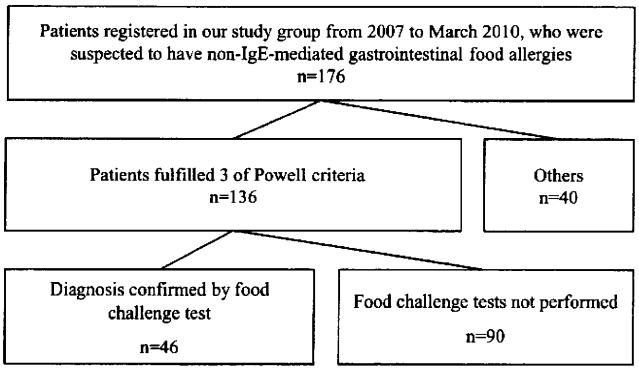

FIG E1. A total of 176 patients with gastrointestinal symptoms who were suspected of having non–IgE-mediated allergy from 1999 to 2009 were registered by doctors of the Japanese Research Group for Neonatal, Infantile Allergic Disorders. Of them, 136 patients fulfilled elements 1 through 3 of the Powell criteria. Forty-six patients underwent food challenge tests and had a positive result, whereas the remaining 90 patients were not tested. Seventeen patients showed no reaction in the oral challenge tests. However, it was unclear whether this was because the patients had outgrown their allergy or because of misdiagnosis. Those 17 patients were excluded from further analysis in this study.

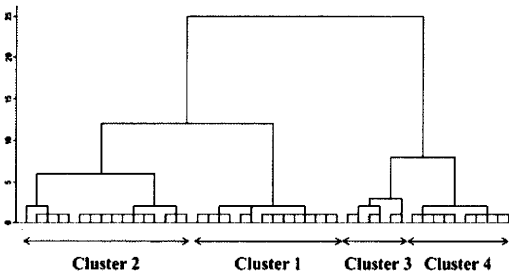

FIG E2. The 46 patients definitively diagnosed with non–IgE-mediated food allergies were analyzed for 5 variables by using an agglomerative (bottom-up) approach and Ward's linkage, and a dendrogram was generated.

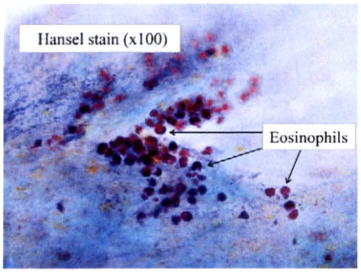

FIG E3. Detection of accumulations of eosinophils in the stool mucus. The mucous part of the stool was thinly smeared on a glass slide and stained by using Hansel stain. The stool sample was taken from a patient in cluster 2 after a positive food challenge test. Representative images were found in a total of 13 patients (Table I).

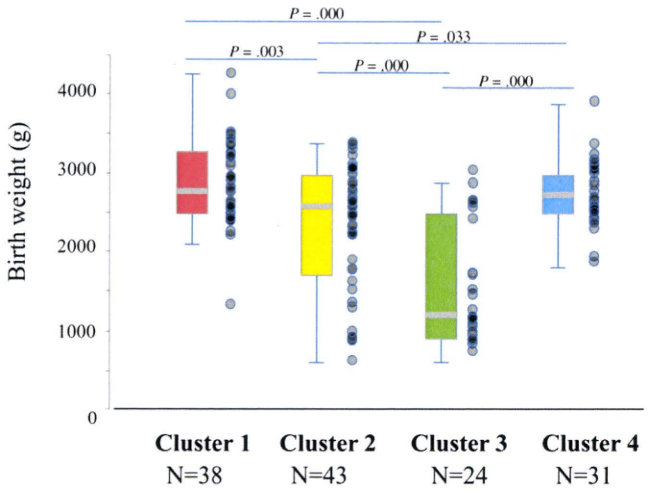

FIG E4. The birth weights in each cluster of the 136 patients who fulfilled 3 elements of the Powell criteria for a non–IgE-mediated allergy are shown.[E2] The birth weights in cluster 3 were significantly lower than in the other clusters. Moreover, 2 subgroups seem to be identified in cluster 3: a lower birth weight group and a normal birth weight group.

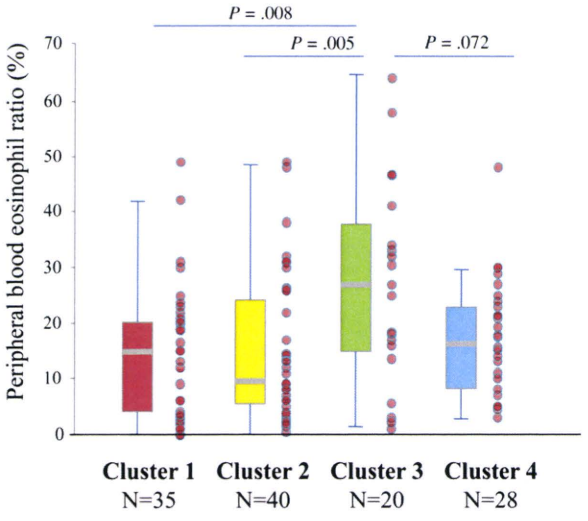

FIG E5. The peripheral blood eosinophil ratios in each cluster of the 136 patients who fulfilled 3 elements of the Powell criteria are shown.[E2] Although eosinophilia was found in all 4 clusters, the eosinophil ratios of the patients in cluster 3 were significantly higher than those of the patients in clusters 1 and 2.

TABLE E1. Clinical features of most severe cases of non–IgE-mediated gastrointestinal food allergies*

Patient no.	Sex	Cluster	Complication	Day of onset	Diet right before the onset of complications	Remarks
1	F	1	Ileus	8	Cow's milk 7 d	
2	M	1	Ileus	5	Cow's milk 3 d, breast milk 6 d	Relieved by surgical operation
3	F	1	Ileus	8	Breast milk 9 d	Relieved by surgical operation
4	F	1	Shock	2	Cow's milk 2-3 times	Massive bloody stool, blood infusion required
5	F	1	Shock	21	Breast milk 18 d	Massive bloody stool, disseminated intravascular coagulation
6	F	2	Ileus	14	Breast milk 2 d	
7	F	2	Shock	36	Breast milk 30 d	Apnea, vomiting
8	M	2	Shock	30	Cow's milk 50 mL by chance	Vomiting
9	M	2	Shock	241	Soy food 2-3 times	Vomiting and diarrhea, ICU admission
10	M	3	Ileus	61	Breast milk 45 d	Cholestasis
11	F	3	Shock	22	Cow's milk 21 d, breast milk 21 d	ICU admission
12	F	3	Severe weight loss	12	Breast milk several months	Developmental retardation
13	M	3	Severe weight loss	46	Cow's milk 30 d, breast milk 30 d	Developmental retardation
14	F	4	Ileus	2	Cow's milk 6 d, breast milk 3 d	Stenosis of sigmoid colon
15	F	4	Ileus	7	Cow's milk 10 d	

F, Female; *ICU*, intensive care unit; *M*, male.
*These patients fulfilled 3 elements of the Powell criteria,[E2] but oral challenge tests were not performed.

