- 虫垂炎
- 腸重積

頻度は低いが、見落してはならない疾患

- Whipple disease
- メッケル憩室
- 食道狭窄
- アカラジア
- Hyper-eosinophilic syndrome

VI. 治療

基本的な考え方

治療を選択するにあたり、最も合理的な方法が何かを追求したいと思います。現時点では

1. 炎症の chronicity、つまり Intermittent か Persisitent か
2. 病理組織で炎症部位を特定する
3. 重症度によって層別化して治療を選択
4. 副作用を回避するため、なるべく局所治療を採用する

以上を考慮して選択することを推奨します。

1. 治療の方法を決めるにあたり

まず

- Intermittent type
- Persistent type

に分けます。

Intermittent type は、年に数回以内の症状出現であり、誘因に常に暴露されているわけではなく、ときどき暴露されて、症状が誘発されるのではないかと推測できます。このため、食物日誌などから誘因を特定することが可能な場合もあります。また、誘発された症状に応じて、短期間の抗炎症治療を行うことができますし、副作用の出現率は低いと考えられます。
また、一度きりの症状出現で、寛解してしまう　一過性タイプもこれに含めます。

Persistent type は、誘因は常に暴露されている食物などに含まれている可能性があります。症状は長期にわたり、QOL の障害も起こりやすくなっています。

薬物治療を行うべき場合と、行わない方が良い場合もあり、慎重に治療法を選択したいと考えます。

2．消化管障害部位の特定法

症状からの推定を行うとよいでしょう

① 嚥下障害　（食道）
② 嘔吐　　（上部消化管）
③ 胸やけ　　（上部消化管）
④ 食欲不振　（上部消化管）
⑤ 腹痛　部位　上腹部　臍周囲　腹部全体　下腹部
⑥ 体重減少　（上部消化管、小腸）
⑦ 低蛋白血症（小腸）
⑧ 下痢　　（小腸、大腸）
⑨ 下血　　（大腸）

消化管内視鏡組織検査による特定

- 食道
- 胃
- 十二指腸
- 空腸
- 回腸
- 結腸
- S 状結腸
- 直腸

3．次に現在の Disease Activity Score から以下の 4 段階に分けます

3　重症　　スコア 40 以上
2　中等症　15 以上 39 以下
1　軽症　　1 以上 14 以下
0　無症状（自覚症状については寛解）

これに薬物の使用をプラスします

- 薬物、副作用が懸念される使用；ステロイドの連日使用、免疫抑制剤副作用が懸念される量：重症度を 2 段階アップ

- 薬物安全域の使用；ステロイド少量間歇または免疫抑制剤副作用のないレベル：重症度を１段階アップ

治療の選択

Persistent type の治療を加味した重症度

3 以上　重症　　ステロイドなど抗炎症薬で寛解導入（寛解維持をどうするか）

※将来はエレメンタルダイエット(ED)または 6FED を考慮；17 ページ

2　中等症　　薬物安全域の使用で QOL を確保、※患者の希望があれば ED または 6FED

1　軽症　　経過観察もしくは薬物安全域の使用

0　無症状　　経過観察

4．障害部位に特異的な治療

食道にターゲットを絞った治療

上部消化管症状がある場合

先ず、PPI による治療を行う（2 歳以下は PPI だけでなく H2-blocker を使用する場合もある)。

薬剤としてはまず最初にプロトンポンプ阻害薬を標準用量以上の用量で投薬する（保険適応なし）。プロトンポンプ阻害薬は好酸球性食道炎と胃食道逆流症が合併している場合には胃食道逆流に伴う症状や病変を軽快・治癒させる。また　好酸球性食道炎の一部がプロトンポンプ阻害薬に反応して軽快する可能性も指摘されている。

プロトンポンプ阻害薬はステロイド治療に比べて　副作用が少ないため　ステロイド治療を始める前に　必ずその有効性を検討することが必要であると考えられる。　プロトンポンプ阻害薬の投与開始後の有効性判定期間は 4-8 週間である。プロトンポンプ阻害薬が有効でない場合には　フルチカゾン、ブデソニド　などの喘息吸入治療用の局所作用ステロイドを口腔内に投与し唾液とともに 30 分かけて嚥下させ　食道粘膜に作用させる。　局所作用ステロイドが有効でない場合には全身ステロイドの投薬が必要になるが　その前に必ず専門医にコンサルトする必要がある。

