

Food Hypersensitivity Reactions Visualised by Ultrasonography and Magnetic Resonance Imaging in a Patient Lacking Systemic Food-Specific IgE

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Key Words

Food hypersensitivity · Intestinal allergen provocation test · Ultrasound · Magnetic resonance imaging

Abstract

Background: Abdominal complaints related to food intake might be due to hypersensitivity. A firm diagnosis of food allergy is often difficult to establish, particularly in the absence of systemic food-specific IgE. Using ultrasonography and magnetic resonance imaging (MRI) we were able to visualise the intestinal response in one such case. **Methods:** A 24-year-old female presented with self-reported food hypersensitivity, particularly related to the intake of egg. Nausea and diarrhoea were predominant symptoms. Double-blind placebo-controlled food challenge with raw egg was positive, but all other conventional tests of food hypersensitivity, including skin prick test, total and food-specific IgE in serum, were negative. A thorough investigation programme could not reveal any organic disease of the gastrointestinal tract. We extended the evaluation to include two new provocation tests, where intestinal wall thickening and the amount of luminal liquid were monitored by external abdominal ultrasound and MRI. **Results:** Both ultrasound and MRI investigations indicated intestinal wall thickening and influx of large

amounts of fluid into the proximal small intestines within 10 min of duodenal challenge with egg. The response was associated with abdominal pain and bloating. **Conclusions:** The response to provocation was typical of an immediate allergic reaction. Our results indicate that local food-induced hypersensitivity reactions can occur in the gut in the absence of systemic indications of IgE-mediated allergy. Abdominal ultrasonography and MRI might become valuable tools for documenting such responses.

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Adverse reactions related to intake of food are commonly experienced in the general population. As many as 25% of the population in Western countries believe that they suffer from food hypersensitivity (FH), whereas a diagnosis of true food allergy in adults is confirmed in only 1–4% of the cases [1]. Establishing a correct diagnosis of gastrointestinal FH is a problematic task, partly due to incomplete understanding of the pathogenetic mechanisms involved.

The term ‘food hypersensitivity’ embraces IgE-mediated and non-IgE-mediated food allergy, as well as non-allergic reactions [2]. In animal models, an IgE-mediated allergic reaction is characterised by mucosal swelling and

exudation of plasma into the intestinal lumen [3]. Human studies using intestinal perfusion techniques have suggested that the allergic response mechanisms are largely the same in man as in animals [4]. When it comes to non-IgE-mediated food allergy, the pathogenetic mechanisms are less well described. Non-IgE-mediated food allergies include reactions which are mediated by food-specific antibodies other than IgE, and reactions where specific T-cell responses predominate. Cell-mediated reactions are also known as 'delayed-type' hypersensitivity. Immediate responses such as luminal influx of fluid and mucosal oedema have not been described in non-IgE-mediated intestinal food allergy. However, studies indicate that local IgE may be detectable in allergic reactions of the intestines [5–7], suggesting that immediate hypersensitivity reactions might be IgE-mediated despite negative skin prick test (SPT) and lack of systemic food-specific IgE.

Due to the lack of appropriate diagnostic tools, the diagnosis of non-IgE-mediated food allergy is particularly challenging. We have recently developed two intestinal provocation tests, where intestinal changes in response to provocation are monitored by external ultrasound and magnetic resonance imaging (MRI). These techniques are able to visualise mucosal swelling and luminal influx of fluid after intestinal allergen challenge. Here we present a double-blind placebo-controlled food challenge (DBPCFC) positive case of non-IgE- or local IgE-mediated intestinal FH, in which ultrasonography and MRI examinations both indicated responses to provocation typical of an immediate local allergic reaction.

