

CONTINUING MEDICAL EDUCATION

The Differential Diagnosis of Food Intolerance

Yurdagül Zopf, Hanns-Wolf Baenkler, Andrea Silbermann, Eckhart G. Hahn, Martin Raithe

SUMMARY

Introduction: More than 20% of the population in industrialized countries suffer from food intolerance or food allergy.

Methods: Selective literature search for relevant publications in PubMed and the Cochrane Library combined with further data from the interdisciplinary database on chronic inflammatory and allergic diseases of the Erlangen University Hospital.

Results: The majority of cases of food intolerance (15% to 20%) are due to non-immunological causes. These causes range from pseudoallergic reactions to enzymopathies, chronic infections, and psychosomatic reactions that are associated with food intolerance. The prevalence of true food allergy, i.e., immunologically mediated intolerance reactions, is only 2% to 5%.

Conclusions: The differential diagnosis of food intolerance is broad. Therefore, a structured diagnostic algorithm with input from multiple clinical disciplines should be applied. The treatment consists of eliminating the offending substance from the diet as well as medications and psychosomatic support, when indicated.

Dtsch Arztebl Int 2009; 106(21): 359–70
DOI: 10.3238/arztebl.2009.0359

Key words: Food intolerance, food allergy, diagnosis, provocative testing, histamine intolerance

Medizinische Klinik 1, Gastroenterologie, Friedrich-Alexander-Universität Erlangen-Nürnberg: Dr. med. Zopf, Prof. Dr. med. Hahn, Prof. Dr. med. Raithe

Medizinische Klinik 3 – Rheumatologie, Immunologie und Allergologie, Friedrich-Alexander-Universität Erlangen-Nürnberg: Dr. med. Baenkler

Psychosomatische und Psychotherapeutische Abteilung in der Psychiatrischen und Psychotherapeutischen Klinik, Friedrich-Alexander-Universität Erlangen-Nürnberg: Dipl.-Psych. Silbermann

The term food intolerance is used to describe a range of food related complaints of varying etiology. Besides structural and functional causes, it is also necessary to distinguish between a toxic and non-toxic pathogenesis of the intolerance (*Figure 1*).

Food intolerance of functional origin is often caused only by an isolated functional disorder (such as lactase deficiency in the small intestine) and is initially unaccompanied by any other anatomical or morphological changes in the gastrointestinal tract. Food intolerance of structural etiology, on the other hand, has its origin in an anatomically and morphologically demonstrable disease involving a structural alteration in the gastrointestinal tract. This results secondarily in food-associated symptoms. Small intestinal diverticula, for example, lead to bacterial overgrowth of the small intestine, which in turn causes postprandial meteorism and diarrhea.

Toxic reactions are due to the actions of toxins, which may be of bacterial, plant, or fungal origin, for example arising from food contamination, as well as other toxins such as glycoalkaloids.

Nontoxic reactions are divided into two further principal mechanisms: immunologically and non-immunologically mediated reactions (1–3). Overall, non-immunologically mediated reactions account for the majority of all reactions to food (15% to 20%). The immune system is not specifically involved in these cases, and therefore non-immunologically mediated forms of food intolerance are not allergies. This spectrum embraces pseudoallergic and pharmacological effects caused by:

- salicylates, biogenic amines (such as histamine, tyramine, serotonin etc.),
- sulfites (present in wine and medications),
- sodium glutamate (flavor enhancer),

Definition

The term food intolerance is used to describe a range of food related symptoms of varying etiology.

Overview of range of food intolerance reactions

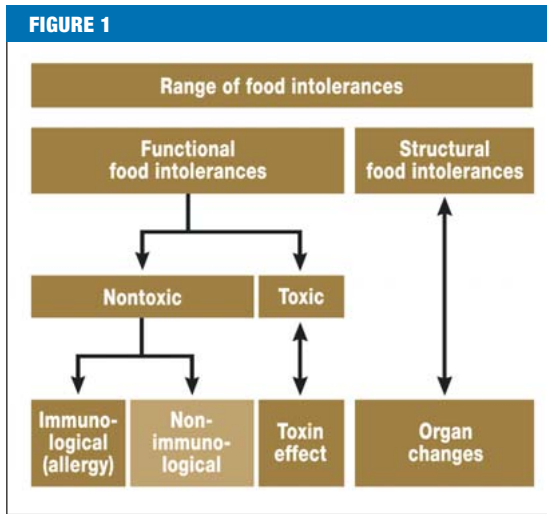


FIGURE 2

Functional food intolerances			Structural food intolerances
Nontoxic		Toxic	<ul style="list-style-type: none"> • Esophagus: Achalasia, stricture • Stomach: Resection • Gallbladder: Fat malabsorption, obstructive jaundice • Pancreas: Chronic pancreatitis • Small intestine: Infection, diverticulum, overgrowth • Large intestine: CIBD, diverticulum, surgical sequelae • Vascular and lymphatic: Abdominal angina, lymphangietasia, right ventricular failure
Immunological	Non-immunological		
Allergy and autoimmunity	Intolerance	Toxin	
IgE	<ul style="list-style-type: none"> • Enzymatic • Transport defect • Pharmacological • Pseudo-allergic • Idiosyncrasy (food additives) 	<ul style="list-style-type: none"> • Acute intoxication • Food poisoning • Chemicals • Chronic intoxication • Mycotoxins • Chemicals 	
Non-IgE			
Celiac disease Anti-tTG antibodies			
Psychogenic	Infections		
<ul style="list-style-type: none"> • Eating disorders • Somatoform disorders 	<ul style="list-style-type: none"> • EHEC, ETEC • Lamblia • Overgrowth of normal flora 		

Examples of important functional and structural causes of food intolerances; anti-tTG antibodies, antibodies to tissue transglutaminase; EHEC, entero-toxic Escherichia coli; ETEC, entero-hemorrhagic Escherichia coli; CIBD, chronic inflammatory bowel disease

Causes of non-immunological food intolerance

- Salicylates, biogenic amines
- Sulfites
- Sodium glutamate
- Colorants and preservatives, sweeteners
- Enzymopathies

- colorants and preservatives (such as tartrazine, benzoates, sorbates etc.),
- sweeteners (aspartame), or
- due to enzymopathy.

The range of differential diagnoses of the non-immunologically mediated forms of food intolerance further includes chronic infections (such as lamblia), neuroendocrine tumors (such as carcinoid), and psychosomatic reactions that cause or can imitate symptoms of intolerance (1, 2, 4–8) (Figures 1 and 2). The specifically immunologically mediated forms of food intolerance are subsumed under the term food allergy and, considering the rising prevalence of food intolerance, pose a differential diagnostic problem for patients and physicians alike. The incidence of food allergies is subjectively overestimated. In one survey, one fourth of the population claimed to be suffering from food allergy (2, 4, 7). The actual prevalence in adults is 2% to 5%, with the different organ systems (skin, gastrointestinal tract, cardiovascular system, lungs etc.) being described with differing frequency as the site of manifestation of the allergy depending on the patient sample studied (3, 4, 6, 9, 10). The prevalence in young children is higher at 5% to 10%, with different foods being responsible for the food allergies in children and adults (e-Table 1).

