

New Horizons Session: Advances in Food Allergy: Session 2
 Thursday, 8 December 2011:10:55 AM-11:20 AM
 World Allergy Congress, Cancun Mexico.

Non-IgE-Mediated Gastrointestinal Food Reactions

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1

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.


2

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.

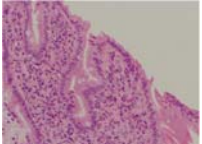
The cause of weight loss was not identified, in spite of various examinations in the university hospital.

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).




3

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.

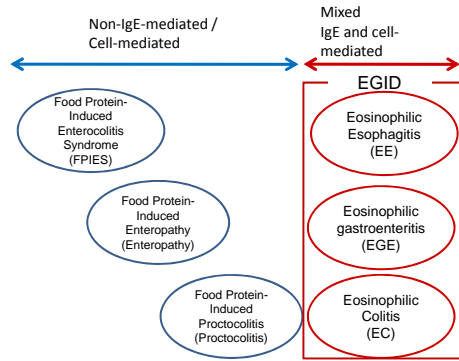


By chronic tolerance test, rice, soy and cow's milk was found to be the cause of GI allergy.
 After the start of elimination of offending food, his weight began to increase. Five months later, he became able to stand at the top of jungle gym.



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

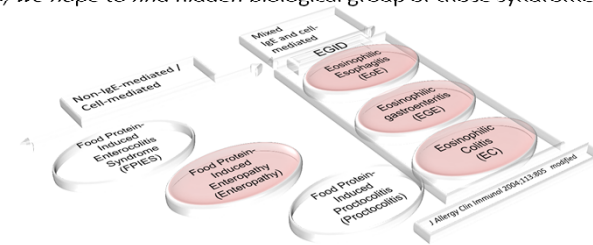


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We just wanted to classify those patients only from initial symptoms, clear-cut, simple clinical data.

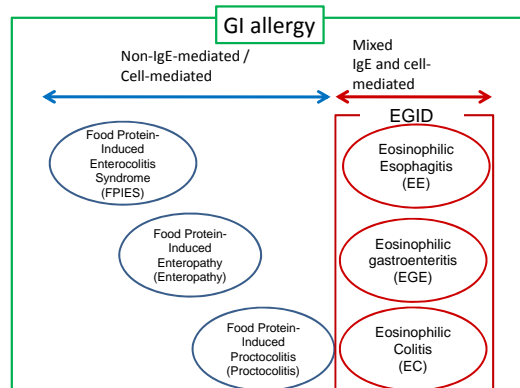
This may lead to the prompt, proper diagnosis and treatment of the affected babies.

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



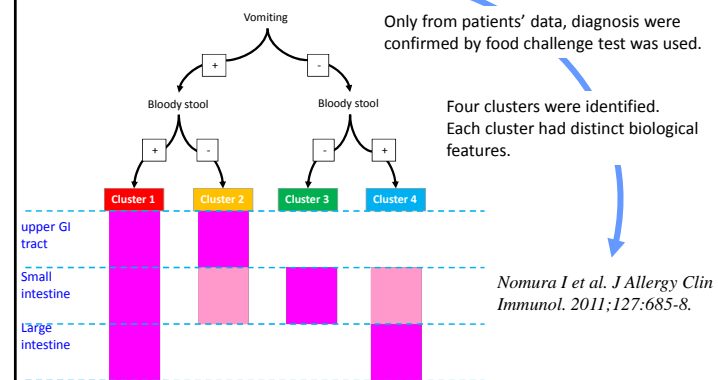
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First, we have included all kinds of those syndromes into the term "GI allergy"

