

Educational Clinical Case Series

Differential diagnosis of food-induced symptoms

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The symptoms of patients presenting with non-allergic food-related reactions may partly mimic allergic responses. Therefore, correct delineation of food allergies is often difficult and various differential diagnoses have to be considered. We describe three cases of differential diagnoses to food-induced symptoms: A 14-month-old with lactose intolerance, an 8-month-old with severe diet-induced malnutrition and subsequent development of kwashiorkor and a 12-yr-old with chronic urticaria due to colouring agents. These cases represent common symptom constellations involving food-induced reactions. A proper and correct diagnosis of food-related symptoms is particularly important for children – not only in order to find the appropriate diet but also to avoid unnecessary exclusion diets, which may lead to severe impairments in growth and development.

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Patients with non-allergic food-related reactions may present with manifold symptoms, partly mimicking allergic responses. Food allergy is an adverse immune response to food proteins, and the symptoms often involve the skin, the gastrointestinal tract or the respiratory tract. To date, the two best understood pathomechanisms allow a distinction between immunoglobulin E (IgE)-mediated and non-IgE-mediated reactions. IgE-mediated reactions lead mostly to the quick onset of clinical symptoms, non-IgE-mediated reactions have a more delayed clinical manifestation (1).

Although almost any food can cause immune responses, the most common offending foods include cow's milk, hen's egg, peanut, wheat, soya, tree nuts, fish and shellfish (2, 3). Food allergy affects about 6% of young children and 2–3% of adults (4). Correct delineation of food allergies is often difficult and various differential diagnoses have to be considered. We describe three cases of differential diagnoses of food-induced symptoms.

Case reports

Case 1

P.N.T. is the first child of non-consanguineous Chinese parents with a positive family history of hay fever and bronchial asthma (mother, grandfather and uncle). Pregnancy and delivery had been uneventful. At 2 months, a moderate atopic eczema was noticed. At 12 months, hospitalization was necessary due to a rotavirus infection. P.N.T. was breast-fed until the age of 14 months, followed by feeding with a cow's-milk formula. Three months after the introduction of the formula, vomiting, extreme flatulence and faltering growth led to a second hospitalization.

Clinical examination revealed a poorly nourished child, whose height and weight had dropped from the 60th percentile to between the 3rd and 10th percentile during the course of the preceding 3 months. Because of the mother's report of increased flatulence and abdominal discomfort shortly after cow's milk consumption, lactose intolerance was quickly diagnosed.

A lactose breath hydrogen test and a genetic test of the -13910 C/T polymorphism confirmed lactose malabsorption and detected a homozygote mutation of the lactase-phlorizin hydrolase (LPH) gene. A lactose-free diet was started. Differential diagnostic work-up including cystic fibrosis, celiac disease and IgE-mediated food allergy (especially to cow's milk) was negative.

Lactose intolerance discussion. Lactase (intestinal LPH) is an enzyme located in the villus enterocytes of the small intestine. It is responsible for hydrolysis of lactose to galactose and glucose (5). Lactase activity is physiologically present in neonates because of their dependency on breast milk. However, between 2 and 3 yr after weaning, an irreversible reduction of its activity starts in the majority of the world's population, which is completed by the age of 5–10 yr (6). In the majority of the world's human population, a transcriptional down-regulation of the LPH gene (LCT) occurs during childhood (so-called lactase non-persistence). In contrast, lactase persistence is an autosomal dominant heritable condition that results in a high level of lactase gene expression throughout adulthood, with sustained lactose tolerance. Lactase persistence has been correlated with a single nucleotide genetic variant (a C $\geq$ T mutation) located 13,910 bases upstream from the lactase structural gene (7). The lactase-persistent phenotype is estimated to be only 5,000–10,000 yr old, consistent with the advantage an adult had to exploit milk as a nutritional source after the introduction of animal husbandry. The lactase-persistent phenotype is most prevalent in North-western Europe (highest frequency in Swedes and Danes) and the frequency is low in the rest of the world, including Asia – our patient was of Asian ethnicity (8).

