Non-IgE-Mediated Gastrointestinal Food Reactions

Ichiro Nomura, MD PhD.
Division of Allergy, National Center for Child Health and Development, Tokyo, Japan

Clinical course of a baby...
She was born in full term and normal birth weight.
She was happy and drinking cow’s formula until 8th day after birth, then she started vomiting once a day.
On the next day, she became less energetic.
On 11th day, bloody stool and diarrhea 20 times a day.
On 12th day, she had apnea and shock.
She was transferred to the Emergency department of Children’s Hospital. At arrival, arterial pulsation was not recognized and cyanosis was apparent
Life support was started and she gradually recovered.
Open abdominal surgery was performed to find no abnormality
Increased peripheral eosinophil count (22%) and milk-specific IgE 3+ was fortunately detected and GI allergy was suspected (only 30% of the patients have positive IgE to food allergens).
She started to take elemental diet and is now recovering.

A one-year old boy transferred from university hospital

he was born with normal birth weight.
The weight gain became slow since 4 months old.
Vomiting, bloody stool, and diarrhea were not seen. He had been fed with breast milk and gradually lost his appetite.
The cause of weight loss was not identified, in spite of various examinations in the university hospital.
In one years old and nine months, he was transferred to our hospital. Weight; -3SD, prominent emaciation, brain atrophy, only sitting in the baby car(stroller).

The gastrointestinal endoscope was done, and there was prominent eosinophilic infiltration from duodenum to large intestine, and the duodenal villi were torn off. Diagnosis of GI allergy was made.

By chronic tolerance test, rice, soy and cow’s milk was found to be the cause of GI allergy.
After the start of elimination of offending food, his weight began to increase. Five months later, he became able to stand at the top of jungle gym.
IgE antibodies do not act main role.
One can not rely on IgE test in diagnosing GI allergy.

Food allergens

Immune reaction

Inflammation in GI tract

IgE antibodies do not act main role

Ten percent of the patients show severe complications.

Table E2 Clinical features of most severe cases of non-IgE-mediated gastrointestinal food allergies *
* Those patients fulfilled three elements of Powell's criteria, but oral challenge tests were not performed.

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Sex</th>
<th>Cluster</th>
<th>Complication</th>
<th>Day of onset of complications (days)</th>
<th>Diet right before the onset of complications</th>
<th>Special note</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>1</td>
<td>ileus</td>
<td>8</td>
<td>Cow’s milk 7 days, Breast milk 6 days</td>
<td>relieved by surgical operation</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>1</td>
<td>ileus</td>
<td>5</td>
<td>Cow’s milk 3 days, Breast milk 6 days</td>
<td>relieved by surgical operation</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>1</td>
<td>ileus</td>
<td>8</td>
<td>Breast milk 9 days</td>
<td>massive bloody stool, blood infusion required</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>1</td>
<td>shock</td>
<td>2</td>
<td>Cow’s milk 2-3 times</td>
<td>vasoconstrictor reaction</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>1</td>
<td>shock</td>
<td>21</td>
<td>Breast milk 18 days</td>
<td>massive bloody stool, DIC</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>2</td>
<td>ileus</td>
<td>14</td>
<td>Breast milk 2 days</td>
<td>apnea, vomiting</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>2</td>
<td>shock</td>
<td>30</td>
<td>Breast milk 2 days</td>
<td>vomiting and diarrhea, ICU admission</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>2</td>
<td>shock</td>
<td>30</td>
<td>Cow’s milk 50 ml by chance</td>
<td>massive bloody stool</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>2</td>
<td>shock</td>
<td>247</td>
<td>Soy food 2-3 times</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>3</td>
<td>ileus</td>
<td>61</td>
<td>Breast milk 45 days</td>
<td>vomiting</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>3</td>
<td>shock</td>
<td>22</td>
<td>Cow’s milk 21 days, Breast milk 21 days</td>
<td>ICU admission</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>3</td>
<td>severe weight</td>
<td>12</td>
<td>Breast milk several months</td>
<td>developmental reannealation</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>3</td>
<td>severe weight</td>
<td>45</td>
<td>Cow’s milk 30 days, Breast milk 20 days</td>
<td>developmental reannealation</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>4</td>
<td>ileus</td>
<td>2</td>
<td>Cow’s milk 6 days, Breast milk 3 days</td>
<td>absence of sigmoid color</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>4</td>
<td>ileus</td>
<td>7</td>
<td>Cow’s milk 10 days</td>
<td></td>
</tr>
</tbody>
</table>

Those clinical entities are already established.

