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Associations between functional constipation and non-IgE-mediated food allergy in infants and children

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Abstract
Background: The non-IgE-mediated food allergy (non-IgE-FA) is less prevalent than IgE-mediated food allergy, and their relationship with functional constipation (FC) needs to be clarified.
Methods: A total of 305 infants and children with constipation treated in the Department of Pediatric Gastroenterology, Children's Hospital of Nanjing Medical University, from July 2020 to December 2021 were included in this study. Four cases with organic lesions were excluded. Among 301 diagnosed with FC, according to ROME IV criteria, 81 cases with allergy-related indicators were further evaluated for food allergy by food-specific IgG antibody test, allergen-specific IgE antibody detection, skin prick test, and food avoidance and reintroduction.
Results: A total of 45 cases with FC were diagnosed with food allergy, and the incidence rate was 15%. Among the 45 patients, 35 cases (77.8%) had FC with non-IgE-FA. The main clinical symptoms or signs included anal fissure, abdominal pain, and pain during defecation. The most prevalent allergic foods were cow's milk, eggs, fish, and shrimp. Ten (22.2%) cases reported FC with mixed food allergy, including both non-IgE-mediated and IgE-mediated food allergy. This study focused on non-IgE-mediated food allergy-related FC.
Conclusion: Our results showed that the incidence of food allergy in infants and children with FC was 15%, which was mainly mediated by non-IgE-FA. The main clinical symptoms or signs in these cases included anal fissure, abdominal pain, and pain during defecation, and the main allergens included milk, eggs, fish, and shrimp.

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Introduction

Functional constipation (FC) is one of the most frequent pediatric chronic diseases with a global prevalence ranging from 0.7 to 29.6%.[1] It is caused by neither an underlying systemic cause nor an anatomical defect. In Asia, the rate of prevalence of FC is estimated to be between 0.5 and 29.6%.[2]

Food allergy has become one of the most common chronic noncommunicable diseases among infants and children worldwide. Food allergy occurs mainly due to the intake of certain foods that cause immunoglobulin E (IgE), non-IgE-mediated, and mixed mediated (both IgE and non-IgE) immune responses, which results in gastrointestinal symptoms, including vomiting, reflux, feeding difficulties, food refusal, abdominal pain, abdominal distension, constipation, gastrointestinal bleeding, growth, and development disorders.[3,4] The manifestations of IgE-mediated hypersensitivity reaction to food range from ordinary urticaria to life-threatening anaphylaxis. The absence of immunological and clinical tolerance to food allergens results in food allergies. The diagnosis of IgE-mediated food allergies is based on the combined use of a detailed medical history, research for the specific IgE via testing in-vivo (skin prick test [SPT]) and in-vitro (specific IgE), the elimination diet, and oral food challenge (OFC). The non-IgE-mediated food allergy (non-IgE-FA) can be diagnosed by observing the clinical symptoms and using the food-specific IgG antibody test. On the other hand, for IgE-mediated food allergy, the onset of symptoms is delayed and they may have a chronic presentation, making their association with the allergen less evident. In most cases, non-IgE-FA is diagnosed based on compatible symptoms and the demonstration of disappearance and reappearance of symptoms once the suspected food has been eliminated and reintroduced, respectively. Food allergies, particularly to cow's milk, can cause constipation. A food history is required the diagnosis, and if the kid is still being nursed, the mother is included in the study. Breast milk, formula milk, and dairy-based foods contain cow's milk protein (CMP) may be factors that could suggest intolerance to CMP.[5]

This study aims to explore the relationship between food allergy and FC, and further investigates the role and significance of non-IgE-FA in infants and children with FC.

Materials and Methods

Patients

The guardians of all selected children signed the informed consent form and voluntarily participated in the examination from July 2020 to December 2021. A total of 305 infants and children hospitalized in the Department of Pediatrics Gastroenterology, Children's Hospital of Nanjing Medical University participated in the study. The patients were aged between 6 months and 16 years. This study was approved by the ethics committee of Children's Hospital of Nanjing Medical University (Approval No. 202110107-2).

Medical history collection

A medical history focusing on food allergy and constipation was obtained from all participants. General information, such as age of onset; gender; duration of illness; frequency and firmness of stools; clinical manifestations including bloody stools, fecal incontinence, rash, abdominal pain, painful bowel movements, loss of appetite, bad breath, bloating, malnutrition; and signs including perianal skin growths, anal fissures, abdominal fecal mass were included in the medical history. The gastrointestinal tract symptoms of the infants and children and their history of allergic diseases, including asthma, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, and allergic enteritis and personal and family history of allergy were inquired. Clinical and laboratory indicators were collected a day before the treatment started and were communicated with the parents. Stressful life events, neurodevelopmental delays or problems, and a search for a positive family history of gastrointestinal diseases were all considered for the study. The Bristol Stool Scale was preferred as the standardized method to describe stool consistency. Evaluation of growth parameters, abdominal examination, inspection of the perianal region, and evaluation of the lumbosacral region were included in the physical examination for children with constipation.[6]

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) Subjects should be aged between 6 months and 16 years; (2) Children with FC were included according to the Rome IV criteria; (3) Suggestive history of food allergy.

The criteria for exclusion were as follows: (1) Subjects aged greater than 16 years or less than 6 months; (2) Presence of organic constipation due to conditions such as sigmoid colon hypertrophy and Hirschsprung's disease; (3) Presence of metabolic disorders such as hypothyroidism and intellectual disability; (4) Surgical history involving the digestive system; (5) Presence of IgE-mediated food allergy–related constipation or mixed-type food allergy–related constipation.

Assessment of constipation severity

The severity of constipation (frequency of defecation, stool hardness, pain) was assessed based on the Bristol Fecal Traits Scale.

