

Anaphylaxis after wheat ingestion in a patient with coeliac disease: two kinds of reactions and the same culprit food

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In recent years, the role of atopic dermatitis epidermal skin barrier defects in inducing a transcutaneous allergic sensitization is highly debated, possibly explaining why some children with eczema are sensitized to foods they have never eaten. In our specific situation, the association between coeliac disease and wheat allergy might be particularly harmful owing to unavoidable strict food avoidance. We describe the case of a young boy affected by coeliac disease who, after an occasional unexpected ingestion of gluten, experienced a complete anaphylactic reaction characterized by urticarial, labial angioedema, wheezing, and hypotension. To better investigate the state of allergic sensitization to wheat in our patient, we then performed the component resolved diagnosis, which showed Tri a19 2 kU/l and Tri a14 0.3 kU/l. These results demonstrated the association of IgE-mediated allergy to wheat and coeliac disease. The natural course of specific IgE in allergic patients who are on a food-free diet needs further investigation, such as the possible influence that the increasing popularity of gluten-free diets may have on the epidemiology of wheat allergy in westernized societies. National and International registers of cases of anaphylaxis may improve the still limited knowledge in this field. The final message of our contribution is that the decision to eliminate a food should take into account a patient's awareness of possible consequences. Eur J Gastroenterol Hepatol 00:000–000
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We report a case of a demonstrated association of Th1 and Th2 reactions against the same culprit food.

Food allergy is the primary cause of childhood anaphylaxis. It has been hypothesized that exclusion of diets in food allergic children might provoke an increase of food-specific IgE levels and consequently the risk of anaphylaxis [1].

We report the case of a 13-year-old boy who experienced an episode of anaphylaxis to wheat proteins after an exclusion of a diet owing to coeliac disease.

Our patient had a positive family history of allergy to inhalants and drugs. Starting from early infancy, he showed severe atopic dermatitis and recurrent obstructive rhinitis, and at 6 months, he showed urticaria and angioedema after ingestion of egg's proteins and subsequent urticarial after skin contact with egg. Since then he has never introduced the egg into his diet. From the age of 8 years, the child showed persistent rhinitis, episodic conjunctivitis, and for about a year, also several acute asthma events. During the subsequent year, he followed a therapeutic cycle with inhaled Fluticasone with improvement; therefore, only rare episodes

of intermittent asthma persisted. At the age of 3 years old, routine screening laboratory examinations showed the presence of anti-human tissue transglutaminase IgA (66.6 UA; positive > 5), EMA positive; despite the absence of clinical symptoms, a duodenal biopsy confirmed the diagnosis of coeliac disease (type 3a villous atrophy in according to Marsh modified by Oberhuber classification). Consequently, the patient began a gluten-free diet. From age 3 to 11 years, coeliac disease was clinically and serologically well controlled, suggesting a good compliance to gluten-free diet. However, at 11 years old after an unexpected ingestion of a small portion of a food containing gluten pasta at school, he experienced a complete anaphylactic reaction characterized by urticarial, labial angioedema, wheezing, and hypotension.

He was taken to the emergency room where he was first treated with intravenous chlorphenamine 10 mg and hydrocortisone 500 mg, but subsequently it also required the administration of adrenaline 0.3 mg intramuscularly with subsequent intravenous fluid support with crystalloids with gradual recovery. The school ensured that the pasta had been seasoned only with fresh tomatoes, therefore without egg, but that an involuntary exchange took place between the gluten-free pasta and wheat pasta of another classmate.

The boy did not have physical activity after the occasional wheat ingestion and he has no sign of infections during that period.

After the described anaphylactic episode, he was therefore referred to our center to perform in-depth allergological investigations. He showed total serum IgE 790 kU/l and elevated specific IgE for many inhalants and food allergens (Table 1). To better investigate the state of

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allergic sensitization to wheat in our patient, we then performed the component resolved diagnosis, which showed Tri a19 2 kU/l and Tri a14 0.3 kU/l. These results demonstrated the association of IgE-mediated allergy to wheat and coeliac disease (Fig. 1).

Several different classifications of wheat and several different species and subspecies have been described [2].

However, there seem to be no clinically significant differences in allergenicity.