TABLE E2. Demographics of the 136 patients who fulfilled 3 elements of the Powell criteria[E2]

Clinical characteristics	Cluster 1 (n = 38)		Cluster 2 (n = 43)		Cluster 3 (n = 24)		Cluster 4 (n = 31)		*P* value
Birth weight (g)	2823 (2501-3267)		2581 (1779-3016)		1363 (1023-2611)		2778 (2512-3100)		.000 *
Male/female	19/19		28/15		13/11		12/19		.16
Initial presentation									
Day of onset	6 (4-8)		29 (7.5-52)		16.5 (9.5-37.5)		7 (2-35)		.01*
Vomiting (%)	100		100		0		0		.000*
Bloody stool (%)	100		0		0		100		.000*
(Laboratory data)†	**n**		**n**		**n**		**n**		
Blood eosinophil ratio (%)	35	15 (3.5-21.0)	40	9 (5.3-25.0)	20	26 (14.1-39.3)	28	17 (8.5-23.8)	.005*
WBC ($\times 10^3$/mL)	32	18.7 (14.5-23.5)	40	13.8 (10.4-22.1)	23	15.9 (13.9-24.4)	27	13.9 (11.4-19.5)	.16
Total IgE (IU/mL)	32	5.2 (4.1-23.1)	40	5.8 (4.0-17.8)	22	13.2 (5.5-122.9)	28	5.0 (3.3-6.0)	.001*
Positive for milk-specific IgE (class ≥1) (%)	31	41.9	38	23.7	20	50	27	19	.24
C-reactive protein (% positive, ≥0.5)	36	61	40	45	20	70	27	33	.69

WBC, White blood cell count.
Data are shown as the median and the interquartile range.
*$P < .05$.
†*n,* Number with medical records.

Eosinophilic gastrointestinal disorders (EGIDs) in infants - A Japanese case series

Running head: EGIDs in infants

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Keywords: Eosinophilic gastrointestinal disorders (EGIDs), eosinophils, bloody stool, allergic colitis, hypereosinophilic syndrome (HES)

Abstract

Background: Eosinophilic gastrointestinal disorders (EGIDs) are disorders characterized by primary eosinophil inflammation in the gastrointestinal tract. There are a small number of reports of eosinophil infiltration in gastrointestinal tracts as EGIDs in infants. In this study, we presented Japanese cases of EGIDs in infants. **Methods:** Five patients diagnosed or strongly suspected as having EGIDs in our hospital from 2008 to 2010 were reviewed. Radiographic contrast enema examinations and/or endoscopies were performed in 4 patients and 3 patients, respectively. **Results:** There were patients with eosinophilic colitis (1 suspected and 2 biopsy-proven), a patient who was suspected of having allergic eosinophilic enterocolitis and a patient with eosinophilic gastroenteritis associated with pediatric hypereosinophilic syndrome (HES). **Conclusions:** The causes and clinical findings of patients with intestinal eosinophil inflammation vary. Therefore, deliberate examination and observation are important for patients with infantile EGID.

Introduction

Eosinophilic gastrointestinal disorders (EGIDs), including eosinophilic esophagitis (EE), eosinophilic gastritis, eosinophilic gastroenteritis (EGE), and eosinophilic colitis (EC), were originally defined as disorders that primarily affect the gastrointestinal tract with eosinophil inflammation to the exclusion of those secondary diseases caused by drug reactions, parasitic infections, and malignancy [1]. Biopsy is the only way to definitively diagnose EGIDs [1]. Most patients with EGIDs are atopic and EGIDs are considered to have properties that fall between IgE-mediated allergies and cellular-mediated hypersensitivity disorders, although EC occurs mostly through a non-IgE-mediated mechanism [1]. In western countries, EE is increasingly diagnosed across all age groups and attracts much attention [2]. On the other hand, eosinophil infiltration in the lower gastrointestinal tract is mostly described as a histological finding of allergic diseases such as food protein-induced proctocolitis (FPIP), whose diagnosis is generally made clinically; therefore, only a small number of series have focused on biopsies [3]. In addition, unlike eosinophilic (procto)colitis, EGE is solely categorized as a disease that generally affects children and young adults, meaning that it is rare in infants [4]. Here, we present a case series of EGIDs in infants, including a rare case associated with pediatric hypereosinophilic syndrome (HES).

Patients and Methods

Patients

During a 2-year period (from June 2008 to May 2010) at Gunma Children's Medical Center, 5 patients were diagnosed or strongly suspected as having EGIDs. The patients were clinically examined by the pediatricians or pediatric surgeons and blood for the analysis of total and differential white blood cell count, levels of IgE, allergen-specific IgE, and the allergen-lymphocyte stimulation test (ALST), as well as fecal samples, were obtained. ALST was performed using LPS-depleted cow's milk proteins at the National Research Institute for Child Health and Development, Tokyo, Japan. Fecal samples were applied on a glass slide either directly or using cytospin, and the slides were then stained with May-Giemsa staining [5].

Radiographic examinations and endoscopies

Four out of 5 patients had a radiographic contrast enema examination. Upper gastrointestinal endoscopy or colonoscopy was performed on 1 and 2 patients, respectively, under general anesthesia. Biopsy specimens for morphology were fixed in phosphate-buffered formalin and embedded in paraffin blocks by using standard methods. Paraffin sections were stained routinely with hematoxylin and eosin and reviewed by a pathologist [6].

Elimination and provocation test

Open cow's milk challenge testing was performed after rectal bleeding disappeared during an elimination diet and the subjects had had good daily weight gain with no demonstration of symptoms [7]. We carefully observed the patients for up to 2 weeks while increasing their intake of milk.