Case Report

A 24-year-old female presented with self-reported FH to milk, wheat and egg, the latter in particular. Her main complaints were nausea and diarrhoea. As a child, she suffered from severe atopic dermatitis, with persistence also in adult age. The eczema usually worsened after intake of certain foods, especially citrus and other fruits. In her early teens the patient developed exercise-induced asthma, as well as allergic rhinoconjunctivitis against grass and tree pollen. With respect to food-related reactions, she had previously experienced oral allergy syndrome several times, which she related to intake of hazelnuts and codfish. There was no allergic disease in her family, except for one aunt with possible FH. The main problems related to food intake began when our patient was in pre-school age, and did not change much over the years. She tried strict diets with elimination of the suspected food items a couple of times, which led to temporary symptom relief. Generally, her reactions started 30 min after intake of food with attacks of abdominal pain, nausea and repeated events of watery diarrhoea. Bloating and fatigue were often associated symptoms.

SPT was negative for all tested food items; that is cow's milk, wheat flour, codfish, peanut, soy, a native wheat flour suspension

in saline, and egg. The only positive responses were against inhalant allergens from timothy grass and dog. Total IgE in serum was within the reference range and food-specific IgEs were negative (i.e. <0.35 kU/l) using the immunoCAP FEIA system (Pharmacia Diagnostics, Uppsala, Sweden). Open oral provocation tests with wheat and milk were negative. However, when challenged with egg, she experienced mouth tingling, itching of the skin, bloating and abdominal pain. DBPCFC was performed with egg (5 random challenges in which two or three were actives and two or three placebos). The patient and the doctor correctly identified in 4 of 5 challenges, which was considered a positive test result [8].

Gastroscopy including mucosal biopsies was normal without indications of *Helicobacter pylori* infection or celiac disease. Serological tests such as specific IgG and IgA antibodies against gluten, casein, lactoglobulin and lactalbumin, as well as the total amount of IgA in serum, were within reference limits. IgA antibodies against endomysium were negative. Stool samples were taken to rule out gastrointestinal infections. Calprotectin in gut lavage fluid was measured and found to be within the reference range [9]. Intestinal permeability, determined from amounts of ⁵¹CrEDTA recovered in urine, was also normal (0.07%). Lactose intolerance was excluded by analysing blood glucose response after a lactose load of 47 g. In conclusion, we found no signs of gastrointestinal pathology that could explain the complaints of this patient. Based on the patient's history and the positive findings from the DBPCFC, she was examined further with two recently developed provocation tests in which intestinal wall thickness and the amount of luminal fluid were monitored by transabdominal ultrasound and MRI.

Methods

Ultrasonographic Intestinal Allergen Provocation Test

The intestinal allergen provocation test was performed by instilling the suspected food allergen through a nasoduodenal feeding tube (Freka® Feeding Tube, Fresenius Kabi, GmbH, Germany; outer diameter 2.8 mm) directly into the duodenum. In this case, 10 ml of a solution consisting of 1/10 of a whole, raw egg diluted in saline was administered through the tube. Transabdominal two-dimensional ultrasound (System Five, GE Vingmed Ultrasound, Horten, Norway) was applied to monitor the intestinal response as described previously [10]. Sonographic examination was performed 5 min before, and 10, 30, and 60 min after the provocation, and the following features were explored: wall thickness and diameter of the duodenal bulb; wall thickness and diameter of proximal jejunum; number of fluid-filled jejunal loops, and peristalsis of the small bowel. Before and during the provocation, the patient scored her gastrointestinal symptoms (abdominal pain, fullness, nausea, bloating and air in the abdomen) using a visual analogue scale.

Magnetic Resonance Imaging of the Small Intestine

On a separate day, another provocation test was performed similarly with the egg solution, but this time MRI was used to monitor the intestinal response. MRI was performed before and 1 h after provocation using a 1.5 T unit (Magnetom Symphony, Siemens). Coronal and axial HASTE (single-shot fast spin-echo) sequences were used to demonstrate intraluminal fluid in the small bowel, and coronal VIBE (3D gradient-echo) sequences to demonstrate wall thickening.