Detection of non-IgE-mediated food allergy

The IgG-specific allergy screening ELISA kit (Haooubo Biomedical Co., Ltd. Suzhou, Jiangsu, China) was used to detect non-IgE-FA. The reactive plate was coated with proteins extracted from 14 foods. A small amount of blood (from the finger) or serum was collected from the patient, diluted, and was added to the reaction plate. The IgG antibody present in the blood was captured on the reaction plate. After this, the binding and chromogenic solutions were added, which resulted in one or more blue spots displayed on the reaction plate. The distribution map was referred to find the foods corresponding to the blue spots. The blue spots indicated a positive reaction, while no color

indicated a negative result. A color ring rather than a spot displayed a negative result. Reaction points 1–14 correspond to different foods. The food distribution map was referred for specific reaction points. The last two reaction holes were negative (−) and positive (+) quality controls, which helped ensure the correct testing process and results. Colorless negative quality control holes and blue spots at the positive quality control holes corresponded to correct test results. The test items included corn, rice, milk, egg, wheat, soybean, tomato, beef, chicken, pork, crab, shrimp, cod, and mushrooms.

Detection of IgE-mediated food allergy

Allergen-specific IgE antibody detection: We used the "Inhalation and food allergen-specific IgE antibody detection Kit (Aumont Blot)" from Aumont, Germany and the EUROBlotMaster II Western Blot for membrane strip detection. Nineteen different inhalation and food allergens were coated in parallel on the test strips. In the first step, buffer-pretreated strips were incubated with patient samples. If the sample is positive, IgE class-specific antibodies bind to the corresponding allergen. To detect the bound antibody, an enzyme-labeled monoclonal antihuman IgE antibody (enzyme conjugate) was added in the second incubation step, followed by the addition of an enzyme substrate, resulting in a colored reaction. Test items included eggs, milk, peanuts, soybean, beef, mutton, sea food combination (cod/lobster/scallop), shrimps, and crabs.

Skin prick test (SPT): SPT was performed with disposable stainless steel pricking needle and allergen skin pricking solution manufactured at the diagnostic reagent factory of the Peking Union Medical College Hospital. Test items included milk, soybean, shrimp, crab, beef, peanuts, and egg.

Avoidance and reintroduction of food

According to the above screening process for food-specific IgG antibody and specific IgE antibody and SPT test, the infants and children who were screened for food allergy had to go through 8 weeks of food avoidance to observe whether the clinical symptoms of constipation improved, and then food was reintroduced food to observe whether the symptoms of constipation reappeared.

Statistics and analysis of data

SPSS 22.0 Software was used for statistical analysis. Data were expressed as mean ± standard deviation. The enumeration data were subjected to x test and measurement data were subjected to t test. A P value < 0.05 was considered statistically significant.

Results

Food allergen detection procedure

A total of 305 infants and children were diagnosed with constipation, of which 4 patients were excluded because of organic constipation (3 cases of congenital colon and 1 case of sigmoid colon). The remaining 301 cases were diagnosed with FC according to the Rome IV diagnostic criteria, of which 81 cases presented with allergy-related indicators including 49 cases with skin lesions such as eczema and atopic dermatitis, 21 cases with allergic diseases outside the gastrointestinal tract, 39 cases with elevated absolute and 43 cases with relative numbers of eosinophils in peripheral blood, and 79 cases reported a personal history and 24 with a family history of allergy. Excluding the number of repeated cases, a total of 81 infants and children with suspected food allergy were screened for food allergens, including food-specific IgG antibody and specific IgE antibody (Tables 1 and 2). The results showed that 59 infants and children were positive for IgG antibody, and 33 cases were positive for IgE antibody. Among them, 44 cases were positive for IgG antibody and negative for IgE antibody, in those 1 was positive after SPT test; 19 cases were negative for IgG antibody and positive for IgE antibody; and 14 cases were positive for both IgG and IgE antibodies. A total of three cases were negative for both IgG and IgE antibodies, of which one case was positive and two were negative after the SPT test. Changes in symptoms were observed in 79 cases after food avoidance and reintroduction on screening for food-specific IgG antibody and specific IgE antibody and SPT test. 34 cases were eliminated after 8 weeks of avoidance and the reintroduction of food. Finally, 45 cases were diagnosed with food allergy. Among the 45 cases, 35 infants and children were diagnosed with non-IgE-mediated food allergic constipation. There were no cases related to IgE-mediated food allergic constipation, and 10 cases had mixed food allergic constipation. The flow chart is shown in Figure 1.

The characteristics of all patients with or without food allergy are summarized in Table 1. A total of 301 infants and children aged between 6 months and 16 years, with FC, were enrolled in this study, of which 45 cases reported with food allergy and 256 cases reported no food allergy. Males composed 49% of the cases of FC with food allergy, (22/45), while females composed 51% (23/45). Of these cases, 26.6% (12/45) had a family history of allergy, while 66.6% (30/45) had a personal allergy history. The main clinical manifestations or signs were anal fissure (64.4%, 29/45), abdominal pain (62%, 28/45), pain during defecation (46.7%, 21/45), anorexia (38%, 17/45), bloody stools (35.5%, 16/45), abdominal distention (35.5%, 16/45), halitosis (15.6%, 7/45), erythema (13.3%, 6/45), malnutrition (6.7%, 3/45), abdominal fecal mass (7%, 3/45), fecal incontinence (2%, 1/45), and perihepatic skin neoplasm (0%, 0/45).

Of the 256 FC cases without food allergy, 46.9% were males (120/256) and 53.1% were females (136/256). 4.7% (12/256) of these cases had a family allergy history, while 27% (69/256) had a personal allergy history. The clinical manifestations or signs were similar to that of those with food allergy, and the rates were as follows: anal fissure (61.3%, 157/256), abdominal pain (59.3%, 152/256), pain during defecation (46.8%, 120/56), anorexia (44%, 112/256), bloody stool (41%, 104/256), abdominal distention (41%, 104/256), halitosis (21%, 53/256), fecal incontinence (4%, 11/256), erythra (5%, 12/256), malnutrition (3.5%, 9/256), perihepatic skin neoplasm (3%, 7/256), and abdominal fecal mass (3%, 1/256).