The learning objectives of this article are to equip the reader to

- differentiate exactly between food intolerances and food allergies
- acquire knowledge of the broad range of differential diagnoses of food allergies and food intolerances
- employ a structured approach to the differential diagnosis of food allergies and food intolerances.

Method

A selective literature search including national guidelines and the databases PubMed, the Cochrane Library, and the Erlangen University interdisciplinary data register of chronic inflammatory and allergic diseases was undertaken to establish the current state of knowledge relating to food intolerances.

The search included German and English language publications and the authors' personal data resources. The articles consulted were selected on the basis of the authors' own subjective assessments and extensive clinical experience. A formal meta-analysis or structured evaluation of all the publications was not undertaken and is hardly practically feasible in view of the volume of available literature.

Prevalence of food allergy

- in adults: 2% to 5%
- in young children: 5% to 10%

Differential diagnosis: non-immunologically mediated food intolerances

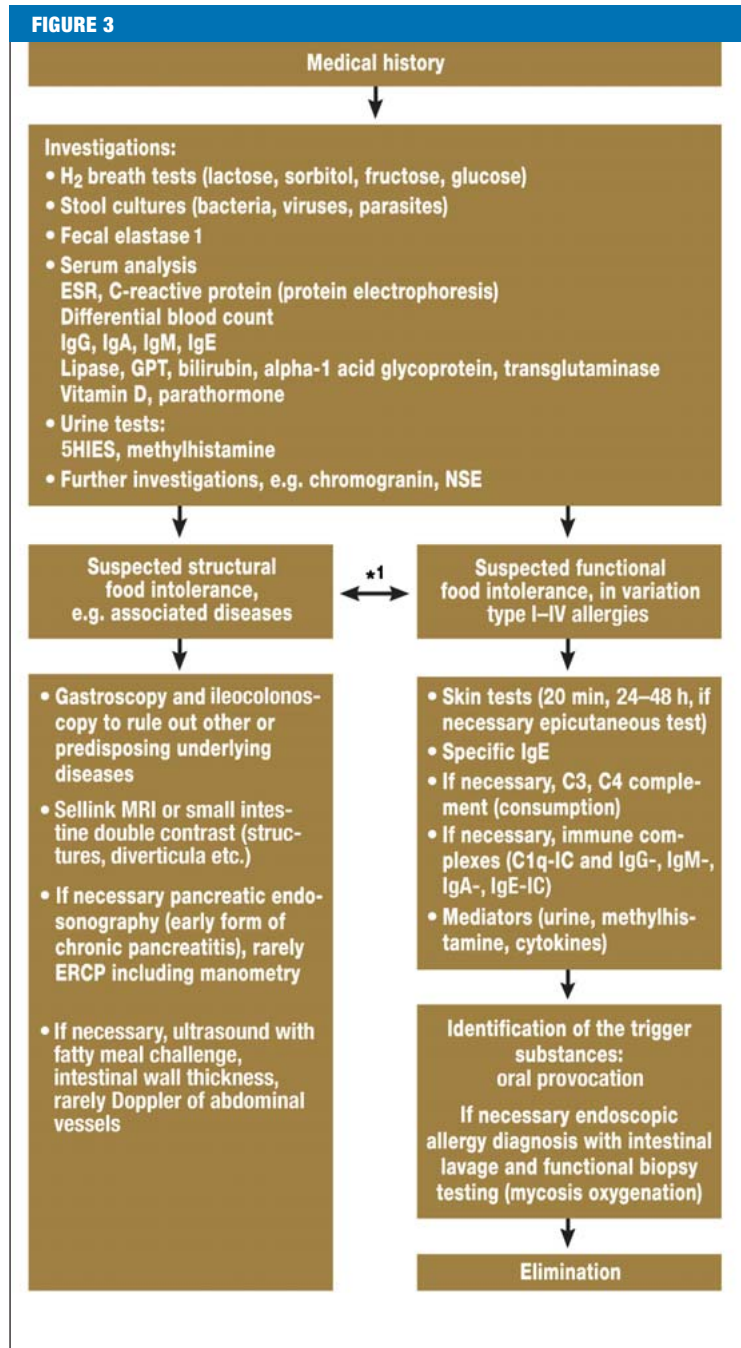
Since the population prevalence of functional and structural, non-toxic and non-immunologically mediated clinical presentations (Figures 1 and 2) are much commoner (15% to 20%) than the immunologically mediated true allergies (2% to 5%) or toxic disease mechanisms, diagnostic evaluation should initially consider the non-immunologically mediated differential diagnoses when it is uncertain what is causing the patient's symptoms (e.g. carbohydrate malabsorption, neurodermatitis, pancreatic insufficiency, mastocytosis, [Figure 3]). This should always be performed before embarking upon detailed immunological investigation aimed at detecting the presence of a systemic or local food allergy. This also appears relevant in view of the frequent association of carbohydrate malabsorption, histamine intolerance, or infections with atopic diseases or food allergy. It is also necessary to rule out the presence of other underlying diseases, intolerances, and pathologies predisposing to food intolerance by means of serum analysis, diagnostic imaging techniques, endoscopic examinations and histological analyses, for example in order to avoid overlooking chronic inflammatory bowel disease, celiac disease, a lymphoma, mastocytosis or tumors etc. (1, 4, 6, 11).

Since this article describes the differential diagnosis of food intolerances and food allergies based on the Erlangen interdisciplinary data register of chronic inflammatory and allergic gastrointestinal diseases, because of the enormously broad spectrum involved, the respective differential diagnoses are listed only in summarized form; detailed descriptions can be found in the literature sources cited.

Differential diagnosis of non-immunologically mediated food intolerances (non-allergic food intolerances)

A transient (single occurrence with complete remission) or chronic (permanent symptoms due to persisting triggering factors) reaction (such as abdominal, autonomic nervous or systemic symptoms) usually does not allow direct inference of the presence of an allergy, intolerance, infection, intoxication, or hyperalimentation but always requires taking an exact medical history and, if necessary, targeted diagnostic measures.

Depending on the patient's medical history, a functional or structural cause of the food intolerance will be suspected (Figures 1 and 2). A suitable basic



Overview of diagnostic approaches to the differential diagnostic spectrum of food intolerances and allergies; *1 both clinical pictures can also coexist; ESR, erythrocyte sedimentation rate; GPT, glutamate pyruvate transaminase; NSE neuron specific enolase; ERCP, endoscopic retrograde cholangio-pancreaticography

Primary differential diagnosis

If the cause of the symptoms is uncertain, first consider the non-immunologically mediated differential diagnoses and perform specific diagnostic testing.