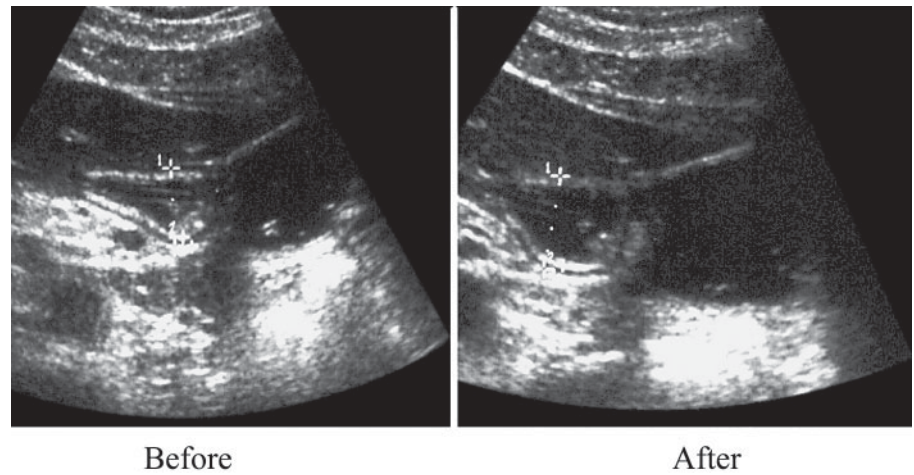


Fig. 1. Sonographic view of the duodenum showing wall thickening and increased diameter in response to intestinal provocation with egg.

Table 1. Sonographic changes and symptom scores in response to intestinal provocation

| Parameter | Time, min | | | |
|--|-------------|------|------|------|
| | -5 (before) | 10 | 30 | 60 |
| Wall thickness of duodenum, mm | 3.0 | 4.3 | 4.9 | 4.2 |
| Diameter of duodenum, mm | 18.1 | 19.1 | 20.9 | 22.5 |
| Wall thickness of proximal jejunum, mm | 1.9 | 1.9 | 2.0 | 2.0 |
| Diameter of proximal jejunum, mm | 19.4 | 20.2 | 21.5 | 24.5 |
| Number of fluid-filled jejunal loops | 1 | 2 | 3 | 3 |
| Peristalsis of small bowel | 1 | 2 | 2 | 2 |
| Sum symptom score, visual analogue scale | 8.0 | 14.5 | 16.5 | 15.0 |

Data are expressed as mean values for sonographic parameters.

Results

When performing the ultrasound-monitored provocation test, an intestinal response was evident already 10 min after allergen challenge (table 1). The response included thickening of the duodenal wall and increased diameter of the duodenum and the proximal jejunum, increased peristalsis of the small bowel, as well as increased amounts of luminal fluid in the proximal jejunal loops (fig. 1). The challenge also elicited symptoms in the form of abdominal pain and bloating.

The MRI-monitored provocation test revealed similar changes. The bowel wall thickness increased from 5 mm before, to about 11 mm after food challenge (a normal bowel wall usually does not exceed 2–3 mm in MRIs) [11]. The diameter of the duodenum also increased, from 19 to 25 mm, and in addition we observed increased amounts of luminal fluid in duodenum and proximal jejunal loops (fig. 2).

Discussion

We have presented a patient with egg hypersensitivity confirmed by DBPCFC. Despite negative SPT and no egg-specific IgE in serum, we were able to document an abnormal intestinal response to egg by both transabdominal ultrasound and MRI.

At present, intestinal FH cannot be reliably diagnosed by any laboratory test. Positive SPT and/or the presence of food-specific IgE in serum are suggestive of IgE-mediated food allergy. However, if these tests are negative, the reactions may still be IgE-mediated [12]. Several recent studies have shown that IgE may be detectable in intestinal lavage fluid and biopsy specimens even if the amount is too small or transient to be detectable in blood [5–7]. Hence, apparent non-IgE-mediated adverse reactions to food may actually be local IgE-mediated allergic reactions of the intestine [3, 4]. This may explain the immediate local hypersensitivity reactions in our patient. The patient's