Table 1 Comparison of clinical data and allergens between non-IgE and mixed food allergy.

	Non-IgE food allergy	Mixed food allergy	Total	P
Patients (n)	35	10	45	-
Age, n(%)				
<6 months	4(11.4)	0(0)	4(9)	
6 months – 6 years	27(77.1)	9(90)	36(80)	0.517
6–16 years	4(11.4)	1(10)	5(11)	
Gender, n(%)				
Male	15(43)	5(50)	20(44.4)	0.688
Female	20(57)	5(50)	25(55.5)	
Family history of allergy, n(%)				
Yes	13(37)	2(20)	15(33.3)	0.310
No	22(63)	8(80)	30(66.6)	
Personal history of allergy, n (%)				
Yes	31(88.5)	8(80)	39(87)	
No	4(11.4)	2(20)	6(13)	0.482
Course of disease (month), n (%)				
<1 year	18(51)	8(80)	26(58)	
1–5 years	16(46)	2(20)	18(40)	0.263
>5 years	1(3)	0(0)	1(2)	
Bristol score, n(%)				
1–3	23(66)	7(70)	30(67)	0.800
4–7	12(34)	3(30)	15(33)	
Frequency in defecation (per week), n(%)				
1–6	30(86)	10(100)	40(89)	0.205
7–14	5(14)	0(0)	5(11)	
Symptoms				
Bloody stool, n(%)	15(42.8)	5(50)	20(44.4)	
Yes	20(57.1)	5(50)	25(55.5)	0.688
No				
Fecal incontinence, n(%)				
Yes	0(0)	1(10)	1(2)	0.058
No	35(100)	9(90)	44(98)	
Erythra, n(%)				
Yes	4(11.4)	1(10)	5(11)	0.899
No	31(88.5)	9(90)	4089(0)	
Anorexia, n(%)				
Yes	16(46)	3(30)	19(42)	0.375
No	19(54)	7(70)	26(58)	
Perihepatic skin neoplam, n(%)				
Yes	1(3)	2(20)	3(7)	0.055
No	34(97)	8(80)	42(93)	
Malnutrition, n(%)				
Yes	2(5.7)	0(0)	2(4.4)	0.439
No	33(94.2)	10(100)	43(95.5)	
Abdominal distention, n(%)				
Yes	12(34.2)	6(60)	18(40)	0.143
No	23(65.7)	4(40)	27(60)	
Halitosis				
Yes	1(3)	1(10)	2(4.4)	0.334
No	34(97)	9(90)	43(95.5)	
Abdominal pain, n(%)				
Yes	20(57)	6(60)	26(58)	0.872
No	15(43)	4(40)	19(42)	
Pain in defecation, n(%)				
Yes	19(54)	4(40)	23(51)	0.425
No	16(46)	6(60)	22(49)	
Anal fissure, n(%)				
Yes	25(71.4)	8(80)	33(73)	0.589
No	10(28.5)	2(20)	12(27)	

Table 1 Continued.

	Non-IgE food allergy	Mixed food allergy	Total	P
Abdominal fecal mass, n(%)				
Yes	0(0)	2(20)	2(4.44)	0.007
No	35(100)	8(80)	43(95.5)	
Food antigens				
Cow's milk, n(%)				
Yes	19(54)	7(70)	26(58)	0.375
No	16(46)	3(30)	19(42)	
Egg, n(%)				
Yes	15(43)	4(40)	19(42)	0.872
No	20(57)	6(60)	26(58)	
Fish and shrimp, n(%)				
Yes	5(14)	0(0)	5(11)	0.205
No	30(86)	10(100)	40(89)	
Wheat, n(%)				
Yes	0(0)	1(10)	1(2.2)	0.058
No	35(100)	9(90)	44(97.7)	
Scallop				
Yes	0(0)	3(30)	3(7)	0.001
No	35(100)	7(70)	42(93)	
Crab				
Yes	0(0)	2(20)	3(7)	0.007
No	35(100)	8(80)	42(97)	
Corn				
Yes	2(6)	1(10)	3(7)	0.632
No	33(94)	9(90)	42(97)	
Peanut				
Yes	2(6)	2(20)	4(9)	0.162
No	33(94)	8(80)	41(91)	
Beef				
Yes	3(9)	5(50)	8(18)	0.003
No	32(91)	5(50)	37(82)	
Mutton				
Yes	1(3)	4(40)	5(11)	0.001
No	34(97)	6(60)	40(89)	

Table 2 Comparison of eosinophil count and IgE level in peripheral blood between non-IgE and mixed food allergy.

	Non-IgE food allergy	Mixed food allergy	Total	P
Number of cases	35	10	45	
IgE > 50 IU/L, n(%)				
Yes	4(11)	1(10)	5(11)	0.899
No	31(89)	9(90)	45(89)	
Eos > 5 × 10^9/L, n(%)				
Yes	14(40)	3(30)	17(38)	0.565
No	21(60)	7(70)	28(62)	
Eos > 5%, n(%)				
Yes	15(43)	3(30)	18(40)	0.464
No	20(57)	7(70)	27(60)	

Food allergy tests were conducted after the diagnosis of FC. A total of 45 infants and children were diagnosed with food allergy, which included 35 cases of non-IgE-FA, 0 cases of IgE-mediated food allergy, and 10 cases of mixed food allergy. Of the 35 cases of non-IgE-FA, 43% were males (15/35) and 57% were females (20/35). Of these cases, 37% (13/35) had a family history of allergy and 88.5% (31/35) had a personal allergy history. The main clinical manifestations or signs included anal fissure (71.4%, 25/35), abdominal pain (57%, 20/35), pain during defecation (54%, 19/35),