Further diagnostic measures

comprise differentiated immunological diagnosis for detection of a systemic or local food allergy.

TABLE 1

Important examples of intolerances due to enzyme deficiency and transport disorder

Enzyme structure	Target structure	Primary deficiency	Secondary deficiency or disorder
Carbohydrates			
Combined disaccharide malabsorption syndrome	Lactose, sucrose, and other disaccharides	autosomal recessive	Bowel inflammation (infections, celiac disease, CIBD)
Isolated disaccharide intolerances	Disaccharide		Bowel inflammation (infections, celiac disease, CIBD)
GLUT 5 transport defect	Fructose		Bowel inflammation (infections, celiac disease, CIBD)
Lactase (β -galactosidase)	Lactose	– congenital – autosomal recessive (very rare) – physiological (from age 3–5 years)	Bowel inflammation (infections, celiac disease, CIBD)
Saccharase (sucrase isomaltase)	Sucrose	autosomal recessive sucrase-isomaltase deficiency	Bowel inflammation (infections, celiac disease, CIBD)
Maltase (alpha-glucosidase)	Maltose	autosomal recessive	Medication with acarbose, miglitol
Trehalase	Trehalose	autosomal recessive	Bowel inflammation (infections, celiac disease, CIBD)
Galactase	Galactose	autosomal recessive	Bowel inflammation (infections, celiac disease, CIBD)
Biogenic amines			
e.g. Diamine oxidase	Histamine etc.	autosomal recessive	Bowel inflammation (infections, celiac disease, CIBD)
Other intolerances			
Fructose intolerance aldolase B	Fructose	autosomal recessive	
Glucose-6-phosphate dehydrogenase	Fava beans	X-chromosomally inherited enzyme defect	Medication with sulfonamides
Alcohol dehydrogenase	Acetaldehyde		Medication with metronidazole

CIBD, chronic inflammatory bowel diseases

Carbohydrate malabsorption

Carbohydrate malabsorption is a frequent consequence of an enzyme disorder.

Intolerances

Medication with sulfonamides and metronidazole can lead to the manifestation of intolerance.

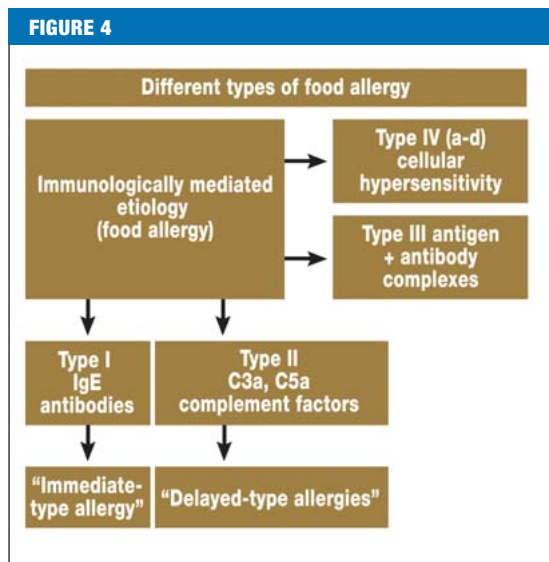
diagnostic program is then implemented. The full gamut of diagnostic modalities outlined in *Figure 3* will not be required for every patient but should be applied on a case by case basis with reference to the history, clinical findings, and possible differential diagnoses, as well as previous findings, in a cost conscious manner (4, 8, 11).

Diagnostic imaging procedures, endoscopy, histology, and stool examinations can assist in diagnosing diseases of structural etiology involving different types of food intolerances, such as fat intolerance in patients with gallstones, reflux esophagitis, or pancreatic insufficiency. Chemical laboratory tests are used, for example, to detect eosinophilia, increased inflammatory activity, or IgA antibody deficiency, and autoantibody assays (transglutaminase, anti-enterocyte antibodies etc.) can provide evidence of, for example, chronic inflammatory bowel disease or an infection.

In many cases, intolerances or food intolerances only develop during the course of the various underlying and concomitant diseases. Some individuals with chronic inflammatory bowel disease, for example, develop meteorism, flatulence, and diarrhea after ingesting milk because of lactase deficiency (*Figure 2*) (1, 4, 8, 11). These intolerances should be identified at an early stage since they aggravate the disease course and complicate dietary management and hence considerably compromise quality of life. The Erlangen database shows that a major diagnostic problem is that today it is often attempted only to exclude structural diseases by means of serological or instrumental diagnostic tests, while the positive detection of functional disorders often remains inadequate. Diseases of structural etiology are understood to include primary organ pathologies of the gastrointestinal tract (such as achalasia), while functional disease is characterized by normal morphology but an isolated functional impairment (such as lactase deficiency).

Carbohydrate malabsorption

Carbohydrate absorption is significantly affected by disorders such as lactase deficiency (intolerance of milk sugar) and diseases affecting the transport of certain mono- and disaccharides. Impairments of the digestion and absorption of simple carbohydrates are the commonest non-immunological food intolerances in the European population (lactose, fructose, sorbitol malabsorption etc. [Table 1]). Carbohydrates cannot be absorbed in the small intestine of patients with, for example, lactase deficiency or a transport defect (such as



Immunological mechanisms in food allergies (gastro-intestinally mediated Grade I-IV allergies) according to Coombs and Gell

GLUT 5 in fructose transport, or GLUT 2 for glucose, galactose and fructose transport) and therefore reach the large intestine in osmotically active form. Here, they are metabolized by bacterial decomposition to short-chain fatty acids, methane, carbon dioxide, and hydrogen which induce meteorism, flatulence, abdominal pain, and diarrhea (1, 4, 8, 11). Since many foods contain carbohydrates, carbohydrate intolerance in the form of malabsorption of fructose, sorbitol and lactose can lead to many undifferentiated intolerances without an exact knowledge of the inducing foods. Other enzyme deficiency states and transport disorders are listed in *Table 1*.

Small bowel bacterial overgrowth

If the H₂ breath tests for fructose, lactose and sorbitol (and possible lactulose) are positive, bacterial overgrowth of the small intestine should be considered as a possible cause of the food intolerance. As with carbohydrate malabsorption, this condition often leads to meteorism, flatulence, diarrhea, and pain in a non-specific pattern involving a variety of foods. Patients with postoperative changes, peristaltic disorders, diabetes mellitus, and patients who are medicated with immunosuppressives or proton pump inhibitors are especially affected. An H₂ breath test for glucose should be performed to rule out small bowel bacterial overgrowth.

Diagnostic procedures

Endoscopy, histology, and stool examinations can reveal structural and infectious diseases that may be associated with various food intolerances.