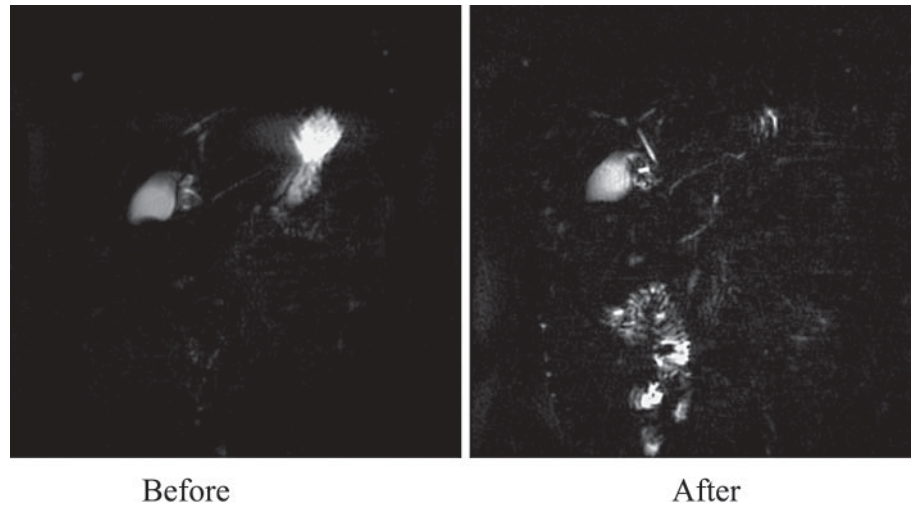


Fig. 2. MRIs show increased amounts of luminal fluid in small bowel in response to intestinal provocation.

history of 'classic' IgE-mediated reactions such as oral allergy syndrome and hypersensitivity towards pollen may support this explanation.

Alternative explanations could be that an allergic response occurred via non-IgE-mediated mechanisms. These include cell-mediated reactions where sensitised T lymphocytes play a major role, as well as reactions that are mediated by antibodies other than IgE [2]. Another possibility is that our patient has a mixed IgE/non-IgE-mediated food allergy. Atopic disease is one typical 'mixed' disorder. Food allergy and atopic dermatitis are often co-existent, as in our patient, but this is still a poorly understood field [13].

The largest group of FH reactions consists of non-allergic reactions [14]. In this patient, common non-immune mechanisms such as enzyme deficiencies, infection and chemical irritation were ruled out. Still, it is possible that the intestinal responses we observed were the results of an unspecific, non-immune-mediated defence mechanism [3]. The DBPCFC, which at present is considered to be the 'golden standard' for diagnosing FH [15], is of no use in discriminating between non-IgE-mediated food allergy and non-immune-mediated (non-allergic) FH. These reactions are all characterised by positive DBPCFC, but negative SPT and/or food-specific IgE results, and at present we have no adequate diagnostic tools at hand that can help us specify the diagnosis.

The diagnosis is particularly difficult to establish when the allergic process is confined to the gastrointestinal tract. The ultrasound method has been used in one prior study [10]. The results suggested that this method is more sensitive than SPT and food-specific IgE. It is also less

cumbersome and provides more objective measures than the DBPCFC. Still, we acknowledge that further work is needed to establish the sensitivity and specificity of this new provocation test.

MRI of the small intestine has recently been introduced as an alternative to conventional X-ray-monitored enteroclysis [11, 16]. It has become the technique of choice in monitoring the activity of Crohn's disease, while its clinical utility in other conditions of the small intestine is not yet fully established. One main advantage of MRI is that it provides high-resolution images and makes detailed morphological evaluation of the bowel wall possible. It also readily visualises luminal fluids, which was particularly important in our case.

Using external abdominal ultrasound and MRI, we have documented an acute intestinal response with mucosal thickening and luminal influx of fluid in a FH patient without systemic food-specific IgE. The results suggest that ultrasound and MRI of the small intestine might become important tools in the diagnostic challenge related to such FH reactions.

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