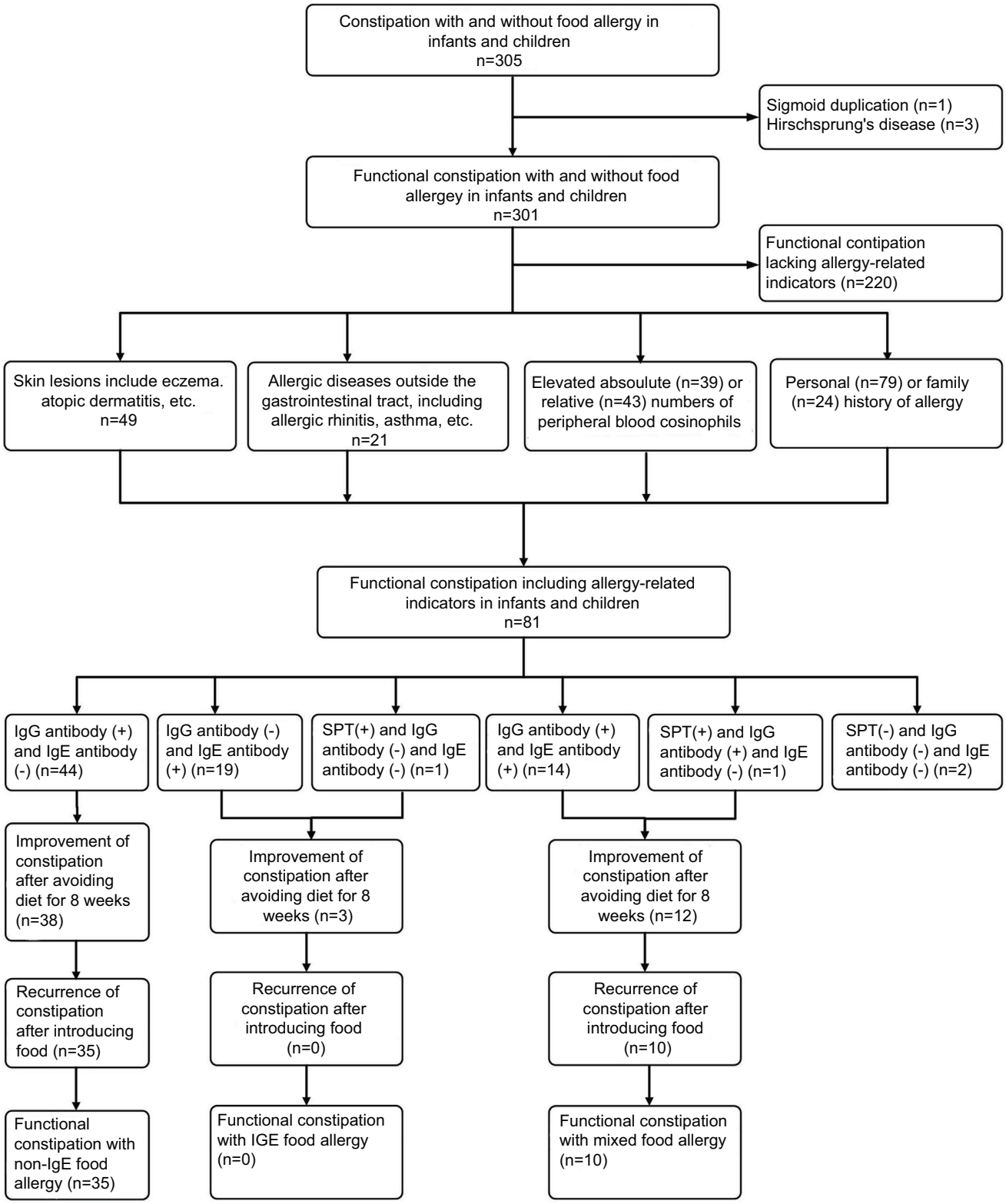

Figure 1 Flow chart of food allergy detection in all infants and children with constipation.

anorexia (46%, 16/35), bloody stools (42.8%,15/35), abdominal distention (34.2%, 12/35), erythra (11.4%, 4/35), malnutrition (5.7%, 2/35), halitosis (3%, 1/35), perihepatic skin neoplasm (3%, 1/35), abdominal fecal mass (0%, 0/35), and fecal incontinence (0%, 0/35). Major food allergens included cow's milk (54%, 19/35), egg (43%, 15/35), fish and shrimp (14%, 5/35), beef (9%, 3/35), corn (6%, 2/35), and mutton (3%, 1/35). Of the 10 infants and children diagnosed of FC with mixed food allergy, 50% were males (5/10) and the remaining 50% were females (5/10). Out of them,

20% (2/10) had a family allergy history and 80% (8/10) had a personal allergy history. The main clinical manifestations or signs included anal fissure (80%, 8/10), abdominal pain (60%, 6/10), abdominal distention (60%, 6/10), bloody stool (50%, 5/10), pain during defecation (40%, 4/10), anorexia (30%, 3/10), erythra (10%,1/10), halitosis (10%, 1/10), perihepatic skin neoplasm (20%, 2/10), abdominal fecal mass (20%, 2/10), fecal incontinence (10%, 1/10) and malnutrition (0%, 0/10). Major food allergens included cow's milk (70%, 7/10), beef (50%, 5/10), egg (40%, 4/10), mutton (40%, 4/10), scallop (30%, 3/12), peanut (20%, 2/10), scrab (20%, 2/10), corn (10%, 1/10), wheat (10%,1/10), and fish and shrimp (0%, 0/10) (Table 2).