Secondary hypolactasia can occur because of epithelial damage and is transient and reversible. It is usually characterized by parallel loss of other brush border functions. In children, secondary loss of lactase is a frequent result of viral infections (e.g. rotavirus) or allergy (9). Alactasia or congenital deficiency of lactase is very rare, but a number of cases have been reported (10).

At 12 months, the child in our case report was suffering from diarrhoea and vomiting due to a rotavirus infection. However, his gastrointestinal symptoms improved quickly and he was symptom-free. It was only at about the age of 17 months that vomiting and extreme flatulence incrementally increased. After exclusion of cow's-milk allergy, lactose intolerance was diagnosed by determining the polymorphism. As mentioned

above, although the gradual lactase disappearance usually does not begin until the child reaches pre-school age (2–6 yr), it can also begin later in life. The timing and rate of decline are genetically determined.

'Lactose intolerance' occurs if lactose malabsorption is associated with clinical manifestations such as cramps, bloating, flatulence, abdominal pain and diarrhoea (11). When lactose in milk is not hydrolysed, it remains in the intestine, where gut bacteria start metabolizing it. The bacteria produce copious amounts of gas, which is responsible for the clinical symptoms. In addition to the clinical findings, various tests underline the diagnosis. The lactose breath hydrogen test is a simple way to diagnose lactose malabsorption, based on detection of hydrogen in exhaled air due to undigested lactose fermented by the colonic microflora (12). In detail, after an overnight fast, 0.5–1 g/kg to 12–25 g lactose (in a watery solution) are administered. Hydrogen, produced by enteric bacteria when there is reduced lactose digestion, can be detected in the air the patient exhales. The whole test takes about 2–3 h. In parallel, blood glucose level can be measured every 10–15 min after ingestion. A 'flat curve' indicates individuals with lactose malabsorption, while the lactase persistent has a significant 'top', with an elevation of typically 50–100% within 1–2 h.

Direct measurement of lactase enzyme activity in small intestinal tissue biopsy samples is possible but invasive. A genetic test of the -13910 C/T polymorphism has been approved for adult-type hypolactasia and enables a cheap and easy diagnostic work-up especially in children (13, 14). Regarding the therapeutic management in lactose-intolerant patients with secondary lactase deficiency, a temporary lactose-free diet until recovery of causative disease is recommended. In primary lactase malabsorption, after a temporary lactose-free diet to obtain remission of symptoms lactose should be gradually re-introduced. Only very few people are lactase deficient to such extent that the remedy is total restriction of dietary lactose. The disorder is often dose-dependent. Many adults with primary lactose deficiency can drink 100–200 ml of milk (5–10 g of lactose) without having symptoms. Furthermore, the fat content, osmolality and the delayed gastric emptying augmented by additional ingredients in the different products also contribute to the diet compatibility. It is particularly crucial in children that adequate nutritional support is provided, particularly with regard to calcium and vitamin intake (11).

In summary, in the case of isolated gastrointestinal symptoms to cow's milk, lactose intolerance should be considered, especially if specific IgE is lacking. Non-IgE-mediated cow's-milk allergy with isolated gastro-intestinal symptoms presenting beyond infancy, after cow's milk has been well tolerated over an extended period, is extremely unlikely. Lactose intolerance is a non-allergic food hypersensitivity due to the deficiency of the enzyme lactase, which is required to digest the predominant sugar in milk. Therapeutically, a lactose-free/reduced diet is recommended.

Case 2

N.S. is the third child of German parents with a positive family history of hay fever (father). Pregnancy and delivery had been uneventful. By the age of 2 months, the infant had developed severe atopic eczema and advice was sought from an alternative medical practitioner. On recommendation of this 'healer', the lactating mother weaned the child at 3 months onto a strictly vegan diet. Central to this diet was the exclusion of cow's milk which the 'healer' identified as the main precipitant of the child's eczema. Without any involvement of a dietician, rice milk and some unfortified soya milk were taken as milk substitutes as well as fruits and vegetables. At the age of 8 months, the underweight and lethargic infant presented with massive generalized oedema in a poor clinical state and was immediately admitted to our hospital. He had marked oedema, ascites, hypoalbuminaemia [23.6 g/l (35–50 g/l)], low plasma protein concentrations [33.8 g/l (65–85 g/l)] and low immunoglobulins. Peripheral blood smear showed moderate hypochromia, microcytosis and macrocytosis, and hypersegmented neutrophils, consistent with iron and vitamin B12 deficiency. Furthermore, he suffered from gastro-intestinal infection with rotavirus and skin superinfection with staphylococcus aureus. His eczema had improved over the past few months but remained significant, with no topical immunosuppressants having been used.