Results

Case 1: A 8-month-old boy who had a congenital syndrome characterized by iris coloboma, ptosis, hypertelorism, and mental retardation, described as Baraitser–Winter syndrome (BWS) [8], was admitted to the allergy and immunology department in our hospital for generalized edema and coldness of limbs, along with exacerbation of full-body eczema. The patient had presented with severe eczema and peripheral blood hypereosinophilia and had been treated with supportive measures since he was a newborn infant. He often had vomiting and loose stool. He was a mixed-fed infant and had never been examined in relation to allergy, elsewhere. On admission, he had peripheral blood leukocytosis with sever hypereosinophilia and granulocytic immature cells (myelocytes and metamyelocytes), hypoproteinemia, and hyponatremia. Radioallergosorbent tests (RAST) for major food allergens were negative except egg-white. A bone marrow biopsy demonstrated an increased number of eosinophil lineage cells and no blasts. His karyotype was normal. Molecular analysis for the Fip1-like1-Platelet Derived Growth Factor Receptor, □□□□□□□□□□□□□□□□[9], was negative. Albumin was administered intravenously because he showed oligouresis and hypotension. Administration of prednisolone (PSL) was started at the same time and the patient responded very well. In addition, elemental diet was used to eliminate multiple allergens. However, when the patient was set on a taper, he required a dose of 1 $mg \cdot kg^{-1} \cdot day^{-1}$ of prednisolone in order to eliminate the eczema with edema and hypereosinophilia. Despite the dose of PSL, frequent vomiting appeared, again and then persisted. Therefore, an upper gastrointestinal endoscopy was performed. Endoscopic findings showed erosion in gastric mucosa and edema in duodenal mucosa. A biopsy revealed increased eosinophilic infiltration with plasma cells and hyperemic edema in the lamina propria in duodenal mucosa (Figure 1A) and increased eosinophilic infiltration, interstitial edema, hyperemia and bleeding in gastric mucosa. This finding motivated us to increase the dose of PSL to 2 $mg \cdot kg^{-1} \cdot day^{-1}$. The higher dose of PSL reduced the frequency of vomiting and diminished the intestinal eosinophil infiltration, according to a reevaluation by endoscope. Although exacerbation of symptoms and hypereosinophilia were observed when tapered the steroid, despite of more than one year treatment of PSL and elemental diet, the PSL was tapered slowly and epinastine and suplatast tosilate had a steroid-sparing effect. Currently, the patient remains completely off steroids and his eosinophil count has been within normal range under these drugs.

Case 2: A 2-month-old girl who had been hospitalized with mild myocarditis that seems to be associated with viral infection, since the age of 55 days, presented mucous and bloody stool after improvement of the

myocarditis. She was a mixed-fed infant and previously healthy. Although peripheral blood eosinophil count was normal range when admitted, laboratory data showed peripheral blood hypereosinophilia and detectable eosinophils in the mucous and bloody stool at that time. The relationship between the bloody stool containing eosinophils and the myocarditis remained unclear. A radiographic contrast enema was performed and presented a finding suggestive of follicular lymphoid hyperplasia. Mucous and bloody stool were the only symptoms. Hydrolyzed formula eliminated the mucous and bloody stool within several days, although spotted blood was detected for a longer time. A normal diet was resumed after confirming that the provocation test was negative. Currently, she has had neither mucous nor bloody stool.

Case 3: A 3-month-old boy was admitted to our hospital due to persistent bloody stool that had appeared a month before the visit. He was a mixed-fed infant and had good feeding and no poor weight gain. Laboratory data showed peripheral blood hypereosinophilia and detectable eosinophils in his stool. The patient was suspected to have a colon polyp and had a colonoscopy. The colonoscopy revealed mucosal edema of cecal and ascending colon and lymphoid hyperplasia of rectum and sigmoid colon. The histological findings showed eosinophil and lymhocytes infiltrations with interstitial edema, hyperemia and bleeding in the lamina propria. The eosinophils were detectable in crypts and seemed to be degranulated (Figure 1B). After switching from mixed feeding to only breast milk feeding, the bloody stool disappeared within a few days.

Case 4: A 2-month-old, mixed-fed baby girl was admitted to our hospital due to sustained bloody stools beginning at 33 days of age, although she was otherwise healthy. Her weight gain had been good despite the bloody stool. Laboratory data showed peripheral blood hypereosinophilia and positive fecal eosinophils. ALSTs of □-lactalbumin and □and albumindata showed peripheralA radiographic contrast enema presented a segmental narrowing with granular mucosa on a serrated wall of the colon. Colonoscopic examination demonstrated several mucosal erythemas of the colon and rectum (Figure 1D). The colonic and rectal biopsies revealed intense eosinophil infiltrations in the crypt epithelium with Charcot-Leyden crystals (Figure 1C). In order to eliminate milk allergens from the breast milk, her mother took in a strict dairy-free diet. After dairy-free breast milk was used, the bloody stool was resolved within a month. After a confirmation of negative in the provocation test, the mother was released from the elimination of dairy in her diet. Since then, her breast milk has not induced any symptoms.

Case 5: An 8-day-old girl in whom bloody stool was detected just after her first artificial milk feeding at 1 day of age was admitted to our hospital due to exacerbation of the symptom with poor milk feeding. The patient was treated with intravenous fluid, without ingesting anything orally. The patient developed vomiting in addition to bloody stool. The next day, milk was resumed and then increased in small increments. Although her daily weight gain and general condition showed some improvement, the symptoms persisted. She was referred to the allergy and immunology department. Her laboratory data showed peripheral blood hypereosinophilia and aggregation of eosinophils in her mucous and bloody stool on consultation of allergists. A radiographic contrast enema at 17 days of age presented a lead-pipe-like stenosis of the descending and sigmoid colon (Figure 2). By 19 days of age, the symptoms had resolved. On day 27, the elimination of milk allergens was started, since her peripheral blood showed persistent hypereosinophila and positive milk-specific IgE. A follow-up radiographic contrast enema at 3 months of age revealed an improvement of the narrowing of the sigmoid colon. At 6 months, as the provocation test was negative, the patient returned to normal formula. Although she had often had mild eczema and recurrent wheeze associated with respiratory viral infection, she has had neither mucous nor bloody stool, currently.

Discussion

EGIDs are heterogeneous disorders categorized by gastrointestinal eosinophil inflammation [1]. We experienced 5 cases of EGIDs, including secondary EGIDs associated with HES (summarized in Table1). Case 1 was a secondary eosinophilic gastroenteritis with HES. The patient presented hypereosinophilia greater than >1,500 eosinophils/μl for more than 6 months (2,980-31,158 cells/μl in stable condition for a last 6 month before admission) and symptoms of organ involvements in skin and gastrointestinal tract. In addition, he also showed mild mitral and tricuspid valve regurgitation and prolapse of mitral valve in heart and stenosis of the ureteropelvic junction. However, a causal linkage between these findings and eosinophilic inflammation could not be confirmed. Elimination of multiple allergens would not be sufficient to improve the symptoms and eosinophilia. Unlike acute allergic reactions, chronic allergy is rarely associated with absolute eosinophil counts of more than >2,000 cells/μl[10]. Besides, the presence of immature granulocytic cells with hypereosinophila in peripheral blood may imply the patient had a primary hematopoietic disorder[11]. About 40 pediatric cases of hypereosinophilic syndromes have been reported, based on the literature in the English language [12]. However, infant-onset of HES is extremely rare. This patient was also associated with a congenital syndrome, BWS. However, no report shows the relationships between hematological disorders or allergic disorders and BWS [8,13]. In addition, although pediatric HES is often associated with chromosomal abnormalities [12], this patient's karyotype was normal. Interestingly, despite 1 $mg \cdot kg^{-1} \cdot day^{-1}$ of PSL, the patient presented symptomatic eosinophilic infiltration of the intestine and a higher dose of PSL was required to resolve the symptom, suggesting that intestinal eosinophil infiltration associated with HES may be more persistent compared to that of primary EGIDs. As another interesting point, splatast tosilate and epinastine were used since anti-eosinophilic effects have been reported