The characteristics of the eosinophil count and IgE-level determination of FC with different types of food allergy, including non-IgE-mediated and mixed food allergies, are summarized in Table 3. There were no significant differences in the elevated IgE level (>50 IU/L) and the elevated absolute (> 5 × 10^9/L) and relative (>5%) number of eosinophils in peripheral blood between both groups (P > 0.05).

Table 3 Comparison of clinical data with or without food allergy.

Characteristics	FC with food allergy	FC without food allergy	Total	P
Patients (n)	45	256	301	-
Age n(%)				
<6 months	4(9)	12(4.7)	16(5.3)	
6 months -6 years	32(71)	198(77.3)	230(76.4)	0.460
6-16 years	9(20)	46(18)	55(18.2)	
Gender, n(%)				
Male	22(49)	120(46.9)	142(47.1)	0.803
Female	23(51)	136(53.1)	159(52.9)	
Family history of allergy, n(%)				
Yes	12(26.6)	12(4.7)	24(8)	
No	33(73.3)	244(95.3)	277(92)	0.000
Personal history of allergy, n(%)				
Yes	30(66.6)	69(27)	99(32.8)	
No	15(33.3)	187(73)	202(67.2)	0.000
Course of disease (month), n(%)				
<1 year	29(64.4)	115(45)	144(47.8)	
1-5 years	15(33.3)	129(50)	144(47.8)	0.052
>5 years	1(2.2)	12(5)	13(7.3)	
Bristol score, n(%)				
1-3	29(64.5)	196(77)	225(74.8)	0.084
4-7	16(35.5)	60(23)	76(25.2)	
Frequency in defecation (per week), n(%)				
1-6	38(84.5)	241(94)	279(92.7)	0.021
7-14	7(15.5)	15(6)	22(7.3)	
Symptom or signs				
Bloody stool, n(%)				
Yes	16(35.5)	104(41)	120(40)	
No	29(64.5)	152(59)	181(60)	0.522
Fecal incontinence, n(%)				
Yes	1(2)	11(4)	12(4)	0.512
No	44(98)	245(96)	289(96)	
Erythra, n(%)				
Yes	6(13.3)	12(5)	18(6)	0.024
No	39(86.6)	244(95)	283(96)	
Anorexia, n(%)				
Yes	17(38)	112(44)	129(43)	0.455
No	28(62)	144(56)	172(57)	
Perihepatic skin neoplam, n(%)				
Yes	0(0)	7(3)	7(2.3)	0.262
No	45(100)	249(97)	294(97.7)	
Malnutrition, n(%)				
Yes	3(6.7)	9(3.5)	12(4)	
No	42(93.3)	247(96.4)	289(96)	0.319

Table 3 Continued.

Characteristics	FC with food allergy	FC without food allergy	Total	P
Abdominal distention, n(%)				
Yes	16(35.5)	104(41)	120(40)	0.522
No	29(64.4)	152(59)	181(60)	
Halitosis				
Yes	7(15.6)	53(21)	60(20)	0.425
No	38(84.4)	203(79)	241(80)	
Pain in defecation, n(%)				
Yes	21(46.7)	120(46.8)	141(46.8)	0.979
No	24(53.3)	136(53.1)	160(53.2)	
Abdominal pain, n(%)				
Yes	28(62)	152(59.3)	180(59.8)	0.719
No	17(38)	104(40.6)	121(40.2)	
Anal fissure, n(%)				
Yes	29(64.4)	157(61.3)	186(61.7)	0.692
No	16(35.5)	99(38.6)	115(38.2)	
Abdominal fecal mass, n(%)				
Yes	3(7)	3(1)	6(2)	0.194
No	42(93)	253(99)	295(98)	

Discussions

Constipation is one of the most prevalent childhood illnesses which not only affects the gastrointestinal function but may also have a great impact on the physical and mental development and quality of life of children.[7,8] More than 95% of the reported cases are for FC. In this study, a total of 301 (99%) infants and children were diagnosed with FC according to the Rome IV diagnostic criteria after 4 patients were excluded because of organic constipation (3 cases of congenital colon and 1 case of sigmoid colon). Studies show that the prevalence of FC in children ranges from 0.5% to 32.2% worldwide, with a pooled prevalence of 9.5% (95% CI 7.5–12.1).[9] Among the 301 FC cases in this study, 230 (76.4%) were aged between 0.5 and 6 years which was consistent with the data reported in a survey conducted previously that 7% of infants and children has FC, with it being more common in ages from 1 to 4 years in China.[10] The main risk factors of FC were genetic susceptibility, insufficient dietary fiber intake, insufficient drinking of water, and lack of exercise. Additionally, studies have reported that FC is also associated with food allergy, including allergy toward milk.[11] However, its underlying causes and mechanisms are still unclear.

Food allergy affects 10% of children globally, and a survey organized by the World Allergy Organization indicated that the prevalence of food allergy among preschool children is 7% in Asia.[12,13] Food allergy can be described as an abnormal or strong immune response caused by food proteins. Food allergy is a group of diseases with symptoms involving the skin, and respiratory, digestive, and cardiovascular systems, and is mediated by IgE or non-IgE, or both. IgE-mediated immediate food allergy usually presents symptoms within 2 h after food exposure, which can be detected by serum-specific IgE test or SPT.[14,15] The diagnosis of IgE-mediated food allergies is based on the combined use of a detailed medical history, in-vivo and in-vitro research of specific IgE, the elimination diet, and the double-blind placebo-controlled food challenge.[16] Non-IgE-mediated gastrointestinal food allergies account for an unknown proportion of food allergies and include food protein–induced enterocolitis syndrome (FPIES), food protein–induced allergic proctocolitis (FPIAP), and food protein–induced enteropathy (FPE).[3] Patch testing andallergen-specific serum IgG antibodies have been shown to be useful in diagnosis of non-IgE-FAs.[17] Among the 301 infants and children with FC in this study, 81 cases presented with allergy-related indicators, including 49 cases with skin lesions such as eczema and atopic dermatitis, 21 cases with allergic diseases outside the gastrointestinal tract, 39 cases with an elevated absolute, and 43 cases with relative numbers of eosinophils in peripheral blood. 79 and 24 cases reported with personal and family history of allergy, respectively. Excluding the number of repeated cases, a total of 81 infants and children with suspected food allergy were screened for food allergens including food-specific IgG antibody and specific IgE antibody. Finally, 44 infants and children with FC, with a positive IgG antibody and negative IgE antibody were suspected with non-IgE-FA; 20 cases of FC with a positive IgE antibody or SPT and negative IgG antibody were suspected with IgE-mediated food allergy; 15 cases of FC with positive IgG and IgE antibodies or SPT were suspected with mixed-mediated food allergy.