Small bowel bacterial overgrowth

If the H₂ breath tests for fructose, lactose, sorbitol (if necessary, also lactulose) are positive, small bowel bacterial overgrowth should be considered as a possible cause of food intolerance.

Histamine intolerance

Histamine intolerance is caused by a disorder of the metabolism of mainly exogenously supplied histamine (histamine-rich foods and semiluxuries). This is most commonly attributed to a deficiency of the enzyme diaminoxidase (DAO) which is responsible for the extracellular biotransformation of histamine (12, 13). But histamine-N-methyltransferase (HNMT) responsible for intracellular histamine breakdown may also be involved. About 1% of the total German population of 82 Mill. is affected by histamine intolerance, 80% being middle-aged women (13).

The symptoms of histamine intolerance are highly variable and affect almost all organs. These range from typical cutaneous effects of histamine (erythema, pruritus, flush, urticaria), gastrointestinal complaints (flatulence, colics, diarrhea), respiratory complaints (nasal obstruction, rhinorrhea, asthma attacks), cardiac complications (hypo- and hypertension, arrhythmias) to headache or dysmenorrhea (13, 14).

A slight increase in histamine concentration above the normal range already causes incipient vasodilatation, increased secretion of gastric fluid and mucus, and contraction of the smooth muscles. A further increase leads to tachycardia, arrhythmias, and typical cutaneous reactions. There may also be hypotension, bronchospasm and, with a rapid rise in histamine concentration, shock or cardiac arrest (12, 13). The gastric acid secretion and smooth muscle contraction which already starts when there are slight increases in histamine levels explains why many people with food intolerances and allergies in whatever form have unspecific abdominal symptoms such as dyspepsia, a sensation of bloating and tension or pain. Typical trigger factors of histamine intolerance are listed in the *e-Box* (12, 14).

Salicylate intolerance

The prevalence of salicylate intolerance in Europe is 2.5% (8). The classical symptoms of salicylate intolerance are respiratory complaints (blocked or runny nose, sinusitis, nasal polyposis, bronchial asthma), but can also lead to gastrointestinal complaints with meteorism, flatulence, diarrhea and, rarely, to colitis with strictures and ulcers (5, 14). The pathogenesis of salicylate intolerance is based on an inhibition of cyclooxygenase-1 by salicylates and other non-steroidal pain medications, but also by salicylate-containing foods and other acids (such as benzoic acid or colorants) resulting in reduced prostaglandin synthesis (5).

In intolerant individuals this leads to activation of the leukotriene metabolism with increased formation of LTB4 and/or LTC4-E4.

This condition is detected by a blood cell test (heparinized blood) with incubation of 5-acetylsalicylic acid and arachidonic acid or by provocation tests (nasal, bronchial, oral [5]).

The recommended treatment is abstinence from the inducing substances; the most important foods concerned are listed in *e-Table 2*.

If dietary therapy alone is insufficient, treatment with leukotriene receptor blockers or deactivation with acetylsalicylic acid should be attempted (5) (see supplementary *case report*).

Differential diagnosis of immunologically mediated food intolerance: food allergy

Among the food intolerances and immunologically mediated diseases, food allergy exhibits the greatest complexity. This is due to the heterogeneous pattern of clinical symptoms associated with food allergies (including intra-individually). Diagnostic assessment should also include the much more common non-immunological intolerances and diseases of other etiology.

Since it is rarely clear at the patient's first visit to a medical practice whether a food intolerance is of non-immunological or immunological etiology or is due to a combination of the two mechanisms, diagnosis of food allergy should focus not only on identifying a specific trigger factor but should also include a detailed evaluation of the possible differential diagnoses and therefore attempt to distinguish the patient's condition from other chronic diseases.

General principles of allergy diagnosis

For the diagnosis of food allergy it should be considered that different sensitivities and specificities may be observed between the various diagnostic tests, depending on the Coombs and Gell type I–IV allergy (*Figure 4*), systemic or local manifestation, type of symptom onset (immediate: <2 hours, intermediate: 2 to 24 hours, delayed >24 hours), intestinal or extraintestinal manifestation, the disease group examined, the allergen present, and the medical discipline involved (2, 4, 8–11, 15, 16). The experienced clinician will therefore base his or her diagnostic strategies and procedure on a precise medical history, physical examination, and an analysis of the pattern of symptoms and time course. Demonstration of a provoked, allergen induced reaction

Salicylate intolerance

The prevalence of salicylate intolerance is 2.5% in Europe.

Food allergy

Food allergy shows the greatest complexity among the food intolerances and allergic diseases.

BOX

Examples of common cross-allergies*1

- **Pollen associated food allergies**
Tree pollen (birch, alder, hazelnut) + **pomaceous fruit** (apple, pear, cherry)
 + **nuts** (hazelnut, walnut, pistachio)
Grass, cereal pollen + flours (wheat, rye, oats) + **tomato, kiwi, celery**
- **Celery-mugwort-spice syndrome**
Mugwort pollen + spice (aniseed, parsley, chamomile) + **celery, raw carrot, nuts**
- **Latex fruit syndrome**
Latex products + fruit (pineapple, kiwi, avocado) + **potato, banana, nuts**
- **Other cross-reactive allergies**
Feathers (e.g. bird species) + **hen's egg + poultry meat + giblets**
House dust mite allergy + crustaceans and molluscs

*1 modified from (8, 16)

in the patient or organ system is regarded as the gold standard (2, 6, 11, 16). Diagnostic approaches vary according to the allergy specialist and dermatologist (e.g. oral allergy syndrome, cutaneous reactions), the lung specialist and otorhinolaryngologist (e.g. nasal or bronchial obstruction) or the internal specialist and gastroenterologist (e.g. abdominal cramps, colitis), since they are dealing with different patient clientèles, differential diagnoses, cross reactions (*box*), and types of allergies. Clear guidelines are available for IgE-mediated food allergies (6, 17), although the frequency of IgE-mediated food allergies varies among young children and adults and between the different allergens and organ manifestations (4, 6, 8, 9, 11, 15–17). In contrast to seropositive IgE-mediated food allergy, for the non-IgE-mediated reaction and for atypical, oligosymptomatic or chronic disease manifestations a more extensive, differentiated, stepwise diagnostic procedure is often required before provocation testing is performed (2, 4, 9, 11, 18, 19).

Stepwise diagnostic procedure for food allergies

Specific allergological routine diagnosis begins with taking a dietary history, completing a nutrition diary,

performing skin tests (e.g. prick test) for food extracts, environmental antigens, mould fungi, spices etc., assay of total IgE and the suspected allergen specific IgE antibodies in serum, in order to detect evidence of IgE specific sensitization (4, 8–11, 20). If clinically unequivocal postprandial reactions are observed which are consistent with the results of skin tests and antigen specific IgE sensitization, this diagnostic approach can in many cases already exactly define and identify the IgE-mediated allergic disease (1, 4, 8, 10, 20). With the typical combination of intestinal and extraintestinal symptoms immediately after allergen ingestion with monovalent or oligovalent sensitization, oral provocation testing in atopy (IgE-mediated allergy) is confirmatory in nature but is still regarded as the diagnostic gold standard (9–11, 16). If the elimination diet is unequivocally successful with this constellation, oral provocation as a confirmatory reaction is unnecessary from the clinical perspective.