原因食物を特定できる場合には原因食物の除去食を行う。6 種食品除去食は実施が困難であるが　可能かどうかの検討を行う。

低身長
食欲不振
胃食道逆流
胃炎
低蛋白血症
下痢
下血　　筑紫病院松井先生から；渡辺守先生が担当された、microscopic colitis ですが、ほとんどが薬剤起因性で、自然に治るものが、95%です

5．抗炎症治療について（早急に充実させたい）

- 全身性ステロイド治療（副作用が懸念される用法、用量）
  - 有利な点
  - 不利な点
  - 副作用
  - 寛解導入-寛解維持（副作用がほとんど出ない）を目指す方法について

- ステロイド局所治療
  - フルチカゾン、ブデソニド嚥下
  - ブデソニド腸溶ステロイド
  - ステロイド注腸

- タクロリムス
  - 有利な点
  - 不利な点
  - 副作用

- シクロスポリン
  - 有利な点
  - 不利な点
  - 副作用

抗アレルギー薬、抗ロイコトリエン薬

6．その他の治療

消化管機能を補助する薬物

コロネル

トランコロン

7．食餌療法について

EGE と EoE は同一の病態を持つ可能性もあり、EoE の欧米での先行研究は参考になります。食餌療法について成人と小児で重要な報告がありました。非常に高い寛解率を示しており、なによりも寛解後の長期耐性テストによって確定診断ができ、完治が目指せる点が魅力となっています。

成人の報告

Elimination Diet Effectively Treats Eosinophilic Esophagitis in Adults; Food Reintroduction Identifies Causative Factors. Gonsalves, Yang, Doerfler, Ritz, Ditto, Hirano. Gastroenterology 2012;142:1451-1459

成人で 6 種除去（牛乳、卵、魚介類、大豆、小麦、ナッツ）が 94%に効果を示し、除去した食物の再摂取によって、悪化した食物が原因食物と特定され、60%が小麦、50%が牛乳によって起きていることが明らかとなった。そして、皮膚プリックテスト（IgE が関与）で予測できた患者は 13%に過ぎなかった（ここからも特異的 IgE 抗体検査が、本質から外れていることがわかる)。

小児の報告

Comparative dietary therapy effectiveness in remission of pediatric eosinophilic esophagitis. Henderson CJ, Abonia JP, King EC, Putnam PE, Collins MH, Franciosi JP, Rothenberg ME. J Allergy Clin Immunol. 2012 Jun;129(6):1570-8.

によると、薬物を使用せず、食餌療法による症状寛解率は

- 96% remission; elemental diet (ED)
- 81% remission; 6-food elimination diet (6FED)
- 65% remission; directed diet

つまり、成人、小児を問わず、成分栄養や 6 種除去治療は、非常に高い寛解率を誇っています。

また EoE のみならず、EGE についても、有望な結果が得られつつあります。成育

医療センターで経験された10名の中等症-重症EGE（診断時平均年齢1.6歳）は消化管の食道から直腸にいたる広い範囲に明らかな好酸球の増加が認められ、低体重、低蛋白血症などがありました。原因食物の探索として除去食を行い、全例、症状寛解、体重、低蛋白血症のcatch-upを認め、寛解後のchronic tolerance testなどから牛乳10名全例、母乳3名、米2名、大豆3名、卵2名、アミノ酸乳（大豆油使用）1名、牛肉1名の原因食物が同定されました（日本アレルギー学会春季臨床大会、野村伊知郎ら、論文化未）。
これが本邦の年長児や成人のEGIDに適応されるかどうかは、いまだ確定はしていませんが、重症者、ステロイド依存など患者さんの事情によっては、導入すべきと考えます。食行動や嗜好が確立した年長児-成人では、除去の困難性は幼児とは比較にならないと思います。患者自身が十分納得した上で行う必要があります。

研究班ではまず10名の、これまでの治療で反応しない患者さん（年長児や成人）で、6種除去を行い、治療効果を判定したいと思います（pilot study）。この結果を見て、今後指針に掲載を続けるかどうか判断いたします。

しかし、その実行には障壁があります

- 患者が治療に向かう意志があるかどうか
- 患者が通常と異なる食事内容に耐えられるかどうか
- 除去法を正確にマスターすることができるか

栄養士の深い参画が必要
患者一人ひとりの食品への嗜好、体質などを考慮しながら詳細に食事療法のレシピを作成することが成功の鍵か

6種除去のやり方については
ノウハウを記した冊子の作成が必要

注意）特異的IgE抗体の検査結果をもとに、食物除去を行うと、成功しないことがある

EGIDが食物除去で改善する場合が多いということであれば、今後これに挑戦する医師も増えると思われる。その時に、ひとまず血液の食物特異的IgE抗体を検査し、皮膚プリックテストを行うであろう。しかし、これらが陽性の食物を除去しても、改善せず、落胆することが多いことに注意すべきである。もちろん検査することは必要であるが、特異的IgE抗体陽性の食物が、直接