Abdominal ultrasound confirmed hepatomegaly and severe ascites. Electrolytes, trace elements, vitamins, amino acids, coagulation factors and iron were supplemented. Allergy diagnostics revealed no sensitization to cow's milk or soya on skin prick or specific IgE testing. After a negative open oral food challenge with cow's milk, his diet was normalized. Slowly, malnutrition was adjusted under the close supervision of our dietician and the boy regained

weight. His eczema responded well to emollients and topical steroids. Consideration was given to the possibility that non-IgE-mediated allergy to soya milk may have been the cause on the child's faltering growth and eczema. However, the dietary history, biochemical markers of malnutrition and lack of worsening symptoms of eczema associated with introduction of soya formula made this unlikely.

Kwashiorkor malnutrition. Infantile malnutrition is rare in industrialized countries, where the most common cause is unconventional ideologically influenced diets. It may be observed in combination with ethnic or religious eating habits, or parental poverty but can also be associated with physical neglect, lack of medical care or food restriction (15–17). In our particular child, atopic dermatitis and an unfounded causal association with cow's-milk allergy was the trigger for starting a strict alternative diet, which led to the above-described grave symptoms. Marasmus and kwashiorkor are clinically distinct manifestations of severe malnutrition, both induced by inadequate protein and energy supply. Whereas marasmus is characterized by wasting and decreased physical activity, but with a relatively normal mental status and appetite, kwashiorkor is characterized by low serum albumin, massive oedema of the hands and feet. The deficiency is predominantly related to the low protein content of the diet, and results in profound irritability, anorexia, a desquamative rash, hair discolouration and an enlarged, fatty liver (18).

Other effects of severe malnutrition include atrophy of the thymus, lowered immune defences with an increased likelihood of opportunistic infections, impairment of renal function (reflected in polyuria, which accounts for dehydration) and decreased bone mass (with mineral loss and delayed ossification). In addition, brain tissue may be atrophic, and neural damage and altered mental functions might occur (15). The factors determining whether kwashiorkor or marasmus develops remain unknown and there are many intermediate forms.

Lactating women who follow a vegan diet out of conviction or for religious reasons and exclusively breast-fed infants of vegan and malnourished mothers are at an increased risk for megaloblastic anaemia (19, 20). In our case, the vegan weaning diet may have been introduced in the misguided belief that the mother was doing the best for the child. As a consequence, the children in such cases are exposed to the risk of impaired neurological development and severe megaloblastic anaemia. The vitamin deficiency

often takes a long time to manifest itself because of normal vitamin re-absorption from bile and vitamin stores, which may last for 3–5 yr. Iron deficiency, which is common in all kinds of vegetarian diet (vegans, lacto-vegetarians, ovo-vegetarians), may mask macrocytosis and a mean corpuscular volume elevation. Other haematological effects in vegetarians may include lower lymphocyte and platelet counts and raised homocysteine and methylmalonic acid levels (21).

Unfortunately, it is by no means uncommon for parents to believe that their child's allergy or atopic dermatitis could be helped by some form of self-imposed strict alternative diet (22, 23). In this context, several case reports have documented severe nutritional deficiencies in infants due to strict alternative diets (16, 24).

In conclusion, an unbalanced and unjustified strict diet in children may lead to severe impairments in weight gain, growth and development. Non-individualized diets should not be recommended. Vegan diets for infants and small children raise pressing ethical concerns. Any diet should be implemented only after a proper diagnosis and under supervision of a dietician.

Case 3

The 12-yr-old S.S. was admitted to our hospital having suffered from chronic urticaria for 6 yr, with intermittent asthma and allergic rhinoconjunctivitis. The only child lived with her mother. Her father suffered from allergic rhinoconjunctivitis and atopic eczema. At 5 yr of age, she developed recurrent episodes of acute urticaria, which diminished spontaneously. Her mother had made an association between these episodes and ingestion of nuts. As a result, the child was avoiding nuts, despite not having had any allergy tests. At the age of 11 and 12 yr, urticaria was observed after consuming various oral antibiotics (including flavouring agents), which had been prescribed due to recurrent upper respiratory tract infections. Urticaria also occurred after consumption of different coloured sweets. A physical examination was unremarkable.