in these drugs [14,15]. These drugs could be effective at least for steroid-sparing in case 1.
Eosinophilic colitis (EC) shows a bimodal age distribution in infant and adolescence. the infantile EC presented at a mean age at diagnosis of approximately 60 days [1]. In infants, EC, allergic colitis (AC), and FPIP are significantly overlapping disorders sometimes approached by different points of view [6,7,16]. It seems reasonable that EC in infants is considered as a histologically proven AC or FPIP. All of cases 2–5 showed bloody stool as an initial symptom. They may be categorized food protein-induced enterocolitis syndrome (FPIES) or FPIP [4]. Interestingly, case 5 appeared to be distinguishable from the other 3. In fact, Case 5 had an earlier and severer onset of vomiting than the other 3 patients and tested positive for milk-specific IgE. Milk-specific IgE was mostly negative in patients with allergic colitis or eosinophilic colitis, which is typically a non-IgE-mediated allergy [1,4]. Therefore, allergic eosinophilic enterocolitis was suspected in Case 5.
Concerning the diagnosis of allergy, in addition to the usual IgE-mediated diagnostic tests, ALST and the atopy patch test are useful as adjunctive diagnostic tests when a non-IgE-mediated allergy is suspected [17]. For a definitive diagnosis, the elimination and challenge of allergens are recommended [7]. As a distinctive approach, the histological findings associated with eosinophil infiltrations—for example, more than 20 eosinophils per HPF (87 and 130 eosinophils/ HPF in case3 and 4, respectively)—are also reported to be good criteria for the diagnosis of allergic colitis [6,18,19]. A cluster of eosinophils in the mucous and bloody stool may be of diagnostic value. Peripheral blood hypereosinophila could be important since the eosinophil count is often checked routinely as a differential count of leukocytes even in those patients not suspected of having allergies. EC (AC) was suspected in case 2 based on peripheral blood and stool examinations[20] after excluding surgical diseases such as colon polyps and intussusceptions. A definitive diagnosis of EC was made by the histological findings in cases 3 and 4.
Although there are a limited number of studies showing radiological findings of allergic colitis, eosinophilic colitis, or enterocolitis, detectable radiological findings are not common [21,22]. Lymphoid hyperplasia has occasionally been presented but is not always a pathological condition[17]. Surprisingly, a radiographic contrast enema revealed a narrowing of the colon in cases 4 and 5. Radiographic examination may be useful as an adjunct to the diagnosis of EC.
Based on the literature, 18% of infants with bloody stool were confirmed by an elimination and provocation test as being allergic to cow's milk [7], whereas another report showed that 64% of patients with rectal bleeding had histological findings-proven AC [6]. The great difference between these 2 groups could be interpreted as follows. First, although cow's milk is the most common cause of AC, milk-associated proteins are not the sole cause of AC, since infants become sensitized to the proteins excreted in breast milk [17]. Second, there is the possibility that the patients have already become tolerant during elimination [17]. A significant proportion of patients developed tolerance in one year of a strict elimination diet [17]. In addition, there are types of eosinophilic colitis that do not present any allergic reactions, like neonatal transient eosinophilic colitis [23]. Indeed, the elimination and provocation tests were negative in our cases. Therefore, it seems important to carefully observe biopsy-proven AC, as well as those patients diagnosed by the elimination and provocation test, which is the gold standard for diagnosis.
Only 18% of patients with AC were allergic to cow's milk, as mentioned above [7]. In addition, AC proved to be benign and self-limiting and, in most cases, cow's milk elimination did not affect the duration of bleeding [7]. Another problem is that the elimination and provocation test for AC is available only in restricted hospitals as compared with the routinely performed provocation test. These facts may discourage pediatricians and pediatric surgeons from the further investigation of allergies, resulting in missing patients with AC.
In conclusion, intestinal eosinophil infiltration would seem to be a common finding in all the patients presented here, but the clinical findings and courses vary. To clarify the cause of gastrointestinal eosinophil infiltration, histological analysis, as well as the elimination and provocation test, would be useful.

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Figure Legends

Figure 1. **Histological and endoscopic findings of the patients**
Histopathologic analysis of the duodenum in Case 1 (A) and the colon in Case 3 (B) and Case 4 (C) was performed by hematoxylin and eosin staining (optical magnifications X 200). The arrow is pointing to a Charcot-Leyden crystal. Panel D represents the endoscopic findings in Case 4. Insets represent blow-ups of original pictures (A-C).

Figure 2. **A radiographic contrast enema examination of the patient**
A radiographic contrast enema examination was performed in Case 5. The arrow is pointing to the narrowing of the colon.

Table 1. Characteristics of Patients with EGIDs

Patient No.	1	2	3	4	5
Age/sex	8 months/male	2 months/female	3 months/male	2month/female	8 days/female
Chief complaint	exacerbation of eczema	Bloody stool	Bloody stool	Bloody stool	Bloody stool
Peripheral blood eosinophils (/μl)	22,410	2,136	3,052	3,154	7,375
Total IgE antibody (IU/ml)	41.5	14.5	5.09	< 2.0	12.6
Positive Specific IgE antibody	Egg-white	-	-	-	Milk
CRP (mg/dl)	0.1	0.0	0.0	0.0	0.0
Stool examination	nd	Eos (+)	Eos (+)	Eos (+)	Eos (+)
ALST	nd	nd	nd	+	nd
Barium Enema	nd	LH	LH	stenosis of colon	stenosis of colon
Endoscopy	Edema in duodenum	nd	LH and edema in colon	Edema and erythema in colon	nd
Histology	Eos with PC	nd	LH and Eos with Ly	Eos with CLC in crypt Epi	nd
Provocation test*	nd	-/1.2y	nd	-/5M	-/7M
Treatment	Prednisolone	Elimination	Breast milk alone	Elimination	Elimination
Diagnosis**	EGE/HES	EC	EC	EC	AEEC

nd, not done; M, months; Y, year; ALST, allergen-lymphocyte stimulation test; Eos, eosinophils; Ly, lymphocytes; PC, plasma cells; Epi, epithelium; CLC, Charcot-Leyden crystal ; LH, lymphoid hyperplasia; AEEC, Allergic eosinophilic enterocolitis; EC, Eosinophilic colitis; EGE, Eosinophilic gastro enteritis; HES, Hypereosinophilic syndrome; Elimination, Elimination of cow's milk allergens

*result of test/ the age when performed provocation test

**including suspected cases

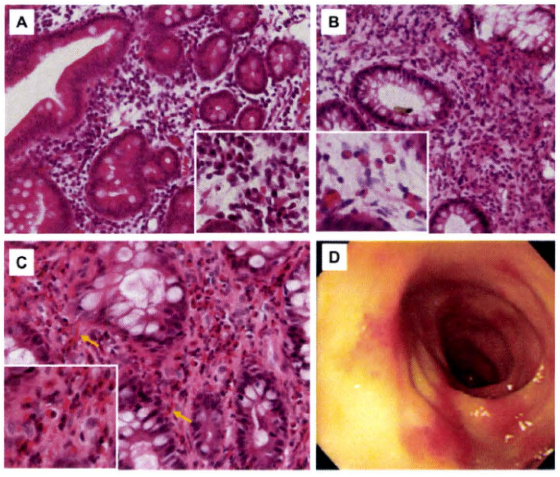

Figure 1. Histological and endoscopic findings of the patients

Histopathologic analysis of the duodenum in Case 1 (A) and the colon in Case 3 (B) and Case 4 (C) was performed by hematoxylin and eosin staining (optical magnifications X 200). The arrow is pointing to a Charcot-Leyden crystal. Panel D represents the endoscopic findings in Case 4. Insets represent blow-ups of original pictures (A-C).