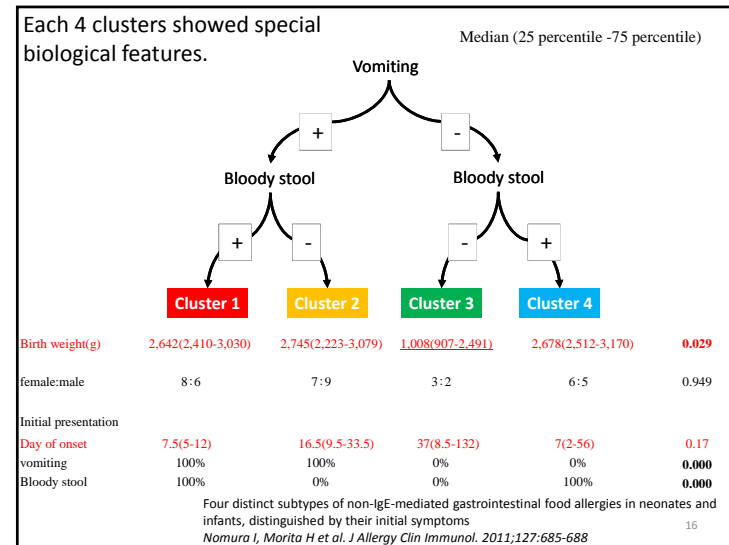
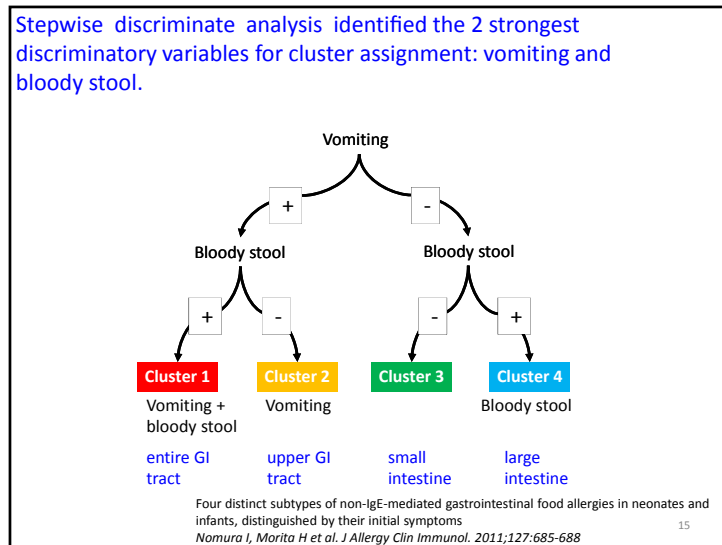
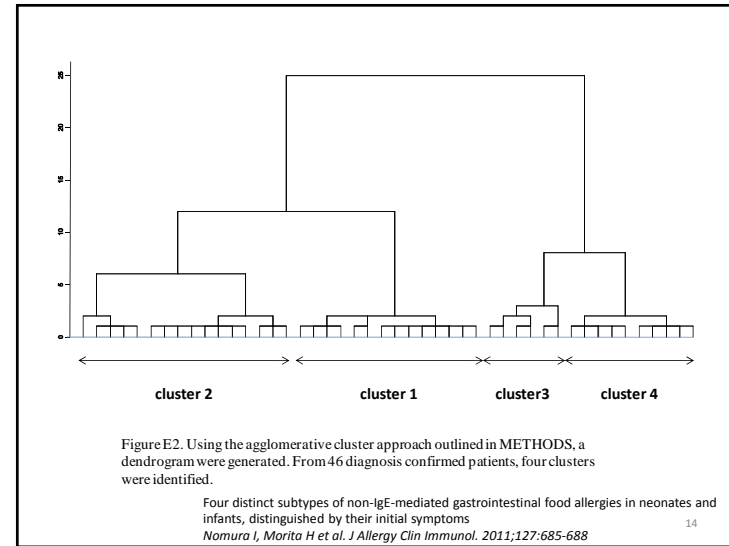
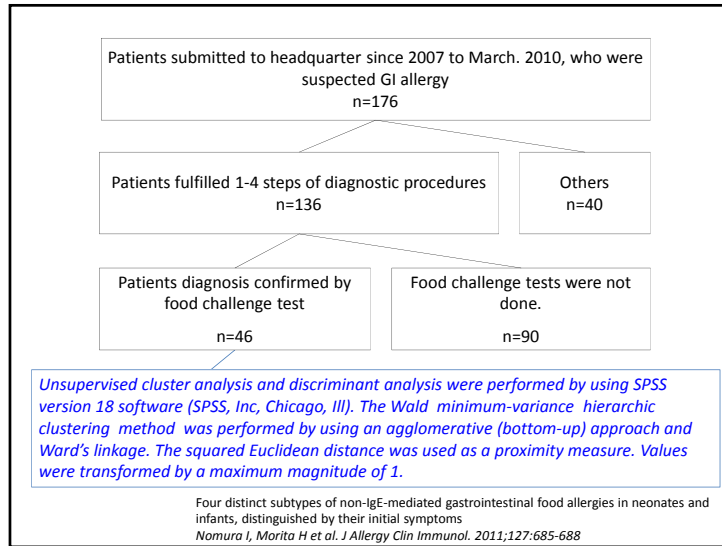