EGIDの原因ではないことを注意したい。もし検査を行うとすれば、本質をあらわすのは、リンパ球刺激試験であろう。これは現時点では新生児や乳児の消化管アレルギーで診断価値が確かめられている。今後成人にまで適応できるよう、このリンパ球刺激試験を整備すべきと思われる。同感です。40例あまりのEoE, EGE を対象に特異的IgE抗体を調べてみましたが　特徴はなく全体に高めですが健常者とのはっきりした差が見られませんでした。(木下先生)

VII.　保険診療について

VIII.　付録；様々な免疫分子、細胞の豆知識

● EoEのマイクロアレイ研究結果

EoE, EGE患者では、多くの患者で血清中に食物や花粉などに対する特異的IgE抗体が検出される。長い間、これが病態に強く関与しているのではないかと信じられてきた。しかし、2006年に発表されたマイクロアレイのデータは、我々に大きな示唆を示した。マイクロアレイは同時に数万のmRNAを測定できるが、EoEや胃食道逆流の患者食道組織を採取して、このmRNAの発現パターンを見たところ、胃食道逆流の発現パターンと全く異なるEoE特異的なパターンが見られた。そして特異的IgE抗体が見られるEoE患者と、見られないEoE患者の間にはこのパターンの差が見られなかった。

Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. J Clin Invest. 2006 Feb;116(2):536-47.

つまり、特異的IgE抗体の有無が、炎症の本質とかかわりがない可能性が示唆されたわけである。もちろん、IgE抗体が炎症の形成に全く関与していないと証明されたわけではないが、少なくとも主体ではないと言える。

● IgE抗体

IgE抗体は本来、寄生虫や原虫などのような巨大な感染生物を認識し攻撃するきっかけを作り、人体をこれらから守るために存在している。現在、最も問題となっているのは、マスト細胞や好塩基細胞とともに即時型アレルギーを引き起こすことである。この反応は、これら細胞上の2分子のIgE抗体が1つのアレルゲンを結合して速やかに反応が開始され、早ければ数分後には、蕁麻疹、呼吸困難、

消化器症状、血圧低下などの症状が出現する。IgE 抗体は人体内で普遍的に存在しており、そのために血液で簡単に測定できるわけだが、かつ、マスト細胞も、多くの組織に存在するため、即時型食物アレルギーでは、皮膚、呼吸器系、消化器系、循環器系などさまざまな器官で反応を起こす。EGID は、消化管に限局した炎症であるため、この点からも、IgE 抗体が主体とは考えにくい。EGID は T 細胞などが主体となった、非即時型アレルギー反応に分類される。また、即時型では反応が速やかに起こるため、原因食物が同定しやすいが、EGID では、原因食物があったとしても、患者自身は気づかないことがほとんどである

Ⅲ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

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Ⅳ．研究成果の刊行物・別刷

Curr Allergy Asthma Rep
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FOOD ALLERGY (D ATKINS, SECTION EDITOR)

Non–IgE-Mediated Gastrointestinal Food Allergies: Distinct Differences in Clinical Phenotype Between Western Countries and Japan

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Abstract Non-IgE-mediated gastrointestinal food allergies, including food-protein-induced enterocolitis, enteropathy, proctocolitis and allergic eosinophilic gastroenteritis, seem to be increasing in several regions in the world. However, unlike the case of IgE-mediated food allergy, development of diagnostic laboratory tests and our understanding of the immunological mechanisms involved in non-IgE-mediated gastrointestinal food allergies lag. Although the clinical entities in Western countries have been well established, the clinical phenotypes might differ somewhat among the human races and geographical regions. In Japan, non-IgE-mediated gastrointestinal food allergies have increased sharply since the late 1990s, and clinicians have sometimes experienced confusion because of differences in the clinical phenotypes from those seen in Western countries. Aiming to solve this problem, we performed clinical research and determined a useful method for dividing patients into four clusters with distinctive clinical symptoms. We are confident this method will help in diagnosing and treating these patients. We also tried to clarify the differences between these patients in Japan and Western countries.

