranges)

CI confidence interval, *non-IgE-GI-FA*s non-IgE-mediated gastrointestinal food allergies, OR odds ratio

^aChromosome abnormalities included trisomies 13 (1 patient), 18 (5 patients), 21 (6 patients), and 46XY inv (9) (p12q13) (1 patient)

^bEsophageal atresia surgeries are overlapping. A total of 14 patients underwent esophageal atresia

Fig. 1 Incidence of non-IgE-mediated gastrointestinal food allergies by type of postoperative enteral feeding non-IgE-GI-FAs, non-IgE-mediated gastrointestinal food allergies



a risk factor of non-IgE-GI-FAs. Second, formula milk was a risk factor of non-IgE-GI-FAs when compared to other types of postoperative nutrition. These two observations will be discussed in detail below.

First, full-layer surgical invasion of the small intestine is a risk factor of non-IgE-GI-FAs. According to the literature [1], small intestinal surgery in general is a risk factor of non-IgE-GI-FAs. Ezaki et al. [1] reported that the incidence of non-IgE-GI-FAs among newborns who did not receive probiotic therapy after small intestinal surgery was 67%. Although in their study, small intestinal surgery only included small intestinal atresia and localized intestinal perforation, both required full-layer invasion of the small intestine. The findings of Ezaki and colleagues resemble our clinical observations. However, we defined small intestinal surgery as full-layer invasion surgery of the small intestine, including the duodenum, jejunum, and ileum. It has also been reported that an infant developed a non-IgE-GI-FA after surgery for fecal peritonitis [14]. Moreover, David et al. [15] reported that infants with gastroschisis were at high risk of the development of non-IgE-GI-FAs. However, in their study, all infants with gastroschisis were reviewed, regardless of full-layer surgical invasion of the small intestine. It has been reported that 6.3% of all infants with gastroschisis had intestinal complications such as intestinal atresia or resection of the intestine [15].

In the normal intestine, allergens are prevented from gaining access to the host through several mechanisms, including the innate intestinal epithelial immune defense and tight junctions [15]. It has been suggested that the association between gastrointestinal surgery and the development of non-IgE-GI-FAs may be linked to a dysfunction of the gastrointestinal tract resulting from surgical invasion or atrophy in the intestinal mucosa caused by extended fasting before and after surgery [9]. In our study, the patients

with *non per os* before surgery and those experiencing a long period of *non per os* after surgery tended to develop non-IgE-GI-FAs; however, this finding was not statistically significant. Impaired intestinal mucosal and immunological defenses, increased mucosal permeability, or atrophy in the mucosa, which can be caused by full-layer surgical invasion of the small intestine, can predispose to non-IgE-GI-FAs [10]. Full-layer surgical invasion such as incision, resection, suture, and anastomosis damages the anatomical and immunological barriers of the intestine, which may lead to the absorption of various allergens.

Second, formula milk as postoperative enteral nutrition was a risk factor of non-IgE-GI-FAs. Infants fed formula milk were more likely to develop non-IgE-GI-FAs than those fed other types of milk. Most infant formula milk consists of cow's milk, which contains higher levels of protein than human breast milk. Cow's milk contains casein and whey proteins (approximately 80% and 20% of the milk proteins, respectively) [16]. As formula milk contains a significantly higher amount of casein, which turns into milk curds in the stomach, than human breast milk, it is harder to digest [17]. Whey proteins consist of α -lactalbumin, β -lactoglobulin, and bovine serum albumin. Whey is easier to digest as it remains in the liquid form [17]. The main protein of human breast milk is whey (approximately 80% of the total milk proteins); β -lactoglobulin is not found in human breast milk [17, 18]. It has been reported that the important allergens of a cow's milk allergy are casein, β -lactoglobulin, and α -lactalbumin [18, 19]. Therefore, it is likely that formula milk, which contains these three proteins, is more closely linked to the development of non-IgE-GI-FAs than human breast milk. Several studies have shown that human breast milk is the best type of enteral nutrition in terms of strengthening the immune system of the gastrointestinal tract and preventing postoperative complications [17, 20]. On the other hand,

Table 2 Detailed characteristics of the 13 patients who developed non-IgE-mediated gastrointestinal food allergies after neonatal gastrointestinal surgery