Basically, wheat is a grass from the Poaceae family. The measurement of wheat-specific IgE and its use for clinical diagnosis is problematic owing to the low specificity when using whole-wheat extract as a test allergen either in Skin Prick Tests or in serum assays. Wheat-specific IgE are commonly found among atopic children without true food allergies: up to 65% of the patients with grass pollen allergy had false-positive IgE-Ab test results to wheat extracts [3]. On the contrary, some allergens are under-represented in whole-wheat extract-based tests owing to their relative insolubility. The WHO/International Union of Immunological Societies Allergen Nomenclature Sub-Committee lists 34 wheat allergens (www.allergen.org).

Many of the not-yet clinically well-studied allergens are homologous to characterized grass pollen allergens or seed allergens from related cereals.

The gliadins and glutenins are the major storage proteins in the wheat grain, also making wheat flour suitable

for baking. Each of these fractions contains allergenic proteins that have been associated with clinical symptoms, but little is known also about the allergenic potential as what comes to heating and processing of the fractions.

Among allergenic proteins, Tri a19, also known as Omega-5 gliadin, is a major allergen, along with Tri a14 (a lipid transfer protein that can induce severe, systemic reactions) and Tri a aA TI (mainly involved in baker's asthma, but also responsible for symptoms of food allergy in children).

Anti-gliadin antibodies IgA and IgG, like those detected in coeliac disease, bind to the α-2 gliadin (57–73) [4]. This site is within the T-cell reactive '33-mer' presented by DQ2.5. The 33-mer peptide, a peptide fragment of 33 residues produced by normal gastrointestinal proteolysis of gluten, is a high-affinity substrate for tissue transglutaminase 2, the enzyme that deamidates three glutamines to glutamic. The deamidated 33-mer was found to be an extremely potent T cell stimulator, several-fold more potent than any other known gluten peptide, and seem to be the major actor in the pathogenesis of this autoimmune disease [5].

Omega-gliadin and the high molecular weight glutenin subunit antibodies have been found most commonly in individuals with exercise-induced anaphylaxis and Baker's allergy and represent a potent class of gluten allergens. Nonglutinous proteins in wheat are also allergens; these include LTP (albumin/globulin), thioredoxin-hB, and wheat flour peroxidase [6,7]. A specific five residue peptide, Gln-Gln-Gln-Pro-Pro motif, has been found to be a major wheat allergen [8].

In 2015, the first reported fatal anaphylactic reaction to wheat in a patient with coeliac disease was described.

In that report, the patient was not sensitized to the major allergen Tri a19 but to the lipid transfer protein Tri a 14 and to Tri a aA TI [9].

In a recent study, omega-5 gliadin-specific immunoglobulin E levels were significantly higher in the allergic group than in the tolerant group ($P < 0.01$), and high levels of wheat- or ω-5 gliadin-specific IgE antibodies were identified as risk factors for persistent wheat allergy [10].

In recent years, the role of atopic dermatitis epidermal skin barrier defects in inducing a transcutaneous allergic sensitization is highly debated, possibly explaining why some children with eczema are sensitized to foods they have never eaten. A significant number of patients with

Table 1. Specific IgE for inhalants and food allergens

Allergen	Speicific IgE (< 0.35 kU/l)
<i>Dermatophagoides pteronyssinus</i>	> 100
<i>Dermatophagoides farinae</i>	>100
<i>Alternaria alternata</i>	9.33
Cat epithelium	13.7
Dog epithelium	4.83
<i>Cupressus</i>	1.15
<i>Olea europaea</i>	12.7
<i>Poa pratensis</i>	28.1
<i>Cynodon dactylon</i>	0.92
<i>Parietaria officinalis</i>	0.44
Birch pollen	0.70
Egg white	2.87
α-Lactalbumin	3.42
β-Lactoglobulin	2.49
Casein	0.403
Wheat	14.1