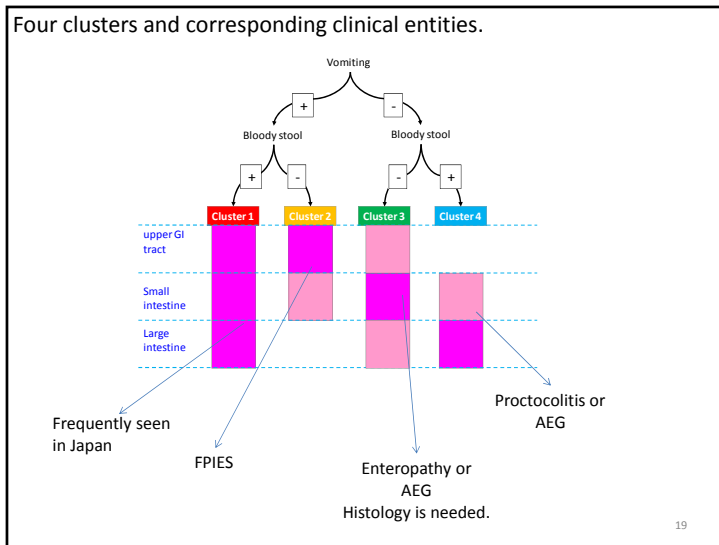
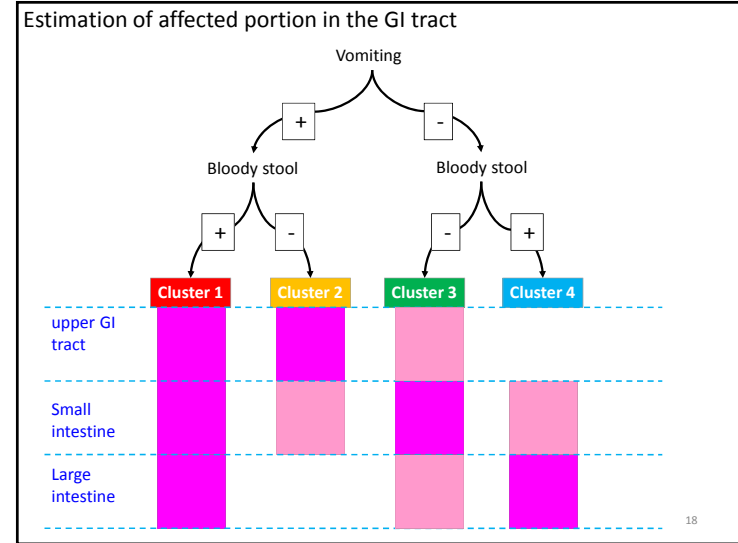
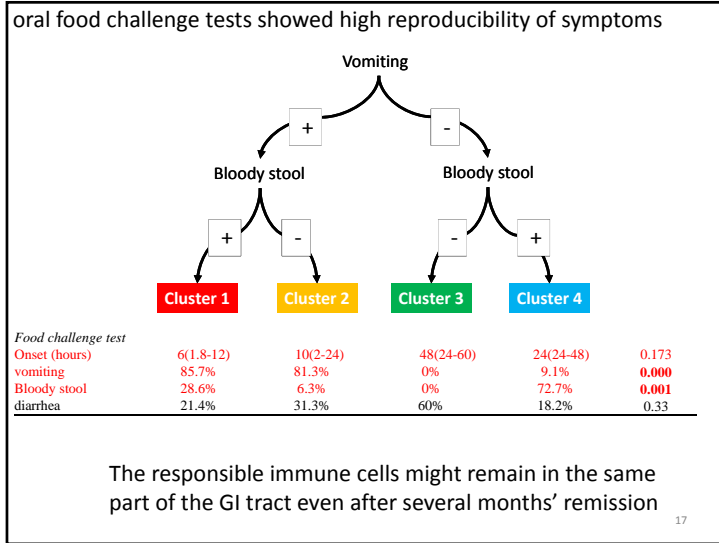
11