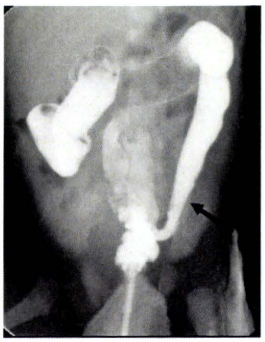

Figure 2

Figure 2. A radiographic contrast enema examination of the patient

A radiographic contrast enema examination was performed in Case 5. The arrow is pointing to the narrowing of the colon.

4. 免疫・アレルギー

新生児－乳児消化管アレルギー

food protein-induced gastrointestinal syndrome

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新生児，乳児における消化管アレルギーは，1995年頃から急激に増加しつつある．摂食不良，嘔吐や血便，ショック，体重増加不良などさまざまな症状をおこす．急性期の確定診断はむずかしい．まず治療的診断を行って，症状が消失し体重増加をみたところで負荷試験を行い確定診断としたい．

診断のポイント

近年，日本で増加してきた新生児－乳児消化管アレルギー（以下，本症とする）については，いまだ疾患概念が確立しておらず，さまざまな病型，さまざまな検査の特徴を示している．欧米でこれまでに確立されているIgE非依存型（細胞性免疫が関与）の消化管食物アレルギーとしては以下がある[1)2)]．

①food protein-induced enterocolitis syndrome (FPIES)[3)4)]：新生児，乳児において，比較的急性の嘔吐，下痢を主徴とする．

②food protein-induced proctocolitis syndrome：新生児，乳児において血便を主徴とし，全身状態は侵されない．

③food protein-induced enteropathy syndrome：乳児において，慢性下痢，体重増加不良を主徴とする．

④celiac disease：乳児において，吸収不良，体重増加不良を主徴とし，原因は小麦蛋白である．

本症患者はこのいずれかにあてはまる場合がある一方，いずれにも該当しないことも多く，新たな疾患概念の構築，サブグループ分けが求められており，疫学調査が進行中である．ただし，これを待っている時間はないため，現時点ではとりあえず新生児－乳児消化管アレルギーとして一括して扱い，診断と治療を行うべきと考えている．

経口食物摂取を行っていて，摂食不良，嘔吐，下痢，血便，ショック，体重増加不良などあらゆる消化器症状が出たときに，本症は鑑別の対象となる．診断と治療は同時に行われるべきであり，五つのステップを設けるとよい．①症状から本症を疑う，②鑑別診断を行う（ここで日数を費やさないように），③ある程度鑑別ができたら，確定できなくても治療乳に変更する．そして，症状消失を確かめる，④体重をチェックし，増加していることを確認する，⑤確定診断のための負荷試験を行う（症状改善後2週間～2カ月が望ましい）．

ステップ②の鑑別診断がもっとも難度の高いところである．現在のところ，単一の検査での確定診断法は開発されておらず，治療的診断を行うしかない場合も多い．中腸軸捻転などの外科疾患，細菌感染症，潰瘍性大腸炎，Crohn病，そのほかあらゆる消化器疾患の検査を進めるとともに，本症に特異的な検査を行う．

1. 末梢血の好酸球数　好酸球は生後20日頃まで増加傾向を示し，かつ，低出生体重児やチアノーゼ心疾患，エリスロポエチン使用時などに増加する．しかし，図1のようにコントロール平均＋3 SD以上を示した場合には，尤度10以上となり，高い診断的価値がある．たとえば，末梢血好酸球が40%などを示した場合には，本症の可能性が非常に高いと考えるべきである．ただし，本症の1/3程度は好酸球10%未満を示すため，少ない場合にも否定することはできない．

2. 便粘液の細胞診　便の粘液部分を薄くスライドグラスに展開し，Wright染色など通常の血球細胞の染色を行う．図2のように好酸球の集塊がみられた場合，診断的価値が高いと考えられる．細胞診が困難である施設も多いこと，定量性がないことから，好酸球の比較的安定な分子であるeosinophi-derived neurotoxin (EDN) の測定を行えるよう，新生児－乳児アレルギー疾患研究会で準備を進めている．

3. 腸粘膜組織検査での好酸球増加　消化管ファイバーにて病変部の好酸球増加（20個以上/high power field）を認めた場合，診断的価値が高いと考えられる．事故のないよう，小児の検査に習熟した術者によって行われなければならない．重症になると

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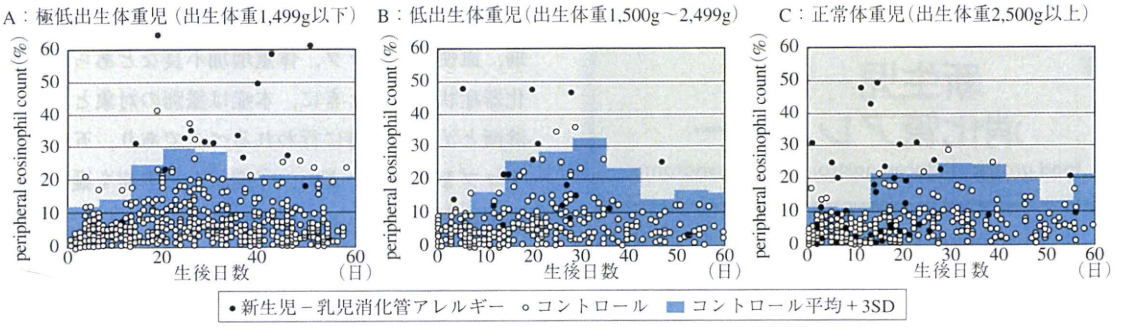

図1　末梢血の好酸球数

新生児では，とくに低出生体重児，チアノーゼ性心疾患，エリスロポエチン使用時に生後3週間をピークとして末梢血好酸球の上昇がみられることから注意が必要である．そのため，各体重別に疾患コントロール平均＋3 SDを青いバーで示した．これ以上の値を1度でもみた場合は本症である可能性が高い