Keywords Non–IgE-mediated gastrointestinal food allergy · Gastrointestinal allergy · GI allergy) · Food protein–induced enterocolitis syndrome (FPIES) · Food protein–induced enteropathy syndrome (enteropathy) · Food protein–induced proctocolitis syndrome (proctocolitis) · Eosinophilic esophagitis (EoE) · Allergic eosinophilic gastroenteritis (AEG) · Food challenge test · Food allergy · Eosinophil · Lymphocyte proliferation test · Cluster analysis · Phenotype · Japan

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Two Japanese Patients with Non-IgE-Mediated Gastrointestinal Food Allergy

Patient 1: A Baby Girl with Vomiting and Bloody Stool

A baby girl was born at full term and normal birth weight. She was happy and drinking dairy-based formula until the 8th day after birth. Then she started vomiting once a day. On the next day she became less energetic. On the 11th day, she had 20 bloody stools. On the 12th day, she developed apnea and went into shock. She was transferred to the emergency department of a children's hospital. On arrival, no arterial pulse could be detected, and cyanosis was apparent. Life support was started, and she gradually recovered. Before 2000, we would never have considered gastrointestinal allergy (GI allergy) as the diagnosis for such a seriously ill patient. But now the order of differential diagnosis has changed. Open abdominal surgery was performed but found no abnormality. An increased peripheral eosinophil count (22 %) and cow's milk-specific IgE (3+) were detected, and

GI allergy (food-protein-induced enterocolitis syndrome; FPIES) was suspected (30 % of patients with FPIES in Japan test positive for IgE to the offending food). She was placed on an elemental diet and recovered.

Patient 2: A Growth-Retarded One-Year-Old Boy with No Apparent GI Symptoms

A one-year-old boy was transferred from a university hospital to National Research Center for Child Health and Development. He was born with a normal birth weight, but weight gain had been slower since 4 months of age. Vomiting, bloody stools and diarrhea were absent. He had been breast fed, but gradually lost his appetite. The cause of weight loss was not identified, in spite of various examinations at the university hospital. At one year and nine months of age, he was transferred to our hospital. His weight was -3SD, with prominent emaciation and brain atrophy, and he only sat in his baby stroller. Gastrointestinal endoscopy revealed prominent eosinophilic infiltration extending from the duodenum to the large intestine, and duodenal villi were torn off. A diagnosis of allergic eosinophilic gastroenteritis (AEG) was made. Chronic tolerance tests revealed rice, soy and cow's milk to be the causes of AEG. After elimination of the offending foods, his weight began to increase quickly. Five months later, he was able to stand at the top of a jungle gym!

Introduction

Non-IgE-mediated gastrointestinal food allergies (GI allergy) appear to have increased around the world in recent decades. Eosinophilic esophagitis (EoE)—which is recognized as a mixed IgE- and cell-mediated disorder—has been the most extensively studied food allergy, and it has increased dramatically [1]. In neonates and infants, there are well-established clinical entities such as food-protein-induced enterocolitis syndrome (FPIES) [2, 3, 4•]. However, these entities are not sufficiently recognized by general pediatricians, and many patients experience rapid worsening of their clinical course. As a result, serious complications can develop, including intestinal obstruction, intestinal perforation, shock and developmental retardation. There also seem to be some differences in the clinical features and laboratory findings among the human races and geographical regions. If clinicians in non-Western countries tried to make a diagnosis based only on the reports and textbooks from Western countries, they might have serious difficulty. The outlines of two severe Japanese cases are presented above to highlight the importance of GI allergy. Next, the differences between IgE-mediated reactions and GI allergy will be discussed, followed by a description of the known clinical entities. Finally, the clinical features of Japanese patients will be reviewed and a simple method for classifying and comparing them with the known entities will be described.

Differences Between IgE-Mediated Food Allergy and GI Allergy

When we think about the time courses of food allergy, there are two types of reactions; namely, immediate reactions (IgE-mediated) and non-immediate type reactions (non-IgE-mediated) [5, 6]. Mast cells and IgE antibodies play key roles in immediate reactions. Allergenic proteins are bound by two molecules of specific IgE antibodies on the surface of mast cells, and high-affinity IgE receptors activate signal transduction pathways leading to the release of histamine, leukotrienes and prostaglandins. Urticaria, wheezing and anaphylactic shock may be induced. On the other hand, since GI allergies are non-immediate type reactions, the central player may be T cells. Antigen-presenting cells, several subsets of T cells, epithelial cells, mast cells and eosinophils may be involved in the reactions, but the precise mechanisms and true effector cells remain elusive.