Cluster analysis was performed from those data.



12





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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.

Nomura I, Morita H et al. *J Allergy Clin Immunol.* 2011;127:685-688

This title was awarded as excellent talk at annual meeting of Japanese society for Pediatric Gastroenterology, Hepatology and Nutrition 2011.

Food protein- induced enterocolitis syndrome (FPIES)

Onset; usually before 3 months of age

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

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

21

5 steps of diagnosis and treatment procedure
Generally, this is useful for almost all patients with GI allergy.

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 tests that is performed after complete resolution of the initial symptoms

22

Food protein- induced enterocolitis syndrome (FPIES)

5 steps of diagnosis and treatment procedure

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5. confirmative diagnosis by oral food challenge test that is performed after complete resolution of the initial symptoms

Patients show prompt responses to those attempts.

23

Food protein- induced enterocolitis syndrome (FPIES)

Laboratory data; **no specific IgE, no eosinophilia**

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

References;

1. Powell GK. Food protein-induced enterocolitis of infancy: differential diagnosis and management. Compr Ther 12:28-37,1986
2. Powell GK. Milk- and soy-induced enterocolitis of infancy. Clinical features and standardization of challenge. J Pediatr 93:553-560,1978
3. [Sampson HA](#). Update on food allergy. J Allergy Clin Immunol. 2004 May;113(5):805-19
4. Sicherer SH, Sampson HA. Food allergy. J Allergy Clin Immunol 2010;125:S116-125.
5. Nowak-Węgrzyn A, Murano A. Food protein-induced enterocolitis syndrome. Curr Opin Allergy Immunol 2009;371-377.

24

Food protein- induced enterocolitis syndrome (FPIES)

Patho-physiology

TNF-alpha is an important key cytokine of FPIES.

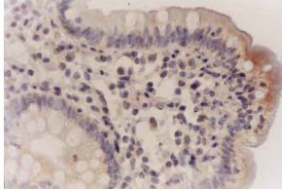


FIG 6. TNF- α expression in both epithelium and mononuclear cells in the lamina propria.

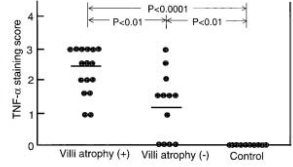
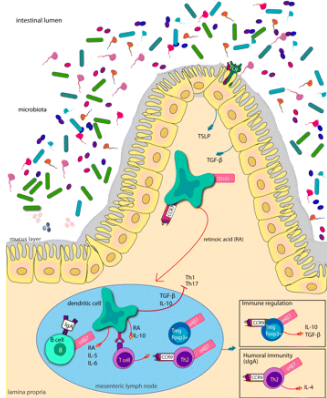


FIG 7. Mucosa TNF- α expression is significantly higher in patients with villous atrophy than in patients without villous atrophy and control subjects.

Chung HL, Hwang JB et al. J Allergy Clin Immunol 2002;109:150-4.

25

TGF-beta blankets Gastrointestinal mucosa and seems to protect it from outrage of immune system.