Non-IgE-mediated / Cell-mediated

Food Protein-Induced Enterocolitis Syndrome (FPIES)

Eosinophilic Esophagitis (EE)

Eosinophilic Gastroenteritis (EGE)

Eosinophilic Colitis (EC)

Mixed IgE and cell-mediated

EGID

Eosinophilic Gastrointestinal disorders

Nowak-Wegrzyn and Muraro
Current Opinion in Allergy and Clinical Immunology 2009, 9:371-377

Today, I want to propose very easy method to classify those entities.

We just wanted to classify those patients only from initial symptoms, clear-cut, simple clinical data.

This may lead to the prompt, proper diagnosis and treatment of the affected babies.

Also, we hope to find hidden biological group of those syndromes.

First, we have included all kinds of those syndromes into the term “GI allergy”

Cluster analysis was performed from those data.

Four clusters were identified. Each cluster had distinct biological features.

Non-IgE-mediated / Cell-mediated

Mixed IgE and cell-mediated

EGID

Eosinophilic Esophagitis (EE)

Eosinophilic gastrenteritis (EGE)

Eosinophilic Colitis (EC)

1. Bloody stool
2. Vomiting

Cluster 1

Cluster 2

Cluster 3

Cluster 4

Cluster analysis was performed from those data. Only from patients’ data, diagnosis were confirmed by food challenge test was used.

Patients submitted to headquarter since 2007 to March, 2010, who were suspected GI allergy
n=176

Patients fulfilled 1-4 steps of diagnostic procedures
n=136

Others
n=40

Patients diagnosis confirmed by food challenge test
n=46

Food challenge tests were not done.
n=90

Unsupervised cluster analysis and discriminant analysis were performed by using SPSS version 18 software (SPSS, Inc, Chicago, IL). The Wald minimum-variance hierarchic clustering method was performed by using an agglomerative (bottom-up) approach and Ward’s linkage. The squared Euclidean distance was used as a proximity measure. Values were transformed by a maximum magnitude of 1.

Four distinct subtypes of non-IgE-mediated gastrointestinal food allergies in neonates and infants, distinguished by their initial symptoms

Figure E2. Using the agglomerative cluster approach outlined in METHODS, a dendrogram were generated. From 46 diagnosis confirmed patients, four clusters were identified.
Four distinct subtypes of non-IgE-mediated gastrointestinal food allergies in neonates and infants, distinguished by their initial symptoms

Stepwise discriminate analysis identified the 2 strongest discriminatory variables for cluster assignment: vomiting and bloody stool.

Each 4 clusters showed special biological features.

Birth weight (g) 2,678(2,512-3,170) 2,678(2,512-3,170) 2,678(2,512-3,170) 2,678(2,512-3,170) 0.829

Sex ratio male:female 8:6 7:9 3:2 6:5 0.949

Initial presentation

Day of onset

- vomiting 100% 100% 0% 0% 0.000

- bloody stool 100% 0% 0% 100% 0.000

Four distinct subtypes of non-IgE-mediated gastrointestinal food allergies in neonates and infants, distinguished by their initial symptoms

oral food challenge tests showed high reproducibility of symptoms

<table>
<thead>
<tr>
<th>Onset (hours)</th>
<th>Vomiting</th>
<th>Bloody stool</th>
<th>Bloody stool</th>
</tr>
</thead>
<tbody>
<tr>
<td>6(1.8-12)</td>
<td>85.7%</td>
<td>28.6%</td>
<td>+</td>
</tr>
<tr>
<td>10(2-24)</td>
<td>81.3%</td>
<td>6.3%</td>
<td>+</td>
</tr>
<tr>
<td>24(24-48)</td>
<td>8.1%</td>
<td>60%</td>
<td>+</td>
</tr>
<tr>
<td>48(24-60)</td>
<td>0%</td>
<td>72.7%</td>
<td>+</td>
</tr>
</tbody>
</table>

vomiting: 85.7% 81.3% 8.1% 9.1%

Bloody stool: 28.6% 6.3% 0% 72.7%

The responsible immune cells might remain in the same part of the GI tract even after several months’ remission.

Four clusters and corresponding clinical entities.

Four clusters and corresponding clinical entities.

Estimation of affected portion in the GI tract

This classification is useful because;
• easily determined, only from initial clinical data
• increase chance to obtain a correct diagnosis
• One can imagine the involved portion of GI tract.
• Outcome of food challenge test can be expected.

This title was awarded as excellent talk at annual meeting of Japanese society for Pediatric Gastroenterology, Hepatology and Nutrition 2011.
Onset; usually before 3 months of age

Symptoms; Protracted vomiting and diarrhea (± bloody), shock

Offending food; Cow’s milk, wheat, rice, soy, etc.