Because of the various symptoms (urticaria, recurrent infections) and the atopic background, a diagnostic work-up was carried out. Normal results were found for blood count, infection parameters and serological tests for hepatitis A, B and C viruses. No pathogens were isolated from stool or throat cultures. Antinuclear antibody, anti-smooth muscle antibody, antineutrophil cytoplasmic antibody, and anti-Ro, anti-La antibodies, cardiolipin and granulocyte cytoplasm antibodies were all negative. Serum IgG,

IgM and IgA levels and IgG subclasses were unremarkable. Serum C3 and C4 levels and lymphocyte subsets were normal. Allergy-diagnostics showed a total IgE of 125 kU/l; no specific serum IgE was detected to common food allergens including nuts. No evidence was found for urticaria after physical challenges with cold or heat, but a dermographism could be elicited.

A pseudo-allergen-free diet was introduced 3 wk before hospitalization. After admittance, a pseudo-allergen-rich meal immediately induced urticarial rash. Single-blind, placebo-controlled provocations with artificial food colourings, benzoate preservative and acetyl acid resulted in negative results for E214, E200, E211, E621, E223. Two placebo provocations also led to no reaction. However, urticaria was elicited after consumption of the following food colourings: Tartrazine (yellow) E102, Sunset yellow E110, Cochineal E122, Amaranth E123, Ponceau 4R E124, Erythrosine E127, Patent blue E131, Indigotine and Indigo carmine E132, Brilliant black E151, iron oxides and hydroxides E127. The child also reacted to 'tutti-frutti' flavouring and cherry flavouring provided by pharmaceutical companies, which added these to the antibiotic preparation that S.S. had reacted to. The girl was treated with H1-antihistamines and in collaboration with our dieticians an avoidance of proved food colouring agents was recommended. Under this treatment, the girl remained symptom-free.

Chronic urticaria to food colouring discussion. In the general population, the estimated incidence of all acute urticaria is 15% to 25% (25). Acute urticaria as a consequence of IgE-mediated food allergy may play a role in some cases. The most common cause, however, are viral infections.

Chronic urticaria (defined as more than 6 wk' duration) may often be diagnosed as physical or idiopathic urticaria. Physical urticaria comprises several forms, such as urticaria factitia (Dermographic urticaria), cholinergic urticaria, delayed pressure urticaria, cold urticaria, solar urticaria, localized heat urticaria and vibration urticaria (26, 27). However, in most cases, a cause for chronic urticaria cannot be identified. In recent years, autoimmune responses have been proposed also in children (28). Indeed, it was shown that children might produce functionally active autoantibodies directed against IgE or IgE receptor. In a group of 93 children with chronic urticaria, Brunette et al. diagnosed autoimmune urticaria in 30% as a result of which the rate of the so-called idiopathic urticaria decreased from 52% to 20% (28). As a diagnostic procedure, the

autologous serum test (ASST) may be used to identify circulating autoantibodies. IgE-mediated sensitization is most often coincidental and not clinically relevant.

Foods or food ingredients are often accused of eliciting urticaria, but a justified relationship is only rarely found. In our case, pseudo-allergic reactions to food additives or to biogenic amines have been proved responsible for the ongoing symptoms (29). In the subgroup of non-IgE-dependent (pseudo-allergic) reactions to food and food ingredients in children with chronic urticaria, Ehlers et al. were able to diagnose pseudo-allergen-induced urticaria in a high percentage of children with suspected food-dependent urticaria. As in our case, the clinical reactions occurred mainly to colouring agents, preservatives, sweeteners and glutamate (30).

In conclusion, most cases of chronic urticaria have an autoimmunological origin and an extensive diagnostic work-up is not necessary. However, with a suggestive history, a specific search is indicated. Oral challenges after a pseudo-allergen-free diet may be meaningful, resulting in a specific diet in proved cases.

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