Since food-specific IgE antibodies do not play a key role in the immunological reaction of GI allergy, we have no effective laboratory tests for identifying offending foods in daily practice. A lymphocyte proliferative response to an offending food protein might have great potential as an in vitro diagnostic test. The mechanism of lymphocyte proliferation is that allergens are endocytosed by APCs and then digested in lysosomes. Next, allergen fragments of around ten amino acids in length are bound by MHC class II molecules and expressed on the surface of the APCs. T cells bearing specific T-cell receptors bind to the MHC class II-peptide complexes. Then the T cells are activated and start cell division. It should be noted that the reaction is initiated by tiny, 10-amino-acid peptides, not large molecules. Hydrolyzed milk contains peptides of around molecular weight 1000, which is close to ten amino acids. This might explain why hydrolyzed milk, which is effective for treatment of IgE-mediated allergy, is not effective in a significant percentage of patients with GI allergy [7•].

The central mechanism of chronic inflammation of the GI mucosa was elucidated by studies on EoE [8, 9]. Offending food proteins contact the surface of the esophageal mucosa and are incorporated by APCs, after which food allergen-specific T cells recognize them and are activated. Lymphocytes begin to produce IL-13 and other cytokines. IL-13 directs epithelial cells of the GI mucosa to produce eotaxin-3. Eotaxin-3 attracts eosinophils into the stratified squamous epithelial layer. However, eosinophils may not be the main effector cells, because depletion of eosinophils by anti-IL-5 treatment does not improve the symptoms of

patients with EoE [10]. We need to identify the main effector cell: is it a certain subset of T-lymphocytes, mast cells or innate immune cells?

GI Allergies Already Established in Western Countries

The following five clinical entities have been well studied and characterized. [5, 6]

In neonates and infants (classified as non-IgE-mediated gastrointestinal food allergies)

1. Food protein-induced enterocolitis syndrome (FPIES)
2. Food protein-induced enteropathy syndrome (enteropathy)
3. Food protein-induced proctocolitis (proctocolitis)

In children to adults (classified as mixed IgE- and cell-mediated gastrointestinal food allergies)

4. Eosinophilic esophagitis (EoE)
5. Allergic eosinophilic gastroenteritis (AEG)

Food Protein-Induced Enterocolitis Syndrome (FPIES)

The main symptoms of FPIES are vomiting, diarrhea and shock. Offending foods are cow's milk, wheat, rice, soy, breast milk, etc. [11]. Onset is usually before 3 months of age, but ranges from the day of birth to 1 year old. Laboratory data show no specific IgE and no eosinophilia [4•]. Since making the correct diagnosis at first glance is almost impossible, medical doctors have to use a "therapeutic diagnosis" to save patients. Five steps of diagnostic and treatment procedures—proposed by Powell in the 1970s [2, 3]—are useful for diagnosing FPIES and may be useful for other subsets of GI allergies. Those steps are: 1) suspect FPIES from the initial symptoms, 2) rule out other disorders in the differential diagnosis, 3) a switch to therapeutic milk leads to resolution of symptoms (therapeutic diagnosis), 4) verify weight gain every month and 5) confirm the diagnosis by oral food challenge tests performed after complete resolution of the initial symptoms. Patients with FPIES show prompt responses to both therapeutic diagnosis and oral food-challenge tests. Oral challenge tests show a specific pattern of response different from IgE-dependent food allergy. If the allergen dose exceeds the threshold of the patient, symptoms (vomiting, diarrhea and sometimes fever) will be provoked within 1 to 24 hours after ingestion of the offending food. Peripheral blood neutrophils will increase more than 3500/microL from the baseline [2]. C-reactive protein may become positive on the next day. Care must be taken not to cause serious damage when conducting food-challenge tests. It is essential to start with a very small amount of the food in severe cases, or not to challenge and wait for 2–3 years with elimination of the offending food(s). To prove remission of FPIES for a food allergen, a chronic tolerance test lasting 2–3 weeks is recommended to exclude possible delayed onset. If the treatment is appropriate, the prognosis is good. Ninety percent of patients enter remission by the age of 3 years. A few reports have investigated the pathophysiology of FPIES. TNF-alpha might be a key cytokine. Chung et al. reported [12] that TNF-alpha is expressed in epithelial cells and mononuclear cells in the lamina propria of the intestinal mucosa. At the same time, TGF-beta, an important cytokine for protecting the GI mucosa from excessive immune system reactions, is decreased in the GI mucosa. However, the precise molecular mechanism of FPIES is unclear. The mechanism of allergen-specific responses not involving IgE antibody and starting a few hours after ingestion of an offending food is a big puzzle in the field of immunology.