5 steps of diagnosis and treatment procedure

1. Suspect FPIES from initial symptoms
2. differential diagnosis from the other disorders
3. a switch to therapeutic milk led to resolution of symptoms (therapeutic diagnosis)
4. verify body weight gain every months
5. confirmative diagnosis by oral food challenge test that is performed after complete resolution of the initial symptoms

Laboratory data; no specific IgE, no eosinophilia

Pathology, Molecular mechanism; TNF-alpha is up-regulated in the GI mucosa.

References:
Food protein-induced enterocolitis syndrome (FPIES)

Patho-physiology

TNF-alpha is an important key cytokine of FPIES.


Food protein-induced enterocolitis syndrome (FPIES)

TGF-beta blanket is not working in FPIES.


Food protein-induced enterocolitis syndrome (FPIES)

Challenge test of FPIES

Symptoms (vomiting, diarrhea and fever sometimes) will be provoked within 1.5 hours - 24 hours.

Peripheral blood neutrophils will be increased more than 3500/microL from base line.

CRP might turn into positive on the next day.

Be careful not to have serious damage. Please start from small amount of challenging food in severe case.

Onset; the first several months

Symptoms; weight loss, sometime diarrhea

Offending food; cow's milk, etc.

Small intestine is most affected organ in GI tract.

Food protein-induced enteropathy (Enteropathy)

5 steps of diagnosis and treatment procedure

1. Suspect FPIES from initial symptoms
2. differential diagnosis from the other disorders
3. a switch to therapeutic milk led to resolution of symptoms (therapeutic diagnosis)
4. verify body weight gain every months
5. confirmative diagnosis by oral food challenge test that is performed after complete resolution of the initial symptoms

Those procedures are sometime very difficult.
We might rely on microscopic findings of GI mucosa

Laboratory data; no specific IgE, no eosinophilia, hypoproteinemia, mal-absorption syndrome

Pathology, Molecular mechanism; a patchy villous atrophy, a prominent mononuclear round cell infiltrate, and few eosinophils. Pathological examination is required to establish diagnosis.

References;
**Food protein-induced enteropathy (Enteropathy)**

Gastrointestinal endoscope, 1 years old boy, Cluster 3
Weight loss since 5 months old, emaciation prominent

Esophagus, mild inflammation; Grade A in LA classification

---

**Food protein-induced enteropathy (Enteropathy)**

Gastrointestinal endoscope, 1 years old boy, Cluster 3
Weight loss since 5 months old, emaciation prominent

Esophagus lower, some erosive area; Grade A in LA classification

---

**Food protein-induced enteropathy (Enteropathy)**

Gastrointestinal endoscope, 1 years old boy, Cluster 3
Weight loss since 5 months old, emaciation prominent

Stomach, pylorus, normal-looking

---

**Food protein-induced enteropathy (Enteropathy)**

Gastrointestinal endoscope, 1 years old boy, Cluster 3
Weight loss since 5 months old, emaciation prominent

Duodenum, normal-looking, white spots +
Ileum to cecum, normal-looking

Transverse colon, lymph follicles

Colon, normal-looking

Esophageal epithelium, eosinophilic infiltration
Duodenal epithelium, eosinophilic infiltration

So, he was diagnosed as having “Allergic Eosinophilic Gastroenteritis”.

How can we distinguish Food-protein induced Enteropathy and Allergic Eosinophilic Gastroenteritis?

I think we need more science to determine this relationship. Microarray of GI mucosa, clinical research, etc.

Body weight was markedly increased after the start of treatment.

More severe cases of Enteropathy

Onset

Symptoms; a more extensive enteropathy leading to malabsorption

Offending food; gliadin found in wheat, rye, and barley

Laboratory data

Pathology and Molecular mechanism; associated with HLA-DQ2, which is present in more than 90% of patients with celiac disease. Pathological examination is required to establish diagnosis.

References:

Onset; first few months
Symptoms; bloody stool, no weight loss
If the patient showed weight loss, a diagnosis of AEG might be more appropriate.
Offending food; breast milk, cow’s milk, soy

Laboratory data; no specific IgE, eosinophilia occasional
Pathology, Molecular mechanism; Lesions are confined to the distal large bowel and consist of mucosal edema, with infiltration of eosinophils.

Several patients in Japan showed different clinical pictures from those entities.

There are many differences between western countries and Japan.
- Cluster 1 patients (vomiting and bloody stool at the same time) is frequently seen in Japan but not in western countries.
- Eosinophilia in the circulating blood is frequent and prominent in Japan.
- IgE antibodies against offending food is positive in 30% of the FPIES patients in Japan.
- AEG is increasing in Japan but EoE is not.

We need international, precise comparison of prevalence and clinical picture of those GI allergies.