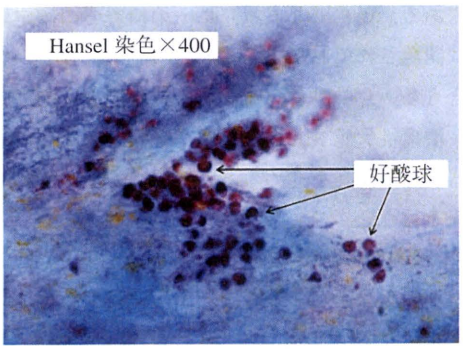

図2　便粘液中好酸球

便の粘液部分を薄くスライドグラスに展開し，エオジン染色を施したもの．好酸球の集塊がみられる

炎症が修飾されて，もはや好酸球が存在しない場合もある．

4．牛乳特異的IgE抗体　新生児や生後半年までの乳児で陽性であれば，本症の可能性が非常に高い．しかし，初発時の陽性率は30%にすぎず，陰性であっても本症を否定してはならない．

5．リンパ球刺激試験　静岡県立こども病院の木村光明先生か，国立成育医療センター研究所免疫アレルギー研究部の森田英明（http://www.fpies.jp/の「特殊検査について」を参照のこと）が行っている．

6．負荷試験　「新生児－乳児消化管アレルギー診断治療指針」から抜粋する．

1）負荷試験の実施時期　診断のための負荷試験は，症状が改善し体重が増加するようになってから行うべきであり，症状改善から最低2週間は間隔をあけ2週間～2カ月の間に行うことが望ましい．状況によって，それ以上間隔をおくことも考慮する．重～最重症の症例に関しては，重大な危険が予測される場合，負荷試験を実施しないことも選択肢とする．

2）負荷試験方法の選択　初発時の重症度を考慮し，**表1**に示す3タイプから適切な負荷試験方法を選択する．

3）負荷試験の具体的な方法

①負荷試験の同意書を取得し，カルテに貼付する．もしくは主治医が厳重に保管する．

②負荷試験前にIgE CAP-RAST（capsulated hydrophilic carrier polymer-radioallergosorbent test）を測定，もしくはプリックテストを行い，即時型反応の危険性を評価する．負荷は原則として**表2**に示す量を1日1回摂取とするが，IgE陽性など即時型反応が予測される場合は3分割し，15分ごとに摂取する．また，負荷試験当日の検査を**図3**に示す．

③**表2**に示す指針は負荷後7日間までの記載となっているが，7日目以降は徐々に量を増やし，計2週間で通常摂取量まで増量する．

④症状については，嘔吐，下痢，血便，活気，体温，血圧，発疹，四肢の動きなどに注目して記載を行う．摂取後6時間はとくに注意して観察する．

⑤夜間や休日に症状が現れることをなるべく避けるため，負荷は週の前半に開始し，朝に行うことが望ましい．

4）負荷試験陽性の判定基準　病的な嘔吐，血便，下痢，発熱，活動性低下，血圧低下などの症状が再現された場合，陽性とする．ただし，本症の中でどの疾患にあたるのかを判定するためには，より詳細

な検討が必要である．

欧米で確立された FPIES の診断基準は以下のとおりである．

①嘔吐・下痢，②便潜血（負荷前陰性⇒負荷後陽性），③便中好酸球（負荷前陰性⇒負荷後陽性），④便中好中球（負荷前陰性⇒負荷後陽性），⑤多核白血球数（好中球＋好酸球＋好塩基球）が負荷前より 3,500/uL 以上増加，の 5 項目のうち，3 項目以上を満たすものを FPIES と定義している．

5）離乳食開始に際する負荷試験　米，大豆，小麦でも症状を認めることがある．そこで，とくに米，大豆，小麦についてはそれぞれ 2 週間程度かけて，症状出現がないかどうかを確認する．最初はごく少量から開始し，徐々に増やして，児が食べることのできる量まで増量する（図 4）．

重症度評価

本症は，軽症から消化管穿孔やショックをおこして死亡する症例まで，さまざまな重症度が存在する．そのため，重症度に応じた対応が必要となる．頻回の嘔吐，無呼吸発作，イレウス，体重増加不良，アシドーシスなどがあれば慎重な対応が必要となる．

とくに，元気で食欲もあるが肉眼的血便のみがみ

表 1　負荷試験選択のための重症度分類

[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	低血圧，重症イレウス	嘔吐，下痢，血便，発熱，活動性低下，体重減少，無呼吸	全身状態が保たれている児 血便，軽度の嘔吐のみ
[illegible]	タイプ 1	タイプ 2	タイプ 3

表 2　負荷量の増量方法

A：タイプ 1（最重症）

生後 0～4 カ月（修正月齢）

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
症状観察	●	●	●	●	●	●	●
負荷量（mL/kg）	0.5	1	2	4	8	8	16
場　所	入院 →						

生後 5 カ月以降

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
症状観察	●	●	●	●	●	●	●
負荷量（mL/kg）	1	2	4	8	8	16	16
場　所	入院 →						

原則入院とし，輸液ラインを留置したうえで行う．負荷量に関しては，初発時に摂取していた量などを考慮し主治医が適切な量を決定してよい

B：タイプ 2（中等症・重症）

生後 0～4 カ月

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
症状観察	●	●	●	●	●	●	●
負荷量（mL/kg）	2	4	[illegible]	4	8	8	16
場　所	入院 →	自宅 →					

生後 5 カ月以降

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
症状観察	●	●	●	●	●	●	●
負荷量（mL/kg）	4	8	8	8	16	16	20
場　所	入院 →	自宅 →					

最初の 2 日間は入院で輸液ラインを留置し，症状を観察することが望ましい．3 日目以降は自宅で行ってもよいが，症例出現時の連絡網を充実させておくことが必要である

C：タイプ 3（軽症）

生後 0～4 カ月

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
症状観察	●	●	●	●	●	●	●
負荷量（mL/kg）	4	4	8	8	16	16	16
場　所	外来 自宅 →						

生後 5 カ月以降

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
症状観察	●	●	●	●	●	●	●
負荷量（mL/kg）	8	8	8	16	16	20	20
場所	外来 自宅 →						

初日は外来受診し，医師の観察のもとで行うことが望ましい．自宅で開始する場合はより少量から（例：1 mL から）開始し，2 週間程度かけて行う．やはり症状出現時の連絡網を充実させておくことが必要である