Pt	Sex	Disease(s)	Surgery	Full-layer surgical invasion	Age at surgery (days)	Age at disease onset (days)	Period of postoperative antibiotics use (days)	Period of NPO after surgery (days)	Period of PN use (days)	Peripheral eosinophil count (/ μ L)	CRP (mg/dL)
1	M	Gastroschisis Adhesive bowel obstruction	Gastroschisis repair Small bowel resection	Yes	0	69	30	32	330	906	3.49
2	F	Strangulated ileus	Small bowel resection ileostomy	Yes	7	48	17	14	93	1424	12.86
3	M	Duodenal atresia	Diamond-shaped anastomosis	Yes	2	74	5	3	75	2287	0.23
4	F	Duodenal atresia	Diamond-shaped anastomosis	Yes	2	52	5	4	11	48	3.2
5	F	Intestinal atresia	End-to-back anastomosis	Yes	2	49	5	4	8	1410	0.68
6	M	Intestinal atresia	End-to-back anastomosis	Yes	1	15	7	5	395	715	13.88
7	F	Immaturity of ganglia	Ileostomy	Yes	12	20	1	2	22	4484	0.06
8	F	CDH	Diaphragm plication	No	3	14	2	3	8	1050	0.03
9	M	Milk curd syndrome	Elimination of the milk plug	Yes	24	81	26	8	56	1089	0.11
10	M	Gastroschisis	Gastroschisis repair Witzel jejunostomy	Yes	0	28	18	14	27	734	1.73
11	M	Hirschsprung's disease	Ileostomy	Yes	3	35	0	3	*	1236	0.10
12	M	Omphalocele	Omphalocele repair, ileostomy	Yes	3	126	1	6	17	93	0.03
13	M	Anorectal malformation	Colostomy	No	1	10	3	2	4	–	0.09

CDH congenital diaphragmatic hernia, CRP C-reactive protein, F female, M male, NPO non per os, Pt patient, PN parenteral nutrition

The asterisk (*) indicates that patient 11 was still receiving parenteral nutrition. – indicates that patient 13 did not undergo an examination of the peripheral eosinophils count

several reports indicated that breast-fed infants also developed non-IgE-GI-FAs and that the use of unmodified human breast milk is not recommended in neonates with digestive symptoms after the introduction of unmodified breast milk [15, 21]. Although three patients who were fed unmodified breast milk developed non-IgE-GI-FAs in our study, formula milk-fed newborns tended to be at higher risk of developing of non-IgE-GI-FAs than breast-fed infants. We can conclude that formula milk should not be administered to newborns who underwent neonatal gastrointestinal surgeries, and in particular, surgeries with full-layer invasion of the small intestine.

This study has two main limitations. First, the sample size of our study was small; this might have weakened the statistical power. For example, including a larger number of newborns might have uncovered a significant association between the different types of postoperative nutrition/ the period of parenteral nutrition use and the development of non-IgE-GI-FAs. Second, the diagnostic criteria of non-IgE-GI-FAs were inadequate and insufficient. Because not all patients suspected of having non-IgE-GI-FAs underwent various allergy tests (such as peripheral eosinophil counts, fecal eosinophils, the ALST, or gastrointestinal endoscopy), the diagnostic criteria in our study consisted of clinical features only. Fecal eosinophils are commonly examined in cases of non-IgE-GI-FAs, with a positivity rate of about 70%, suggesting that this might be a useful test to screen for this condition [22, 23]. However, fecal eosinophils can be positive even in normal neonates; therefore, we must be careful when interpreting positive fecal eosinophils in newborns [24]. The ALST is another useful laboratory test for diagnosing non-IgE-GI-FAs, with a positivity rate of 88% [19]. However, it was difficult to perform this test in all patients suspected of non-IgE-GI-FAs at our hospital as testing needs to be outsourced. However, as non-IgE-GI-FAs are not well-defined and difficult to diagnose, it is important to not only confirm the symptoms but also conduct an ALST to accurately diagnose the disease [2, 25]. In our study, some newborns had symptoms that were suggestive of non-IgE-GI-FAs after they were introduced to breast or formula milk, and the symptoms disappeared after the elimination of the milk. However, as no investigation of various allergy tests was conducted, they were excluded from our analysis. It is possible that the number of non-IgE-GI-FAs would have been different from our study if these patients' various allergy tests had been examined.

In conclusion, this study shows that full-layer surgical invasion of the small intestine and formula milk as postoperative enteral feeding are risk factors of non-IgE-GI-FAs. We recommend that formula milk should not be administered to newborns who underwent neonatal gastrointestinal surgeries with full-layer invasion of the small intestine. By not doing so, the development of non-IgE-GI-FAs and the

need for long periods of fasting may be prevented. Further studies including more patients are needed.

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Compliance with ethical standards

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent was not required. This retrospective study was approved by the ethics committee of the Tokyo Women's Medical University.

Conflict of interest The authors declare that they have no conflicts of interest.

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