The diagnosis of food allergy becomes much more difficult if oligo- to polyvalent IgE sensitizations are present, if the patient's symptoms are atypical (chronic clinical picture) or if local IgE-mediated or delayed reactions (non-IgE-mediated allergy types II–IV), or contradictory signs of sensitization are present. Although the structured, blinded oral provocation test is the gold standard in this case, with this constellation initially the

Gold standard

Demonstration of a provoked allergy-induced reaction in the patient or organ system is regarded as the gold standard.

Stepwise diagnostic procedure for food allergies

- Dietary history
- Nutrition diary
- Skin tests
- Total IgE assay

non-immunologically mediated differential diagnoses should be considered and ruled out and oral provocation testing should be placed at the end of the diagnostic chain. Besides the aforementioned diagnostic modalities for IgE-mediated food allergies, a search is made for signs of a non-IgE-mediated food allergy that show to what extent the suspicion of an allergic reaction is justified (Figure 3). When important differential diagnoses are ruled out and the routine diagnostic parameters (skin tests, antigen specific IgE) are uninformative, the presence of a local IgE-mediated (seronegative) form of allergy, a non-IgE mediated allergy, or an intolerance may be considered (1, 9–11, 18, 20–22). For non-IgE-mediated type II–IV allergies, the diagnostic repertoire is much smaller than for systemic immediate-type reactions.

Possible signs of delayed type II–IV food allergies are (9–11, 15, 17, 21, 23, 24):

- the delayed positive skin test evaluated after 24 to 48 hours
- determination of the C3 and C4 complement factors (consumption in type II)
- detection of immune complexes (IC-IgG, -IgA, -IgM and -IgE; for type III)
- cytokine analysis (tumor necrosis factor alpha, interferon; for type IV).

As an important supplementary component it is also recommended to use screening techniques to detect the presence of an allergic disease in the gastrointestinal tract or increased mediator production with excretion of methylhistamine in 12-hour urine; allergen identification can then be achieved through targeted gastroenterological allergy testing (4, 11, 20, 21). The methylhistamine test shows that patients with food allergies and involvement of the gastrointestinal tract eliminate significantly more methylhistamine after ingesting whole food than on a hypoallergenic elimination diet, such as a hypoallergenic potato-rice diet. Mediator production is diet related. In mastocytosis patients it is much higher and remains elevated at a constant level on different types of diet. Although this simple functional test for methylhistamine excretion in urine is not specific for food allergies, it is very useful for providing objective evidence of histamine related symptoms (3). This test determines endogenous histamine, which should be distinguished from exogenously supplied histamine which can induce histamine intolerance.

If the clinical problem cannot be defined with the usual IgE and/or non-IgE based routine diagnostic tests

(Figure 3) in the presence of elevated methylhistamine excretion, either an oral provocation test (extraintestinal symptoms) or more extensive medical differential diagnostic tests with targeted endoscopic allergy diagnosis (intestinal symptoms) is advisable. A specimen can be taken endoscopically. Immunohistochemical analysis is then performed to determine

- whether and in which intestinal segments intestinal eosinophilia or increased numbers of mast cells are present
- whether gross lesions are present in these segments and whether intestinal IgE antibodies (local type I allergy) or increased TNF alpha (local type II to IV allergy) are produced in the intestinal secretion as the expression of an allergic gastrointestinal tract (2, 4, 17, 18, 21, 23–25).

For detection of the intestinal IgE antibodies it is recommended to perform endoscopically controlled segmental intestinal lavage (20, 22), which includes the entire gastrointestinal tract, but which is particularly effective in the terminal ileum, cecum, and rectosigmoid junction (20). Patients with food allergies and atopy or local Th2 immunodominance (seronegative type I allergy) much more commonly have intestinal IgE in the relevant intestinal segments. The combination of IgE and eosinophilic cationic protein (ECP) from the endoscopic lavage has proved to be a good predictive parameter for recognizing allergic bowel disease (2, 20). It can be diagnosed against which foods the intestinal IgE antibodies are directed. In patients with non-IgE-mediated allergy (types II–IV) it was found that no intestinal IgE is usually present in the lavage, and rather that elevated TNF concentrations are found in the absence of inflammation.

In combination with the results of the medical history, cutaneous, serological or intestinal IgE analysis (skin, blood, intestine) and the intestinal cytokine concentrations, finally, a potential range of allergens corresponding to the presumed allergy type (IgE versus non IgE) are assessed for their clinical relevance in the provocation test (2, 11, 16). The guidelines recommend standardized oral provocation testing (6, 11, 22). Alternatively, mucosal oxygenation and segmental intestinal lavage can be used to test the suspected foods. To obviate the need for elaborate oral provocation testing, the trigger allergens are identified ex vivo on the basis of their quantitative mediator and cytokine release (2, 21, 23) (see supplementary case report). Although this method is not explicitly included

Stepwise diagnostic procedure for food allergies:

Detection of an allergic disease in the gastrointestinal tract or increased mediator production by methylhistamine excretion testing.

Detection of intestinal IgE antibodies

Endoscopically guided segmental intestinal lavage is recommended in the entire gastrointestinal tract, and is most effective in the terminal ileum, cecum, and at the rectosigmoid junction.

in the guidelines at present, it was evaluated in comparison to blinded oral provocation testing and was found to be a valuable additional diagnostic resource for gastrointestinal allergic manifestations, when oral provocation is too hazardous or if the patient refuses provocation testing (2, 21, 23, 25).

Differential diagnosis of diseases associated with food intolerances

If non-specific evidence of food reactions is found, other conditions which may present with symptoms similar to those seen in intolerances or allergies should be ruled out, such as chronic inflammatory bowel diseases, chronic pancreatitis, irritable bowel syndrome, eosinophilic gastroenteritis, systemic mastocytosis, celiac disease, and microscopic colitis.

Infections

The commonest (chronic) infections are lambliasis, chronic salmonellosis, infections with *Blastocystis hominis*, but also infections caused by parasites such as ameba, ascaris, pinworms, and *Strongyloides*. Further infections which because of infection-triggered immune responses (skin reactions, eosinophilia, IgA elevation, diarrhea) direct suspicion towards food intolerance as the cause of the symptoms, are urogenital infections and/or bacterial overgrowth.