Serum-specific IgE testing and SPT has provided additional diagnostic value. However, OFC is considered the gold standard for IgE-mediated food allergy.[15] Additionally, studies on IgG and IgG isotypes measured in samples of children with suspected food allergies showed positive results for IgG or IgG4 in certain foods.[18] Although increased levels of IgG and IgG4 may reflect the body's long-term exposure to the food ingredients, the diagnostic value of

IgG and IgG4 tests for food allergies needs to be further determined.[19] Therefore, in order to determine whether the above infants and children screened by food-specific IgG antibody, specific IgE antibody, or SPT were diagnosed with food allergy, further verification is needed to observe whether the symptoms of constipation subsided after food avoidance and constipation reappeared after reintroduction of food.

OFC is considered the gold standard for the diagnosis of IgE and non-IgE-mediated food allergies. Most children with non-IgE-FAs do not need day-care hospitalization, because they are not at risk of anaphylaxis. According to the recommendation of the Food Adverse Reaction Committee of the American Society of Allergy, Asthma and Immunology, if the patient's skin test is negative, the serum food-specific IgE level cannot be detected, and there are no convincing immediate food allergy symptoms (e.g., only limited to behavioral changes or symptoms of delayed/chronic gastrointestinal symptoms), suspected allergic foods can be introduced gradually at home (OFC).[20] Patients with suspected FPIES are exceptional because they are at risk of dehydration and require inpatient medical supervision from OFC.[20] In this study, a total of 79 infants and children were finally suspected with food allergy after the screening procedure of food-specific IgG antibody, specific IgE antibody, or SPT. Further, we investigated the changes of constipation symptoms after food avoidance and reintroduction. The results showed that there were 38 infants and children in the suspected non-IgE-FA group, 3 cases in the suspected IgE food allergy group, and 12 cases in the suspected mixed food allergy group, whose symptoms of constipation improved after food avoidance for 8 weeks. After reintroduction of suspected allergenic foods, symptoms of constipation recurred in 35 cases of suspected non-IgE-FA and 10 cases of mixed food allergy, while no symptoms were reported in cases of suspected IgE-mediated food allergy. Finally, 35, 0, and 10 infants and children with FC were diagnosed with non-IgE, IgE, and mixed food allergy, respectively, in this study.

In a Spanish study, symptoms of constipation were resolved in 35 of the 69 children (51%) on a cow's milk–free diet, and 27 children (39%) developed constipation after the reintroduction of cow's milk, which suggested that there exists a clear association between cow's milk consumption and constipation in more than one-third of the children.[21] Iacono et al. reported that perianal lesions and anal fissures in 44 of the 65 children (68%) were resolved after replacing cow's milk with soy milk.[22] In another study, cow's milk allergy (CMA) was regarded as the most frequent cause of constipation in 99 out of 136 children (72.8%) during the first 3 years of life, and the improvement of constipation symptoms after introduction of the elimination diet was observed in all children with food allergy.[23] In this study, 45 of the 301 infants and children (15%) with FC were finally diagnosed with food allergy, including non-IgE-mediated and mixed food allergies. The prevalence of anal fissures was noticed in 64.4% cases of FC with food allergy. Abdominal pain and pain during defecation were as high as 62 and 46.7%, respectively, which were some of the main clinical symptoms in infants and children with food allergic constipation. In addition, cow's milk was found to be the main allergen (in 58% of the cases) followed by eggs and beef, with a prevalence of 42 and 18%, respectively, in this study.

Constipation caused by CMA could be due to increased resting anal sphincter pressure and aberrant anal canal relaxation due to the presence of allergic rectal mucosa inflammation (defined by increased eosinophil and mast cell infiltration upon rectal biopsy).[24] After a CMP elimination diet, both the inflammatory reaction and the motility issues vanish. Visceral allodynia, which is defined by an aberrant perception of physiological stimuli such as intestinal distention and peristalsis, has also been implicated as a source of abdominal and defecation pain in CMA-associated constipation.[25] The pathophysiology of the link between CMA and constipation, on the other hand, is still being contested.[26,27] In this study, cow's milk, eggs, fish, and shrimp were the main food allergens in non-IgE-mediated food allergic constipation, and cow's milk was the leading cause of mixed food allergic FC. Food allergies, particularly to cow's milk, can cause constipation. A food history was required, and if the kid was still being nursed, the mother was included in the study. Breast milk, formula, and dairy-containing foods include CMP.[5] Non-IgE-FAs generally manifest several hours, if not days, after exposure. Non-IgE gastrointestinal symptoms are usually long-term and arise from frequent exposure to the food allergen. According to the EuroPrevall investigation, the prevalence of challenge-proven non-IgE-FAs to CMP was minimal, at roughly 1%. The cumulative incidence of all allergens in the UK birth cohort of this study was 2.4% (cow's milk 1.7%).[28,29] However, questions have been raised concerning selection bias in the EuroPrevall study, as participation in that study is contingent on the level of knowledge of gastrointestinal food allergy clinical indications.[30] The true prevalence of non-IgE-FA is likely to be higher, as it is frequently misdiagnosed or unrecognized because these symptoms commonly occur during early infancy and in breastfed infants. FPIES, EoE, FPIAP, FPE, and food protein–induced dysmotility disorders (GORD and constipation) are just a few of the diseases that fall under the term of "non-IgE-mediated gastrointestinal food allergies." Non-IgE-mediated gastrointestinal illness is difficult to diagnose clinically. Although each disease has its own set of symptoms and indications, they might overlap and differ in severity. It is also not uncommon for many organ systems to be affected. SPT and serum IgE measurement have been used to diagnose non-IgE-FAs in a small number of studies.[31,32] The importance of taking an allergy-focused history and using it to guide the elimination diet has been consistently highlighted in consensus documents guiding clinical practice. If there is a stop or reduction in symptoms, the allergen must be reintroduced or OFC must be supervised to confirm the proper diagnosis and necessity for continuous exclusion. A diagnostic elimination diet for non-IgE-FA might last anywhere from 8 weeks, depending on the criteria. Chebar Lozinsky et al. discovered that majority of the children with non-IgE-mediated allergies improved their symptoms after 4 weeks; however, the data was based primarily on non-breastfed children.[33] Cow's milk is the most widely known causative food for non-IgE-mediated allergies with gastrointestinal symptoms. Lactoglobulin (levels vary from 0.9 to 150 g/L) is the only easily detectable dietary