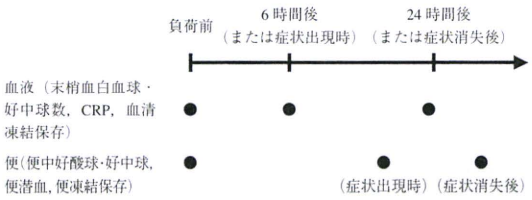

図3　負荷試験当日の検査（タイプ1～2の場合）

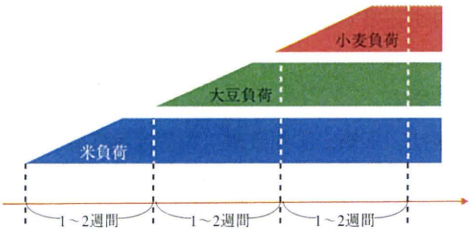

図4　離乳食開始の方法
これら固形食物でも消化管アレルギーがおきることがあり，米，大豆，小麦についてはそれぞれ2週間程度かけてchronic tolerance（長期の負荷試験）を行う必要がある

られる場合は，food-protein induced proctocolitis，allergic colitisとよばれ，早期に寛解することが多い．

基本病態

一般的にアレルギーのおこる機序としては，特異的IgE抗体を介する即時型反応と，IgEを介さない非即時型反応とがある．もっともよく知られているミルクアレルギーはIgEを介する即時型反応（じんま疹，呼吸困難，嘔吐など）をおこすタイプであるが，本症はIgEを介さない非即時型アレルギー反応が主体となっておきるとされていて，食物摂取後1～2時間で症状が出現することもあるが，数時間以上経過してから発症することもあるため気づかれにくい．この本態はいまだ明らかになっていないが，細胞性免疫，すなわち抗原提示細胞，アレルゲン特異的リンパ球，好酸球，患部の上皮細胞などが関与して成立すると考えられている．

消化管の部位としては，口腔から直腸までいずれの部分が含まれてもよいと考えられている．消化管ファイバーによる組織検査では好酸球性炎症をみることが多いが，消化管穿孔にまで至った場合，これはみられず，非特異的炎症像を示すことが多い．

発熱やCRP陽性をみる場合もあり，これは従来のTh2サイトカイン，好酸球性の炎症で説明されてきたアレルギー炎症の概念とは一線を画している．

治療の実際

本症が疑われ，ある程度鑑別がついたら，経口摂取を一時的に止め，治療乳を開始するとよい（図5）．治療乳には，①母乳（乳製品除去あり・なし），②加水分解乳（MA-1®），③アミノ酸乳（エレンタール®P，エレメンタル・フォーミュラ®），がある．母乳の場合，母親が乳製品を除去すべき場合と必要ない場合があると思われるが，まずは乳製品除去で開始し，体重が増加してきたら母親の乳製品摂取を始めるとよい．

原因食物が除去されているにもかかわらず炎症が寛解しない場合は，ステロイドなどの抗炎症治療も必要な場合がある．

最新ガイドライン

現在，本症について3種類のガイドラインが存在する．それぞれ視点が異なっており，長所と短所がある．今後は小児アレルギー学会，食物アレルギーガイドライン委員会によって統一されていくことが予想される．

①新生児乳児アレルギー疾患研究会（厚生労働省難治性疾患研究，国立病院機構ネットワーク研究）作成の診断治療指針の最新版がホームページ（http://www.nch.go.jp/imal/FPIES/icho/pdf/fpies.pdf）に掲載されている．

②静岡県立こども病院，木村光明先生作成ホームページ（http://www3.tokai.or.jp/atopy/eiicma/framepage-icma.html）参照．

③昭和大学小児科作成の「ハイリスク新生児入院施設における新生児ミルクアレルギー疑診時の診療の手引き」．

近年のトピックス

口腔潰瘍と発熱，CRP陽性などを主徴とした患者の報告があり，かつ原因ミルクの再投与で症状が再現された．新たな病型である可能性があり，注意が必要である．

急性期の診断方法が存在しないことが治療の遅れにつながっているため，確定診断可能な検査法の開発を試みている．リンパ球刺激試験，便EDN検査，血清サイトカインなどの検査を受け付けている（http://www.fpies.jp/）．

本症の実態はいまだ明らかになっているとは言い

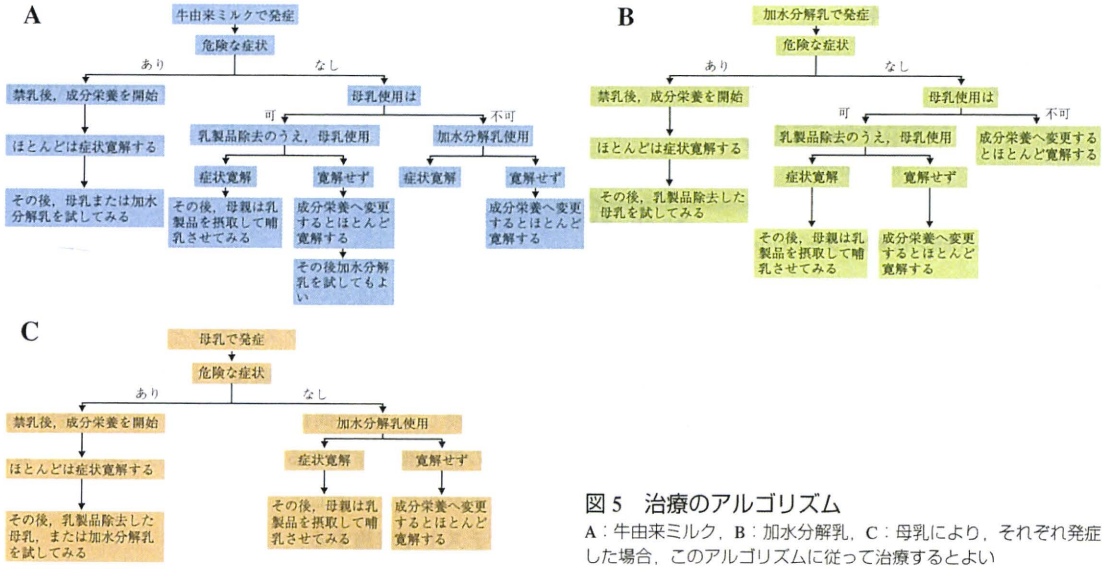

図5　治療のアルゴリズム
A：牛由来ミルク，B：加水分解乳，C：母乳により，それぞれ発症した場合，このアルゴリズムに従って治療するとよい

難い．1,000名以上を目標に詳細な医療情報を集めるため，全国からインターネットオンラインでの登録を募っている（詳細はhttp://www.fpies.jp/を参照のこと）．

ピットフォールと対策

エレンタール®P，エレメンタル・フォーミュラ®などのアミノ酸乳でも，炎症の再燃がみられる場合がある．エレンタール®Pはダイズ油が使用されているため，これが原因である可能性がある．

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野村伊知郎

ミルクアレルギー赤ちゃん急増

血便・嘔吐…500人に1人か

赤ちゃんの消化管アレルギー診断と治療の手順　厚労省研究班の診療指針から

ステップ1	嘔吐、下痢、血便などの消化管の症状や体重増加の不良
ステップ2	血液検査、便の検査などで他の病気の可能性を排除
ステップ3	アレルギーを起こしにくいミルクを与えてみる
ステップ4	1カ月ごとに症状がないことや体重増加が順調か確認
ステップ5	よくなってから、原因と見られる食事を与えてみて確定診断