Mastocytosis

The symptoms of systemic mastocytosis can include not only cutaneous signs but also episodic gastrointestinal complaints such as nausea, burning abdominal pain, diarrhea, ulcer diseases, gastrointestinal bleeding and malabsorption (60% to 80% of affected patients) (e1). The severity of the symptoms can vary from mild nausea and pain to acute gastric ulcer and bleeding. The symptoms resemble those of the underlying diseases, most likely histamine intolerance or food allergy. The causal factor is the triggered release of mediators from immature proliferating mast cells in the bone marrow, gastrointestinal tract, or skin (e2). Release may occur spontaneously and may be triggered by a wide variety of physical, pharmacological, and/or psychological stimuli.

The pathogenesis of systemic mastocytosis is based mainly on a mutation of transmembrane c-kit receptor tyrosine kinase, which is responsible for the proliferation and maturation of mast cells. Tyrosine kinase usually requires stem cell factor for this process. The receptor can become permanently activated due to a mutation of

TABLE 2

Differential diagnosis of food allergy

Differential diagnoses	Findings/diagnostic interventions
Anaphylaxis	Allergen, specific IgE, serum tryptase
Angioedema	Skin changes, C1 inactivator
Carcinoid	Prostaglandins, serotonin, NSE, chromogranin
Pheochromocytoma	Blood pressure, catecholamines in urine
Mastocytosis	Mediators of mast cell activation
Neuroendocrine tumors (VIP, Zollinger-Ellison syndrome etc.)	VIP, gastrin in serum, NSE, chromogranin
T-cell lymphomas	B-symptoms, β 2-microglobulin, bone marrow

the c-kit, however, and thereby increase mast cell proliferation and also facilitate the release of mast cell mediators (e1).

A symptom scoring system and the determination of serum tryptase and methylhistamine excretion in urine are central diagnostic indicators. The diagnosis has to be confirmed by a histological analysis of tissue (skin, gastrointestinal tract) or bone marrow biopsy to demonstrate mast cell infiltration.

The most important therapeutic measures are:

- avoiding the known trigger factors
- mast cell stabilization (cromoglycate, corticosteroids, cyclosporin)
- reducing mast cell growth (cladribine, interferon)
- antagonizing secreted mediators (H_1 and H_2 antihistamines, leukotriene receptor blockers) (e2).

The first therapeutic studies evaluating multityrosine kinase inhibitors such as imatinib as a further option are now available (e3).

Eosinophilic esophagogastritis

A characteristic feature of eosinophilic esophagogastritis is eosinophilic infiltration of the esophageal, gastric and intestinal mucosa. Isolated organ segments or their combinations may be affected (1, 2, 4). The typical complex of symptoms consists in episodic abdominal pain, nausea, vomiting, and diarrhea.

In 40% to 65% of patients eosinophilia is found in the differential blood count. Chronic inflammatory bowel diseases, parasitic infections, and tumors should be excluded. In addition, evidence of allergy with IgE

Associated diseases are

- infections (such as lambliasis, chronic infections or bacterial overgrowth)
- mastocytosis
- eosinophilic esophagogastritis

Indicators of mastocytosis

- Cutaneous signs
- Episodic gastrointestinal symptoms such as nausea, burning abdominal pain, diarrhea
- Ulcer disease
- Gastrointestinal bleeding and malabsorption

elevation or evidence of specific IgE is present in 40% to 50% of patients as evidence of an associated food allergy. Esophagogastroduodenoscopy and colonoscopy with biopsy specimens should be performed for diagnostic clarification. With abstinence, a hypoallergenic liquid diet, and medical treatment (antihistamines, budesonide, cromoglicic acid, and prednisolone), the prognosis is very good.

Neurovegetative, psychological and somatoform disorders

In addition to other rare organic differential diagnoses (table 2), food related symptoms should always prompt consideration of a possible psychological, neurovegetative, or somatoform component (for example an eating disorder).

There has been little research to date on the relationship between food allergies and intolerance reactions and psychological symptoms and stress factors has been little researched to date. However, the study results available thus far suggest the existence of indirect and direct interactions (1, 11). For example, psychoimmunoneurological testing has now shown that following the release of adrenaline as a response to stress, mast cells are stimulated through noradrenergic nerve fibers and react by releasing messenger substances such as histamine. On the other hand, chronic physical distress such as a food intolerance is in itself also a psychological stressor which compromises quality of life and can secondarily induce or exacerbate depression and anxiety disorders.

Conflict of interest statement

The authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

Manuscript received on 26 January 2009, revised version accepted on 29 April 2009.

Translated from the original German by mt-g.

REFERENCES

1. Crowe SE, Perdue MH: Gastrointestinal food hypersensitivity: basic mechanisms of pathophysiology. *Gastroenterology* 1992; 103: 1075–95.
2. Raithel M HE, Baenkler HW: Klinik und Diagnostik von Nahrungsmittelallergien (Gastrointestinal vermittelte Allergien Grad I–IV). *Dtsch Arztebl* 2002; 99(103): 717–28.
3. Teitelbaum JE FG: Immune mechanisms of food allergy. *Curr Opin Gastroenterol* 1998; 14: 498–503.
4. Aiuti F, Paganelli R: Food allergy and gastrointestinal diseases. *Ann Allergy* 1983; 51(2 Pt 2): 275–80.