CMP in human breast milk.[34] Because beta-lactoglobulin is not found in human breast milk, its presence suggests that the lactoglobulin came from the mother's consumption of milk of cows, goats or sheeps. Other allergens, such as soy, wheat, and eggs, can cause non-IgE-FAs through breast milk and should be explored during the history taking and diagnostic workup.[35] By combining current randomized controlled studies, we hope to conduct a comprehensive review and meta-analysis to assess the relationship between FC and non-IgE-FA in infants and children.

In conclusion, the results of this study showed that the incidence of food allergy in infants and children with FC is 15%, which is mainly mediated by non-IgE-FA. Anal fissure, abdominal pain, pain during defecation are the main clinical symptoms or signs of non-IgE-FA constipation. In addition to milk and eggs, fish and shrimp are also the main allergens responsible for non-IgE-FA constipation.

Ethical Disclosures

Confidentiality of data

The authors declare that no patient data appears in this article.

Right to privacy and informed consent

The authors declare that no patient data appears in this article.

Protection of human subjects and animals in research

The authors declare that the procedures followed were in accordance with the regulations of the Clinical Research Ethics Committee and the World Medical Association and the Helsinki Declaration.

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Conflict of Interest

We declare that there are no conflicts of interest relevant to this work. The author for correspondence is in possession of the related documents of this study. All authors read and approved the manuscript.

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References

1. Philichi L. Management of childhood functional constipation. J Pediatr Health Care. 2018;32(1):103–11. https://doi.org/10.1016/j.pedhc.2017.08.008
2. Mugie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: A systematic review. Best Pract Res Clin Gastroenterol. 2011;25(1):3–18. https://doi.org/10.1016/j.bpg.2010.12.010
3. Labrosse R, Graham F, Caubet JC. Non-IgE-mediated gastrointestinal food allergies in children: An update. Nutrients. 2020;12(7):2086. https://doi.org/10.3390/nu12072086
4. Tordesillas L, Berin MC, Sampson HA. Immunology of food allergy. Immunity. 2017;47(1):32–50. https://doi.org/10.1016/j.immuni.2017.07.004
5. Singh H, Connor F. Paediatric constipation: An approach and evidence-based treatment regimen. Aust J Gen Prac. 2018;47(5):273–77. https://doi.org/10.31128/AFP-06-17-4246
6. Buisseret PD. Common manifestations of cow's milk allergy in children. Lancet. 1978;1(8059):304–5. https://doi.org/10.1016/s0140-6736(78)90072-7
7. Leung AK, Hon KL. Paediatrics: How to manage functional constipation. Drugs Context. 2021;10:2020-11-2. https://doi.org/10.7573/dic.2020-11-2
8. Yang W, He T, Zhang W, Gu L, Tu R, Liu H. Effectiveness and safety of lactobacilli in children with functional constipation: Study protocol for a meta-analysis and systematic review. Medicine (Baltimore). 2019;98(20):e15675. https://doi.org/10.1097/MD.0000000000015675
9. Koppen IJN, Vriesman MH, Saps M, Rajindrajith S, Shi X, van Etten-Jamaludin FS, et al. Prevalence of functional defecation disorders in children: A systematic review and meta-analysis. J Pediatr. 2018;198:121–30.e6. https://doi.org/10.1016/j.jpeds.2018.02.029
10. Huang Y, Tan SY, Parikh P, Buthmanaban V, Rajindrajith S, Benninga MA. Prevalence of functional gastrointestinal disorders in infants and young children in China. BMC Pediatr. 2021;21(1):131. https://doi.org/10.1186/s12887-021-02610-6
11. Connor F, Salvatore S, D'Auria E, Baldassarre ME, Acunzo M, Di Bella G, et al. Cows' milk allergy-associated constipation: When to look for it? a narrative review. Nutrients. 2022;14(6):1317. https://doi.org/10.3390/nu14061317
12. Chafen JJS, Newberry SJ, Riedl MA, Bravata DM, Maglione M, Suttorp MJ, et al. Diagnosing and managing common food allergies: A systematic review. JAMA. 2010;303(18):1848–56. https://doi.org/10.1001/jama.2010.582
13. Prescott SL, Pawankar R, Allen KJ, Campbell DE, Sinn JKh, Fiocchi A, et al. A global survey of changing patterns of food allergy burden in children. World Allergy Organ J. 2013;6(1):21. https://doi.org/10.1186/1939-4551-6-21
14. Anvari S, Miller J, Yeh CY, Davis CM. IgE-mediated food allergy. Clin Rev Allergy Immunol. 2019;57(2):244–60. https://doi.org/10.1007/s12016-018-8710-3
15. LaHood NA, Patil SU. Food allergy testing. Clin Lab Med. 2019;39(4):625–42. https://doi.org/10.1016/j.cll.2019.07.009
16. Barni S, Liccioli G, Sarti L, Giovannini M, Novembre E, Mori F. Immunoglobulin E (IgE)-mediated food allergy in children: Epidemiology, pathogenesis, diagnosis, prevention, and management. Medicina (Kaunas). 2020;56(3):111. https://doi.org/10.3390/medicina56030111
17. Bethlehem S, Bexley J, Mueller RS. Patch testing and allergen-specific serum IgE and IgG antibodies in the diagnosis of canine adverse food reactions. Vet Immunol Immunopathol. 2012;145(3–4):582–9. https://doi.org/10.1016/j.vetimm.2012.01.003
18. McKendry RT, Kwok M, Hemmings O, James LK, Santos AF. Allergen-specific IgG show distinct patterns in persistent and transient food allergy. Pediatr Allergy Immunol. 2021;32(7):1508–18. https://doi.org/10.1111/pai.13567