Food Protein-Induced Enteropathy Syndrome (Enteropathy)

Food protein-induced enteropathy syndrome (enteropathy) affects infants and children aged 0–2 years. The main symptoms are weight loss and sometimes diarrhea. Offending foods can be cow's milk, soy, wheat, eggs, etc. The small intestine is the most affected organ of the GI tract. Laboratory data show no specific IgE or eosinophilia, but hypoproteinemia and malabsorption syndrome occur. Pathological studies show patchy villous atrophy, a prominent mononuclear cell infiltrate and few eosinophils. The five steps of diagnostic and treatment procedures described above may not be effective for enteropathy, and pathological examination is required for diagnosis [13]. Also, we are unable to distinguish enteropathy from allergic eosinophilic gastroenteritis (AEG) without observing the pathology of the intestinal mucosa. Scientific studies, such as microarray analysis of the GI mucosa, clinical research, etc., are needed to elucidate the differences.

Food-Protein-Induced Proctocolitis (Proctocolitis)

Food-protein-induced proctocolitis (proctocolitis) affects babies aged 0–6 months [14–16]. The main symptom is bloody stool. There is no weight loss. If a patient shows weight loss, a diagnosis of AEG might be more appropriate. Offending foods are breast milk, cow's milk, soy, etc. Laboratory data show no specific IgE, and eosinophilia is occasionally seen. Lesions are confined to the distal large bowel and consist of mucosal edema with infiltration of eosinophils. Although patients show a rather slow response to therapeutic diagnosis and the food-challenge test, the above-mentioned five steps of diagnostic and treatment procedures might be useful. A chronic tolerance test, lasting

up to 2 weeks, is needed for diagnosis of proctocolitis. The prognosis is good if treatment is appropriate.

Eosinophilic Esophagitis (EoE)

Eosinophilic esophagitis (EoE) is now increasing in Western countries. EoE affects a wide age range, from 1-year-old children to adults. Symptoms are gastroesophageal reflux, excessive spitting-up or emesis, dysphagia, etc. Offending foods are cow's milk, wheat, eggs, etc. Some patients have multiple food allergens, which can be difficult to determine, especially in older children. Pathological examination is required to establish diagnosis [17].

Allergic Eosinophilic Gastroenteritis (AEG)

AEG affects infants to adults. Symptoms vary among patients due to differences in age and the affected GI organs. Recurrent abdominal pain, irritability, easy satiety, vomiting and weight loss may occur. The offending foods are sometimes difficult to determine, especially in older children. Food-specific IgE and a positive prick-test are seen in 50 %. Eosinophilia is also seen in 50 % of patients. Pathological examination is required to establish diagnosis, and eosinophil infiltration of the mucosa is observed [18].

Incidence of These Syndromes in Western Countries

In Israel, the prevalence was investigated in a large scale, population-based study. The cumulative incidence of FPIES was 0.34 %. Bloody diarrhea was seen in only 4.5 % of patients [19•].

Spergel et al. reported the prevalence of EoE and AEG in the USA as 52 and 28/100,000, respectively [20]. Chang et al. reviewed retrospective data for the USA and found that, unlike EoE, AEG is a rare disease [21]. Based on those results, EoE is much more prevalent in the USA compared to AEG.

GI Allergy in Japanese Neonates and Infants

GI Allergy Is Increasing in Japan

GI allergy in neonates and infants has been increasing in Japan since the late 1990s. Today, its incidence is 0.21 % [22]. There are three major differences in the clinical features of GI allergy between Western countries and Japan. (1) In FPIES, bloody stool is rare in Western countries, but frequent in Japan (47 % of patients). (2) Food-specific IgE antibody is negative in Western countries, but positive in 32 % of Japanese patients. (3) Peripheral blood eosinophils are normal in Western countries but often increased in Japan (Table 1). Since GI allergies are poorly described in Japanese textbooks and literature, doctors have to rely on accounts from Western countries. But if the clinical features of the patients differ in regard to the above three points, reaching a correct diagnosis can be difficult. Confusion and delayed diagnosis and treatment might occur. Approximately 10 % of patients develop severe complications such as mechanical ileus, perforation of the GI wall, shock and