5. Baenkler H: Salicylatintoleranz: Pathophysiologie, klinisches Spektrum, Diagnostik und Therapie. *Dtsch Arztebl* 2008; 105(8): 137–42.
6. Bruijnzeel-Koomen C OC, Aas K et al.: Position paper: Adverse reactions to food. *Allergy* 1995; 50: 623–35.
7. Knibb RC, Armstrong A, Booth DA, Platts RG, Booth IW, MacDonald A: Psychological characteristics of people with perceived food intolerance in a community sample. *J Psychosom Res* 1999; 47: 545–54.
8. Sampson HA: Food allergy. Part 1: immunopathogenesis and clinical disorders. *J Allergy Clin Immunol* 1999; 103(5 Pt 1): 717–28.
9. Bengtson U N-BU, Hanson LA, Ahlstedt S: Double blind, placebo controlled food reactions do not correlate to IgE allergy in the diagnosis of staple food related gastrointestinal symptoms. *Gut* 1996; 39: 130–5.
10. Lack G: Clinical practice. Food allergy. *N Engl J Med* 2008; 359(12): 1252–60.
11. Vatn MH, Grimstad IA, Thorsen L, Kittang E, Refnin I, Malt U et al.: Adverse reaction to food: assessment by double-blind placebo-controlled food challenge and clinical, psychosomatic and immunologic analysis. *Digestion* 1995; 56: 421–8.
12. Giera B, Straube S, Konturek P, Hahn EG, Raithel M: Plasma histamine levels and symptoms in double blind placebo controlled histamine provocation. *Inflamm Res* 2008; 57 Suppl 1: S73–4.
13. Jarisch R GM, Hemmer W, Missbichler A, Raithel M, Wantke F: Histamin-Intoleranz. Histamin und Seekrankheit. 2. Aufl. Stuttgart, New York. Thieme Verlag 2004.
14. Mahler V: Bei Weinüberempfindlichkeit gibt es viele Verdächtige. *Allergo J* 2008; 17: 432.
15. Iacono G, Ravelli A, Di Prima L, Scalici C, Bolognini S, Chiappa S et al.: Colonic lymphoid nodular hyperplasia in children: relationship to food hypersensitivity. *Clin Gastroenterol Hepatol* 2007; 5: 361–6.
16. Kleine-Tebbe J, Ballmer-Weber B, Beyer K et al.: In-vitro Diagnostik von IgE-vermittelten Nahrungsmittelallergien. Leitlinie der Deutschen Gesellschaft für Allergologie und klinische Immunologie (DGAKI), des Ärzteverbandes Deutscher Allergologen (ÄDA) sowie der Gesellschaft für Pädiatrische Allergologie und Umweltmedizin (GPA) in Kooperation mit der Österreichischen Gesellschaft für Allergologie und Immunologie (SGAI). *Allergo J* 2009; 18: 132–46.
17. Niggemann B ES, Fuchs Th, Henzgen M et al.: Standardisierung von oralen Provokationstests bei IgE-vermittelten Nahrungsmittelallergien. Aktualisierte Leitlinie der Deutschen Gesellschaft für Allergologie und klinische Immunologie (DGAKI), des Ärzteverbandes Deutscher Allergologen (ÄDA) sowie der Gesellschaft für Pädiatrische Allergologie und Umweltmedizin (GPA). *Allergo J* 2006; 15: 262–70.
18. Andre F, Andre C, Colin L, Cavagna S: IgE in stools as indicator of food sensitization. *Allergy* 1995; 50: 328–33.
19. Moneret Vautrin DA, Sainte-Laudy J, Kanny G: Ulcerative colitis possibly due to hypersensitivity to wheat and egg. *Allergy* 2001; 56: 458–9.
20. Raithel M, Weidenhiller M, Abel R, Baenkler HW, Hahn EG: Colorectal mucosal histamine release by mucosa oxygenation in comparison with other established clinical tests in patients with gastrointestinally mediated allergy. *World J Gastroenterol* 2006; 12: 4699–705.
21. Paajanen L, Vaarala O, Karttunen R, Tuure T, Korpela R, Kokkonen J: Increased IFN-gamma secretion from duodenal biopsy samples in

Eosinophilic esophagogastritis
is characterized by eosinophilic infiltration of the esophageal, gastric and intestinal mucosa.

Neurovegetative psychological and somatoform disorders
Research results to date suggest indirect and direct interactions between food allergies/intolerance reactions and psychological symptoms.

- delayed-type cow's milk allergy. *Pediatr Allergy Immunol* 2005; 16: 439–44.
22. Schwab D, Raithel M, Klein P, Winterkamp S, Weidenhiller M, Radespiel-Troeger M et al.: Immunoglobulin E and eosinophilic cationic protein in segmental lavage fluid of the small and large bowel identify patients with food allergy. *Am J Gastroenterol* 2001; 96: 508–14.
23. Heyman M, Darmon N, Dupont C, Dugas B, Hirribaren A, Blaton MA et al.: Mononuclear cells from infants allergic to cow's milk secrete tumor necrosis factor alpha, altering intestinal function. *Gastroenterology* 1994; 106: 1514–23.
24. Weidenhiller M, Muller S, Schwab D, Hahn EG, Raithel M, Winterkamp S: Microscopic (collagenous and lymphocytic) colitis triggered by food allergy. *Gut* 2005; 54: 312–3.
25. Molderings G KU, Scheurlen Ch, Brüss M, Frieling Th, Raithel M, Homann J: Die gastrointestinal betonte systemische Mastzell-erkrankung – Checkliste zur Diagnosefindung. *Dtsch Med Wochenschr* 2006; 131: 2095–100.

Corresponding author

Dr. med. Yurdagül Zopf
 Medizinische Klinik 1
 Universitätsklinikum Erlangen
 91054 Erlangen, Germany
 yurdaguel.zopf@uk-erlangen.de



For e-references please refer to:
www.aerzteblatt-international.de/ref2109

Case report, e-Box, and e-Tables available at:
www.aerzteblatt-international.de/article09m359

Further Information on CME

This article has been certified by the North Rhine Academy for Postgraduate and Continuing Medical Education.

Deutsches Ärzteblatt provides certified continuing medical education (CME) in accordance with the requirements of the Chambers of Physicians of the German federal states (Länder). CME points of the Chambers of Physicians can be acquired only through the Internet by the use of the German version of the CME questionnaire within 6 weeks of publication of the article, i.e., by 5 June 2009. See the following website: cme.aerzteblatt.de

Participants in the CME program can manage their CME points with their 15-digit "uniform CME number" (einheitliche Fortbildungsnummer, EFN). The EFN must be entered in the appropriate field in the cme.aerzteblatt.de website under "meine Daten" ("my data"), or upon registration. The EFN appears on each participant's CME certificate.

The solutions to the following questions will be published in volume 28–29/2009. The CME unit "Disorders of Pubertal Development" (volume 17/2009) can be accessed until 5 June 2009.

For volume 25/2009 we plan to offer the topic "Constipation."

Solutions to the CME questionnaire in volume 13/2009:

Geißler HJ, Schlensak C, Südkamp M, Beyersdorf F : Heart Valve Surgery Today: 1c, 2b, 3d, 4a, 5b, 6d, 7c, 8e, 9a, 10e

Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1:

Which food intolerance is the commonest among all reactions to foods?

- a) Non-immunological
- b) Immunological
- c) Somatoform
- d) Mastocytosis related
- e) Infectious

Question 2:

How high is the prevalence of food allergies in adults?

- a) 0% to 1%
- b) 2% to 5%
- c) 6% to 8%
- d) 9% to 11%
- e) 12% to 14%

Question 3:

What is a possible cause of a functional food intolerance?

- a) Achalasia
- b) Chronic pancreatitis
- c) Right ventricular failure
- d) Obstructive jaundice
- e) Enzyme deficiency disorder

Question 4:

Which symptom is typical of carbohydrate malabsorption?

- a) Melena
- b) Constipation
- c) Steatorrhea
- d) Diarrhea
- e) Hematochezia

Question 5:

What is detected with segmental intestinal lavage?

- a) IgD antibodies
- b) IgA antibodies
- c) IgM antibodies
- d) IgE antibodies
- e) IgG antibodies

Question 6:

What is a classical symptom of salicylate intolerance?

- a) Sinus tachycardia
- b) Sinusitis
- c) Chronic venous insufficiency
- d) Retrosternal pain on pressure
- e) Heart failure

Question 7:

With which medication can a small bowel bacterial overgrowth occur?