19. Kochuyt AM. Sensitivity and specificity of food specific IgE and IgG determinations for the diagnosis of food allergy. Acta Gastroenterol Belg. 2006;69(1):43–8.
20. Fiocchi A, Assa'ad A, Bahna S, Adverse Reactions to Foods Committee, American College of Allergy, Asthma and Immunology. Food allergy and the introduction of solid foods to infants: A consensus document. Adverse Reactions to Foods Committee, American College of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol. 2006;97(1):10–20. https://doi.org/10.1016/s1081-1206(10)61364-6
21. Irastorza I, Ibañez B, Delgado-Sanzonetti L, Maruri N, Vitoria JC. Cow's-milk-free diet as a therapeutic option in childhood chronic constipation. J Pediatr Gastroenterol Nutr. 2010;51(2):171–6. https://doi.org/10.1097/MPG.0b013e3181cd2653
22. Iacono G, Cavataio F, Montalto G, Florena A, Tumminello M, Soresi M, et al. Intolerance of cow's milk and chronic constipation in children. N Engl J Med. 1998;339(16):1100–4. https://doi.org/10.1056/NEJM199810153391602
23. Kamer B, Dółka E, Pyziak K, Blomberg A. Food allergy as a cause of constipation in children in the first three years of life—Own observations. Med Wieku Rozwoj. 2011;15(2):157–61.
24. Borrelli O, Barbara G, Di Nardo G, Cremon C, Lucarelli S, Frediani T, et al. Neuroimmune interaction and anorectal motility in children with food allergy-related chronic constipation. Am J Gastroenterol. 2009;104(2):454–63. https://doi.org/10.1038/ajg.2008.109
25. Saps M, Lu P, Bonilla S. Cow's-milk allergy is a risk factor for the development of FIGDs in children. J Pediatr Gastroenterol Nutr. 2011;52(2):166–9. https://doi.org/10.1097/MPG.0b013e3181e85b55
26. Crowley ET, Williams LT, Roberts TK, Dunstan RH, Jones PD. Does milk cause constipation? A crossover dietary trial. Nutrients. 2013;5(1):253–66. https://doi.org/10.3390/nu5010253
27. Vandenplas Y, Gottrand F, Veereman-Wauters G, De Greef E, Devreker T, Hauser, B,et al. Gastrointestinal manifestations of cow's milk protein allergy and gastrointestinal motility. Acta Paediatr. 2012;101(11):1105–9. https://doi.org/10.1111/j.1651-2227.2012.02808.x
28. Schoemaker AA, Sprikkelman AB, Grimshaw KE, Roberts G, Grabenhenrich L, Rosenfeld L, et al. Incidence and natural history of challenge—Proven cow's milk allergy in European children—EuroPrevall birth cohort. Allergy. 2015;70(8):963–72. https://doi.org/10.1111/all.12630
29. Grimshaw K, Bryant T, Oliver EM. Incidence and risk factors for food hypersensitivity in UK infants: Results from a birth cohort study. Clin Transl Allergy. 2016;6:1. https://doi.org/10.1186/s13601-016-0089-8
30. Koletzko S, Heine RG. Non-IgE mediated cow's milk allergy in Euro Prevall. Allergy. 2015;70(12):1679–80. https://doi.org/10.1111/all.12681
31. Mehl A, Rolinckwerninghaus C, Staden U. The atopy patch test in the diagnostic workup of suspected food-related symptoms in children. J Allergy Clin Immunol. 2006;118(4):923–29. https://doi.org/10.1016/j.jaci.2006.07.003
32. Turjanmaa K, Darsow U, Niggemann B, Rancé F, Vanto T, Werfel T. EAACI/GA2LEN position paper: Present status of the atopy patch test. Allergy. 2006;61(12):1377–84. https://doi.org/10.1111/j.1398-9995.2006.01136.x
33. Chebar Lozinsky A, Meyer R, De KC. Time to symptom improvement using elimination diets in non-IgE mediated gastrointestinal food allergies. Pediatr Allergy Immunol. 2015;26(5):403–8. https://doi.org/10.1111/pai.12404
34. Host A, Halken S. Hypoallergenic formulas—When, to whom and how long: After more than 15 years we know the right indication! Allergy. 2004;59 Suppl 78:45–52. https://doi.org/10.1111/j.1398-9995.2004.00574.x
35. Martín-Muñoz MF, Pineda F, Garcia Parrado G. Food allergy in breastfeeding babies. Hidden allergens in human milk. Eur Ann Allergy Clin Immunol. 2016;48(4):123–28.