PNAS March 15, 2011 vol. 108 no. Supplement 1 4607-4614

26

Food protein- induced enterocolitis syndrome (FPIES)

TGF-beta blanket is not working in FPIES.

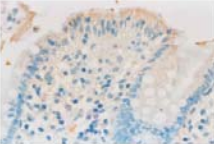


FIG 1. TGF- β 1 expression along the villi and upper part of the crypt.

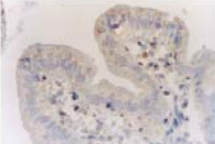


FIG 2. TGF- β 1 expression on both apical and basolateral membranes of the villus and epithelium.

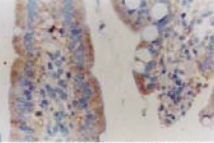


FIG 3. TGF- β 1 receptor expression on both apical and basolateral membranes of the villus and epithelium.

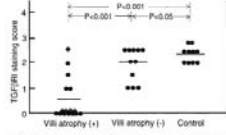


FIG 4. Epithelial expression of TGF- β 1 is significantly lower in patients with villous atrophy than in patients without villous atrophy and control subjects.

Chung HL, Hwang JB et al. J Allergy Clin Immunol 2002;109:150-4.

27

Food protein- induced enterocolitis syndrome (FPIES)

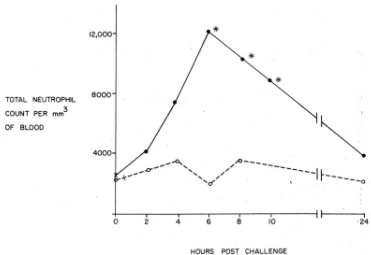
Challenge test of FPIES

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



Powell GK. J Pediatr 93:553-560,1978

28

Food protein- induced enteropathy (Enteropathy)

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.

29

Food protein- induced enteropathy (Enteropathy)

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;

Savilahti E. Food-induced malabsorption syndromes. J Pediatr Gastro-enterol Nutr 2000;30(suppl):S61-6.

30

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

31

Food protein- induced enteropathy (Enteropathy)

Gastrointestinal endoscope, 1 years old boy, Cluster 3

Weight loss since 5 months old, emaciation prominent

Esophagus, lymphatic follicules+

32

Food protein- induced enteropathy (Enteropathy)

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

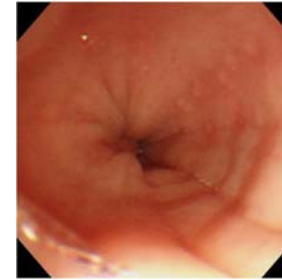


Esophagus, mild inflammation; Grade A
in LA classification

33

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

34

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

35

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 +

36

Food protein- induced enteropathy (Enteropathy)

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

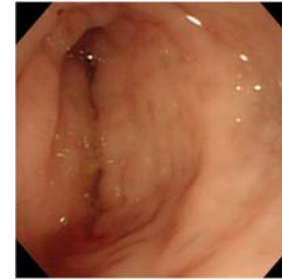


Ileum to cecum, normal-looking

37

Food protein- induced enteropathy (Enteropathy)

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

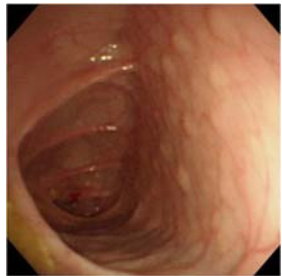


Colon, normal-looking

38

Food protein- induced enteropathy (Enteropathy)

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

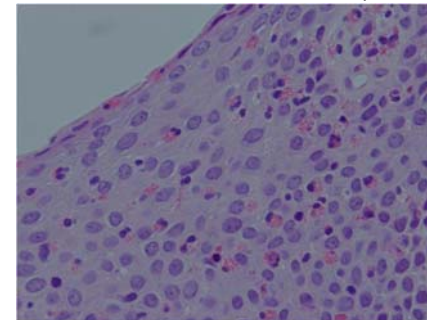


Transverse colon, lymph follicles+

39

Food protein- induced enteropathy (Enteropathy)