日本小児科学会などの関連学会で。厚労省研究班調べ

体に合わないミルクを飲むことで、赤ちゃんが血便や嘔吐（おうと）などの症状を起こす「新生児・乳児消化管アレルギー」が増加し、少なくとも500人に1人の割合で、毎年全国で2千人以上が発症している可能性のあることが、厚生労働省研究班の調査で分かった。まれに重症になる危険はあるが、アレルギー用の市販ミルクで治療できる。研究班は診療指針を作って公開、異常があれば、受診を呼びかけている。（小坪遊）

このアレルギーの半数は生後1～7日で起こる。症状は嘔吐や下痢、血便が中心で、多くはミルクの中のたんぱく質に反応して起こるようだ。原因は牛乳から作ったミルクが4割、母乳と人工乳との混合も4割、母乳だけも1割以上あった。食後まもなく、じんましんや呼吸困難になることで知られる食物アレルギーと違い、食後数時間でじわじわ症状が出るのが特徴。体重が増えなくなることが多い。

治療では、アレルギーの原因となるたんぱく質を分解したミルクなどに切り替えれば、7～8割が回復する。これらは、じんましんなどを起こすミルクアレルギー用に、粉末で850グラム3千円程度で一般に広く売られている。

このミルクで治らない赤ちゃんには、たんぱく質をさらに細かくした特殊なミルクを使えば、大半は治療できるという。これは医師が処方するほか、340グラム3千円ほどで市販もされている。

日本小児科学会など関連学会では、03年に埼玉で死亡例、08年には愛知で腸が壊死（えし）した重症例が報告された。

研究班（主任研究者＝国立成育医療研究センターの野村伊知郎医師）は東京都内すべての産科、小児科、総合病院、計約1085施設にアンケート（回答率約47％）したところ、08年9月～09年8月に103例の発症例が確認された。この数字をもとに出生数から試算すると、発症率は0・21％で、全国では毎年生まれる赤ちゃん約100万人のうち、2千人以上が発症している可能性のあることがわかった。原因は不明だが、子どもに重症のアトピー性皮膚炎などのアレルギーも増えていることから、研究班は発症者の実数が増えているとみている。

研究班は、治療に役立てるため、診断治療指針も作成した。ホームページ（http://www.fpies.jp/）に指針を掲載、病院からは診断例の報告を募っている。

野村医師は「すぐに命にかかわることは少なく、勝手に母乳をやめたり、素人考えでアレルギー用のミルクを使ったりすると、栄養不足などから発育不良になりかねない。適切に診断、治療すれば大丈夫なので、まずは医師に相談して欲しい」と話す。

治療ミルクで回復

06年に国立成育医療研究センターで生まれた女児も、消化管アレルギーと診断された。生まれた直後は元気だったが、生後5日目からミルクや母乳を飲む量が減り、10日目からは嘔吐が始まった。11日目には真っ赤な血便がみられるようになり、体重は減るばかり。「この子はどうなってしまうの」。両親はかなり不安がっていたと、主治医の野村医師は振り返る。

消化管アレルギーを疑い、たんぱく質を分解したミルクに替えると、症状は1、2日でなくなった。野村医師は「その後は体重も増えて、今では母親と一緒におしゃれを楽しんでいます」と話す。

10年夏には、1歳3カ月の男児が他の医療機関から同センターに検査を依頼され、受診した。生後しばらくは順調に育っていたが、5カ月以降、体重が増えなくなった。11カ月以降は日に1、2度嘔吐もあった。たんぱく質の分解ミルクで症状が改善し、体重はぐんぐん増えたという。

中国・重慶　反日デモ

総領事館前

【重慶＝峯村健司】中国重慶市で26日午後、反日デモが起きた。約千人の若者が「日本製品ボイコット」などと叫びながら市中心部を行進、日本総領事館の前で抗議行動をした。多数の武装警察官が出動し、約1時間半後に解散させた。

＝9面に関係記事

今月16日以降、日本の総領事館がある都市でのデモは初めて。

中国当局は政府批判や社会不安につながりかねないデモの取り締まりを強めているが、内陸部の主要都市での発生を抑えきれなかった。

26日、重慶市中心部の日本総領事館前でデモをする若者ら＝峯村写す

天声人語

色づき始めた[illegible]木が雨に煙り、青磁色の[illegible]に揺れていた。4年前[illegible]た商業施設「表参道ヒル[illegible]、街がそのまま屋内に続く造りになっている。元の同潤会青山アパートのように、早く当たり前の景色になりたいと▼東京の一等地。老朽住宅の建て替えは難渋した。設計者が市場原理に逆らい、高さを並木に合わせるなどの頑固を通したのが一因だ。文化勲章を受ける安藤忠雄さん(69)である▼勉強は嫌い、家計も厳しく大学進学は頭になかった。工業高校2年でプロボクサーになるも、長続きしない。卒業後の無職を見かね、知人が持ってきたバー設計の仕事が転機だった。建築の教科書を読みあさり、家具や内装の注文を手当たり次第こなした▼履歴は〈独学で建築を学び、28歳で建築研究所を設立〉と始まる。東大教授に迎えられる前には、ハーバードなど米国の有名どころで教え、昔のリング名「グレート安藤」がすっかり別の意味で似合う。学歴信仰を笑う、徒手空拳の人生だ▼狭い長屋に育ち、住環境にかかわる原点は怒りだった。最初期の「都市ゲリラ住居」では、無秩序に増殖する街への反抗を、コンクリむき出しの無愛想に込め

日航、想定の3倍で購入

が、5億円前後でも買い手がつかない状況という。

と具体的に振り返る。土地所有者側はこの後、2

与もなかった」と話している。しかし、一貫して契約に

で1時間弱かかる。当時は水道やガス、電気も未整備で、

た。

＝38面に関係記事

和解協議後に記者会見した

2010年（平成22年）
10月27日
水曜日
読書週間（11月9日まで）

天気　6　9　12　15　18　21(時)

東京	晴	晴	晴	晴	晴	10	14 / 11
横浜	晴	晴	晴	晴	晴	10	14 / 11
千葉	晴	晴	晴	晴	晴	10	14 / 10
さいたま	晴	晴	晴	晴	晴	0	14 / 10
札幌	雨	雨	曇	曇	晴	60	7 / 2
仙台	曇	曇	晴	晴	晴	10	11 / 5
名古屋	晴	晴	晴	晴	晴	10	16 / 8
大阪	曇	曇	晴	晴	晴	20	15 / 10
福岡	曇	曇	晴	曇	晴	10	17 / 11

朝日新聞
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しつもん！ドラえもん　292　こっかい編

国会議事堂（こっかいぎじどう）は左右（さゆう）二つの建物（たてもの）に分（わ）かれているけど、それぞれなん