- a) Proton pump inhibitor
- b) ACE inhibitor
- c) Anticoagulants
- d) Anticonvulsants
- e) Antihypertensives

Question 8:

Which etiological agent is most commonly associated with food intolerances?

- a) Norovirus
- b) Clostridium difficile
- c) Giardia lamblia
- d) Helicobacter pylori
- e) Enterohemorrhagic *Escherichia coli*

Question 9:

How is eosinophilic esophagogastroenteritis treated?

- a) Reduction diet, non-carbonated mineral water, betamethasone
- b) Mashed food, wormwood tea, cortisone
- c) Parenteral nutrition, antibiotics, abstention oral fluids
- d) Fasting, hypoallergenic liquid diet and prednisolone
- a) Enteral nutrition, high-calorie liquid diet, dexamethasone

Question 10:

Of what intolerance is an X-chromosomally inherited enzyme deficiency the cause?

- e) Trehalase deficiency
- f) Lactase deficiency
- g) Glucose-6-phosphate dehydrogenase deficiency
- h) Alcohol dehydrogenase deficiency
- i) Galactase deficiency

CONTINUING MEDICAL EDUCATION

The Differential Diagnosis of Food Intolerance

Yurdagül Zopf, Hanns-Wolf Baenkler, Andrea Silbermann, Eckhart G. Hahn, Martin Raithe

Case Report

The Differential Diagnosis of Food Intolerance

Case 1

A 51-year-old female patient with long history of ulcerative colitis proved refractory to the standard treatment with mesalazine and steroids.

She reported recurrent postprandial symptoms and acute episodes. The patient has a history of polinosis and chronic eosinophilia. Serological tests showed IgE (92 U/L) still in the upper range of normal and an elevated methylhistamine level in urine (14 µg/mmoL creatinine x m² BSA [BSA, body surface area]). The functional blood test using peripheral leucocytes incubated with 5-acetylsalicylic acid showed a pathological result. This was confirmed clinically by oral provocation followed by bloody diarrhea and fever.

Abstinence from salicylates in foods and medications including mesalazine led to complete remission of the ulcerative colitis.

As a differential diagnosis for ulcerative colitis, the patient may retrospectively be seen to have had allergic enterocolitis or salicylate intolerance colitis spuriously presenting as ulcerative colitis over a period of years. This underlines the wide range of symptoms observed in patients with food intolerance and clearly illustrates that structured diagnosis is indispensable to verify the reported symptoms.

Case 2

A 47-year-old female lawyer with first diagnosis of ulcerative proctosigmoiditis in 1998. No other diseases known. Family history of atopic dermatitis.

The patient received drug treatment for the colitis with prednisolone and 5 ASA from 1998 to 2003.

The patient reported recurrent postprandial symptoms with bloody diarrhea and abdominal pain, especially after consuming bread and pastries. For more than three years she had also noticed intolerance of legumes and oranges.

Prick testing

Positive skin reaction to house dust mites, negative to spices, foods and mold fungi. Serology: no elevated IgE (27 U/L), no specific IgE against foods. Antibody against transglutaminase was negative.

Diagnostic evaluation with oral provocation could not be performed due to the patient's professional commitments.

Segmental endoscopic lavage

An elevated total IgE value of 9.3 U/mg protein was determined in the rectum (normal range <0.35 U/mg protein) and a specific IgE to soya (0.60 U/mg protein), rye flour (0.80 U/mg protein) and wheat flour (0.55 U/mg protein) (22).

Mucosa oxygenation

Testing of the viable intestinal biopsies for the mediators histamine, eosinophil cationic protein, mast cell tryptase and TNF-alpha revealed significantly concentration-dependent increased release of these immune mediators on rye (23).

An elimination diet of wheat, rye and soya produced a complete remission which has now been persisting for more than four years. Concluding diagnosis: local (seronegative), IgE-mediated allergic enterocolitis.

CONTINUING MEDICAL EDUCATION

The Differential Diagnosis of Food Intolerance

Yurdagül Zopf, Hanns-Wolf Baenkler, Andrea Silbermann, Eckhart G. Hahn, Martin Raithel

E-REFERENCES

- e1. Horny HP SK, Valent P, Hartmann K: Mastocytosis— A Disease of the Hematopoietic Stem Cell. *Dtsch Arztebl Int* 2008; 105(40): 686–92.
- e2. Buske-Kirschbaum A, Geiben A, Hellhammer D: Psychobiological aspects of atopic dermatitis: an overview. *Psychother Psychosom* 2001; 70: 6–16.
- e3. Vega-Ruiz A, Cortes JE, Sever M, Manshouri T, Quintas-Cardama A, Luthra R et al.: Phase II study of imatinib mesylate as therapy for patients with systemic mastocytosis. *Leuk Res* 2009.

CONTINUING MEDICAL EDUCATION

The Differential Diagnosis of Food Intolerance

Yurdagül Zopf, Hanns-Wolf Baenkler, Andrea Silbermann, Eckhart G. Hahn, Martin Raithe

E-BOX**● Foods with high histamine content**

Especially microbially produced foods (e.g. long ripened cheese, pickled cabbage, red wine) and microbially contaminated high-protein diet (e.g. tuna fish, mackerel, sausage)

● Foods that inhibit diaminoxidase

Especially other amines (black tea, maté tea, colorants), alcohol

● Foods that release increased amounts of histamine

Citrus fruits, nuts, wheat germ, alcohol (acetyldehyde)

● Other accompanying factors that promote histamine release

Infections, sports, emotional upset (stress), chronic diseases (e.g. chronic renal insufficiency), medications (NSAIDs, acetylsalicylic acid (ASA), metamizole, radiographic contrast media, opiates)

CONTINUING MEDICAL EDUCATION

The Differential Diagnosis of Food Intolerance

Yurdagül Zopf, Hanns-Wolf Baenkler, Andrea Silbermann, Eckhart G. Hahn, Martin Raithel

E-TABLE 1

Common allergens in food allergies

Children, adolescents	Adults
Cow's milk, milk constituents Hen's eggs (albumin), wheat Nuts, soya products Fruit Mould fungus products Vegetables, cereals Meat, fish	Nuts, soya products, celery, pollen-associated foods (e.g. fruit) Wheat, rye Vegetables, oats, milk constituents Fish, seafood, meat Mould fungus products Cow's milk, hen's eggs Poultry

E-TABLE 2

Salicylate content of foods as nutritive triggers of symptoms in salicylate intolerance

Food	Salicylate content (mg/kg)
Curry	2180
Peppers	2030
Oregano	660
Mustard	260
Cayenne pepper	176
Sultanas	78
Raisins	66
Pepper	60
Oranges	23
Apples	4
Pears	3
Potatoes	1–3
Bananas	0.1