Table 1 Differences in clinical features of FPIES between Western countries and Japan

		FPIES	
		Western countries	Japan
Symptoms and signs	Onset	First day-1 year	First day-1 year; mostly neonatal period
	Offending foods	Cow's milk, soy, etc.	Cow's milk, breast milk, rice, soy
	Vomiting	Frequent	Frequent
	Diarrhea	Frequent	Frequent
	Bloody stool	Rare	Frequent (47 %)
	Shock	10-15 %	10-15 %
	Weight loss	Present	Present
Laboratory data	Prick test	Negative	Negative
	Food-specific IgE antibodies	Negative	Positive in 30 %
	Peripheral blood eosinophils	Normal range	Often elevated maximum 70 % of white blood cells
	Stool mucous eosinophils	Sometimes positive	Often positive, especially with bloody stool
Food challenge test		Vomiting (3–4 hr) Diarrhea (5–8 hr)	Vomiting (3–4 hr), diarrhea (5–8 hr), bloody stool (next day)
Prognosis		Good	Good; remission by 3 years old

developmental retardation due to delayed start of treatment. Also, enteropathy and allergic eosinophilic gastroenteritis (AEG) require histological examination—which is not an easy technique for many pediatricians—for diagnosis.

Four Clusters Were Identified for GI Allergies in Neonates and Infants

We worried about this situation and tried to establish a method for classifying patients based only on the initial symptoms and clear-cut, simple clinical data [7•]. The goal would be prompt, proper diagnosis and treatment of affected babies. First, we included all the patients with suspicion of non-IgE-mediated gastrointestinal food allergies into one term, "GI allergy." We constructed a nation-wide database by using an internet online system. To date, clinical data for 450 babies have been collected from all over Japan (130 were treated in our department). We performed cluster analysis among patients whose confirmatory diagnosis was established by food challenge test, using five clinical parameters: birth weight, day of onset, severity of vomiting, severity of bloody stool and milk-specific IgE antibody titers. Four clusters were identified, and the discriminatory variables for cluster assignment were found to be vomiting and bloody stool (Fig. 1). Cluster 1 showed both vomiting and bloody stool. Since vomiting is the representative symptom of damage of upper GI tract and bloody stool is that of lower GI tract, inflammation of the GI mucosa can be imagined to spread to the entire GI tract. Cluster 2 showed vomiting but not bloody stool. So inflammation is imagined as prominent at the upper GI tract but not at lower GI tract. Cluster 3 showed neither vomiting nor bloody stool, but there was weight loss. Since weight loss seems to result from disturbed absorption of nutritional elements, the small intestine might be site of the main lesion in Cluster 3. Cluster 4 had bloody stool but no vomiting. Because many patients had red-colored fresh bloody stool, the bleeding sites may be located in the large intestine. At first, we did not know whether or not these four clusters had any important biological meaning, so we compared the clinical and laboratory data among the clusters. The day of onset was earlier in Clusters 1 and 4 (median 7th day of life) compared to Clusters 2 (median 16th day) and 3 (median 37th day). The birth weight was significantly less in Cluster 3 patients. The blood eosinophil percentages were significantly higher in Cluster 3 (median 26 %), although other clusters also showed abnormally high percentages. We can thus conclude that the 4 clusters have distinct biological differences. The greatest surprise was seen in the results of the food-challenge tests: in most patients, even after several months' remission, food-challenge generated the same symptoms as had been seen at initial onset of the disease. That means that the responsible immune cells remained in the same part of the GI tract.