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

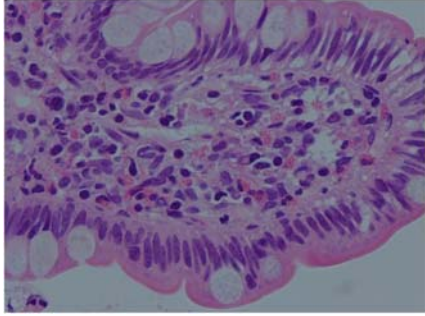


Esophageal epithelium, eosinophilic infiltration

40

Food protein- induced enteropathy (Enteropathy)

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



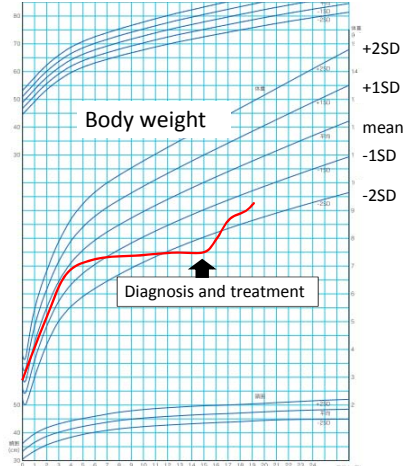
Duodenal epithelium, eosinophilic infiltration

So, he was diagnosed as having "Allergic Eosinophilic Gastroenteritis".

41

Food protein- induced enteropathy (Enteropathy)

Body weight was markedly increased after the start of treatment.



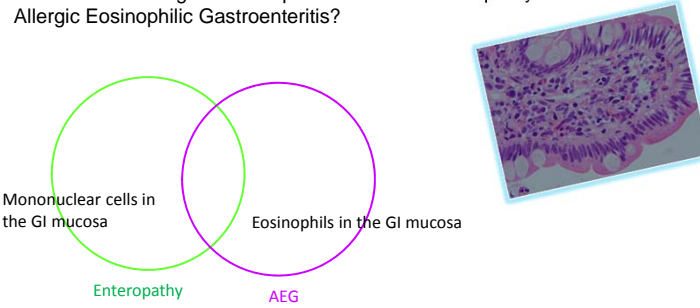
Body weight

Diagnosis and treatment

42

Food protein- induced enteropathy (Enteropathy)

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



Mononuclear cells in the GI mucosa

Eosinophils in the GI mucosa

Enteropathy

AEG

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

Reference;
[J Pediatr Gastroenterol Nutr](#), 2006 May;42(5):516-21.
 Allergic eosinophilic gastroenteritis with protein-losing enteropathy: intestinal pathology, clinical course, and long-term follow-up.
[Chehade M](#) et al.

43

Celiac disease

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;
 Sollid LM, Thorsby E. HLA susceptibility genes in celiac disease: genetic mapping and role in pathogenesis. *Gastroenterology* 1993;105: 910-22.

44

Food protein-induced Proctocolitis (Proctocolitis)

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

45

Food protein-induced Proctocolitis (Proctocolitis)

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.

Prognosis;

References;

1. Lake AM. Food-induced eosinophilic proctocolitis. J Pediatr Gastro-enterol Nutr 2000;30(suppl):S58-60.
2. Arvola T, Ruuska T, Keränen J, Hyöty H, Salminen S, Isolauri E. Rectal Bleeding in Infancy: Clinical, Allergological, and Microbiological Examination. Pediatrics 2006;117:e760-e768
3. Xanthakos SA, Schwimmer JB, Melin-Aldana H, Rothenberg ME, Witte DP, Cohen MB. Prevalence and Outcome of Allergic Colitis in Healthy Infants with Rectal Bleeding: A Prospective Cohort Study. J Pediatr Gastroenterol Nutr. 2005 Jul;41(1):16-22.

46

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

J Allergy Clin Immunol 2004;113:805 modified

47

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.

48