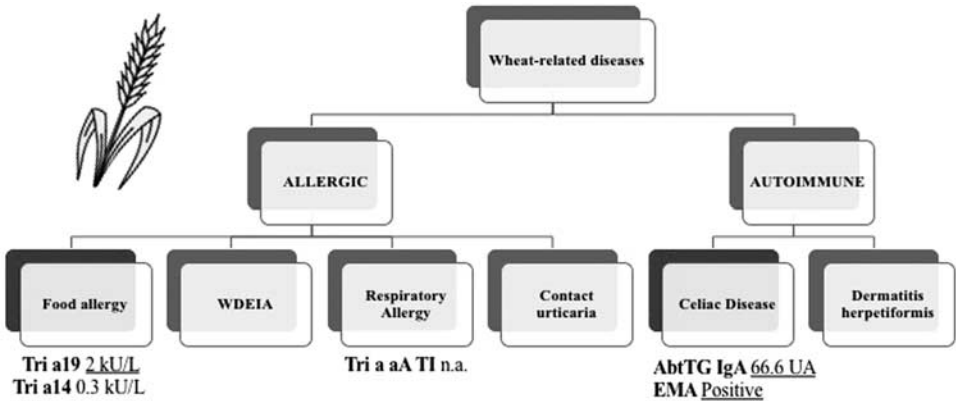


Fig. 1. Wheat-related diseases in our patient. AbtTG, anti-human tissue transglutaminase; NA, not available; WDEIA, wheat-dependent exercise-induced anaphylaxis.

food-triggered atopic dermatitis may develop immediate-type reactions. Strict elimination of diets needs to be thoughtfully prescribed as they may lead to decreased oral tolerance [11].

In our specific situation, the association between coeliac disease and wheat allergy might be particularly harmful owing to unavoidable strict food avoidance. The natural course of specific IgE in allergic patients who are on a food-free diet needs further investigation, such as the possible influence that the increasing popularity of gluten-free diets may have on the epidemiology of wheat allergy in westernized societies. National and International registers of cases of anaphylaxis may improve the still limited knowledge in this field.

The decision to eliminate a food should therefore be able to consider a patient's awareness. All this could allow the best management of accidental ingestion.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

- 1 Barbi E, Berti I, Longo G. Food allergy: from the loss of tolerance induced by exclusion diets to specific oral tolerance induction. *Recent Pat Inflamm Allergy Drug Discov* 2008; 2:212–214.
- 2 Sapone A, Bai JC, Ciacci C, Dolinsek J, Green PH, Hadjivassiliou M, *et al.* Spectrum of gluten-related disorders: consensus on new nomenclature and classification. *BMC Med* 2012; 10:13.
- 3 Constantin C, Quirce S, Poorafshar M, Touraev A, Niggemann B, Mari A, *et al.* Micro-arrayed wheat seed and grass pollen allergens for component-resolved diagnosis. *Allergy* 2009; 64:1030–1037.
- 4 Bateman EA, Ferry BL, Hall A, Misbah SA, Anderson R, Kelleher P. IgA antibodies of coeliac disease patients recognise a dominant T cell epitope of A-gliadin. *Gut* 2004; 53:1274–1278.
- 5 Qiao SW, Bergseng E, Molberg Ø, Xia J, Fleckenstein B, Khosla C, *et al.* Antigen presentation to celiac lesion-derived T cells of a 33-mer gliadin peptide naturally formed by gastrointestinal digestion. *J Immunol* 2004; 173:1757–1762.
- 6 Weichel M, Glaser AG, Ballmer-Weber BK, Schmid-Grendelmeier P, Cramer R. Wheat and maize thioredoxins: a novel cross-reactive cereal allergen family related to baker's asthma. *J Allergy Clin Immunol* 2006; 117:676–681.
- 7 Sánchez-Monge R, García-Casado G, López-Otín C, Armentia A, Salcedo G. Wheat flour peroxidase is a prominent allergen associated with baker's asthma. *Clin Exp Allergy* 1997; 27:1130–1137.
- 8 Tanabe S, Arai S, Yanagihara Y, Mita H, Takahashi K, Watanabe M. A major wheat allergen has a Gln-Gln-Gln-Pro-Pro motif identified as an IgE-binding epitope. *Biochem Biophys Res Commun* 1996; 219:290–293.
- 9 Dondi A, Ricci G, Matricardi PM, Pession A. Fatal anaphylaxis to wheat after gluten-free diet in an adolescent with celiac disease. *Allergol Int* 2015; 64:203–205.
- 10 Koike Y, Yanagida N, Sato S, Asaumi T, Ogura K, Ohtani K, *et al.* Predictors of persistent wheat allergy in children: a retrospective cohort study. *Int Arch Allergy Immunol* 2018; 176:249–254.
- 11 Chang A, Robison R, Cai M, Singh AM. Natural history of food-triggered atopic dermatitis and development of immediate reactions in children. *J Allergy Clin Immunol Pract* 2016; 4:229–236.e1.