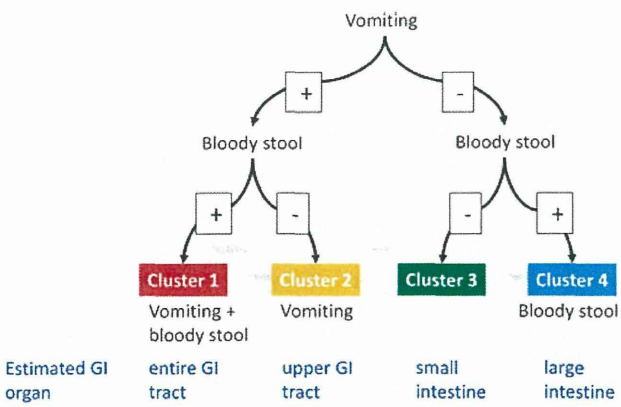

Fig. 1 Four clusters of GI allergies in neonates and infants. This classification can be used in any patients with suspected GI allergy. Estimation of affected organs in GI tract and prediction of the outcome in the food-challenge test are possible. When patients have both vomiting and bloody stool at initial presentation, they are classified as Cluster 1. One can estimate the affected organs of Cluster 1 as the entire GI tract. If patients have neither vomiting nor bloody stool but show weight loss, they can be classified as Cluster 3. The most affected organ might be the small intestine. (*Adapted with permission from* Nomura I, Morita H, Hosokawa S, et al.: Four distinct subtypes of non-IgE-mediated gastrointestinal food allergies in neonates and infants, distinguished by their initial symptoms, J Allergy Clin Immunol, volume 127(3):685–688.e8. Copyright 2011; Mosby, Inc.)

Cluster 1 showed vomiting and bloody stool at the same time. Bloody stool in FPIES has not often been reported in Western countries. However, Cluster 1 should be included in FPIES because the response in the food-challenge test is similar to FPIES. Cluster 2 is compatible with FPIES, but eosinophilia was seen in many patients. Although the blood of 30 % of Cluster 1 and 2 patients was positive for milk-specific IgE, these clusters could be diagnosed as FPIES. That is because they did not show any IgE-mediated reactions like urticaria or wheezing even in the food-challenge test at 5–8 months old, prick tests were all negative, reactions were confined to the GI organs, most symptoms started more than 2 hours after ingestion, and the food-challenge test showed reactions typical of FPIES. Cluster 3 resembles enteropathy or AEG. In Cluster 4, the diagnosis should be proctocolitis when weight gain is normal, but AEG when it is poor.

This classification is useful because it is easy to apply, using only the initial clinical data, and it will increase the likelihood of achieving a correct diagnosis. The involved portion of the GI tract can be deduced, and the outcome of the food-challenge test can be predicted.

A limitation of this cluster method is that it can be used only for babies under 6 months old. For older patients, another analytical method is needed. The symptoms during the first month after onset of the disease should be used, because a longer duration of chronic inflammation may lead to many other GI symptoms.

Remaining Problems in GI Allergies in Neonates and Infants

Two important problems remain to be solved. One is the difficulty of differential diagnosis at the initial presentation of the disease because of an absence of diagnostic tests. The other is a lack of in vitro tests to determine which food is responsible for the disease. Actually, this second issue is easier to circumvent in babies—who do not refuse an elimination diet aimed at identifying the offending food—than it is in teenagers suffering from AEG or EoE. In infants, when developing a diagnostic test, it is very important not to overlook GI allergy.

The lymphocyte proliferation test for GI allergy has been largely neglected by scientists in recent years. There was controversy regarding its diagnostic value for FPIES [23], but now it seems likely to become a reliable diagnostic method [24].

Pathological examination using advanced molecular techniques would be a very powerful diagnostic tool [8] for distinguishing the inflammation patterns of each clinical entity. Ohtsuka et al. performed microarray analysis of mucosal samples in infant with proctocolitis and reported expression of CCL-1 and CXCL-13 [25].

Since many patients begin to manifest symptoms within 2 weeks after birth, intrauterine sensitization is suspected. It would be of interest to investigate the immune mechanism of intrauterine sensitization. More importantly, risk factors for the development of GI allergy should be identified, enabling prevention of these diseases.

Older Children and Adults with EoE and AEG in Japan

EoE (eosinophilic esophagitis) and AEG (allergic eosinophilic gastroenteritis) are the two main GI allergy diseases in older children and adults. EoE is increasing in Western countries, and is now more prevalent than AEG. AEG seems to have only 10-50 % of EoE's prevalence [19•, 20]. In contrast, Japanese reports suggest that prevalence of pure EoE might be much lower than that of AEG's [26, 27]. For these reasons, systematic review of GI allergy from childhood to adults is needed to clarify the differences in the clinical features, laboratory data and histological distribution among human races, regions and age groups.

Conclusions

Much work remains to be done regarding non-IgE-mediated GI allergies. Clinical studies to elucidate the precise natures of these diseases are the most important. The frequencies of each offending food, prognosis and complications should be investigated. Systematic review of clinical data from all over the world is needed to compare racial and regional differences. Because prenatal exposure to risk factors may cause GI allergy in neonates, those factors must be investigated and identified. Immunological research is needed to develop reliable diagnostic tests for determination of offending foods and to understand the disease mechanisms. International cooperation to save babies living far from medical resources is important. Combination of these efforts will decrease the incidence of diseased babies and save lives.

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