

# **Celiac disease and wheat allergy may coexist: two case reports**

**Running title: wheat allergy and celiac disease**

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Wheat flour (*Triticum aestivum*) is certainly the most important global source of foods and it is contained, for instance in bread, pasta, cereals. Wheat, can cause different diseases including: IgE-mediated food allergy, wheat-dependent exercise-induced anaphylaxis, respiratory allergy (Baker's Asthma), celiac disease and non celiac gluten sensitivity. Wheat allergy is an IgE response to any of the proteins present in wheat, including gluten. Its prevalence varies depending on the age and region, from 0.4% to 4% [1], and around 65% of children outgrow this allergy by the age of 12 months.. Celiac disease is an autoimmune disorder with an aberrant response to gluten proteins (present in wheat, barley, and rye) with subsequent atrophy of intestinal villi, impaired intestinal absorption and malnutrition. The symptoms of wheat allergy can range from mild to life-threatening: skin rash, nausea, abdominal pain, vomiting/diarrhea, respiratory symptoms, until anaphylaxis. The symptoms related to wheat allergy usually begin within minutes, more rarely within 1-2 hours. The diagnosis of wheat allergy can be roughly made by skin-prick test or specific serum IgE assay. Nonetheless, the assessment of IgE with the whole wheat extract is poorly sensitive and specific, due to the cross-reactivity with other allergenic molecules. Wheat proteins are classified into albumins, salt-soluble globulins, and insoluble prolamins (gliadins and glutenins). The molecular tests can identify the presence of specific gE against individual components: glutenins, gliadin, omega 5 gliadin, alpha-amylase inhibitors, Lipid Transfer Proteins, Tri a 14 [2, 3]. We report herein, probably for the first time two cases of concomitant celiac disease and IgE-mediated allergy to wheat proteins.

**Case 1.** CS, 15 year-old girl was diagnosed with celiac disease at the age of 6 years, based on symptoms, positive anti transglutaminase IgA level (240 UI/mL, normal value <7 UI/mL, ThermoFisher Scientific, Uppsala Sweden), anti-endomysial IgA (1:256) and duodenal biopsy. She remained on gluten-free diet, with clinical benefit and normalized immunological test. She came to our Emergency Department with generalized urticaria, lip swelling, abdominal pain, diarrhea, vomiting, and respiratory distress (PaO<sub>2</sub>=89 mmHg). She promptly recovered after intravenous methylprednisolone and intramuscular epinephrine. Symptoms had occurred thirty minutes after eating flat bread during a party. No consumption of alcohol or medications could be documented. Tryptase serum levels was increased (14 µg/mL) during the acute phase, but returned normal (7.4 µg/mL) after 48 hours, this supporting the diagnosis of anaphylaxis. IgE to wheat were 1.5 kU/L, with gluten-specific IgE 2.4 kU/L. The molecular diagnosis

revealed a sensitization towards: gliadin (4.9 kU/L), rTri a 19.0101 (omega 5 gliadin) (5.6 kU/L), with Tri a 14 negative. The skin prick test, performed 2 weeks after the episode, were positive for gliadin (ALK-Abellò Copenhagen) (8 mm) but negative for the whole wheat extract. We deduced that the anaphylactic reaction was elicited by omega 5 gliadin. The detailed clinical history revealed that, after years of strict diet the patient started to eat wheat occasionally. The occasional consumption of wheat-containing food, after a long period of gluten-free diet may have induced a sensitization to omega 5 gliadin. The patient was instructed again to avoid the culprit allergens and received the epinephrine self-injector. Despite this, she again had repeated wheat ingestion-induced anaphylaxes. No exercise-induced condition was documented.

**Case 2.** MO. a 54 year-old had a documented celiac disease since the age of 26. She remained therefore on gluten-free diet, but a the clinical history revealed some episodes of anaphylaxis after the ingestion of wheat-containing foods, with raised serum tryptase (15.8 ng/mL), that was normal at baseline (4.3 ng/mL). She was referred to our Emergency Department with hypotension, generalized urticaria, lip swelling, abdominal pain, diarrhea/vomiting, and dyspnea. The episode was rapidly controlled with intramuscular epinephrine, intravenous steroids-antihistamines plus rehydration. The patient was taking nebivolol, that was cautiously withdrawn. She had previously experienced allergic oral syndrome with peach but no systemic signs. The skin prick test performed 3 weeks after the reaction were positive for whole wheat extract (diameter: 7 mm), but negative for gliadin and LTP. Serum IgE were positive for: wheat flour, hazelnut, carrot, peach and apple. The molecular diagnosis showed positive results for: Tri a 14 (3.5 kU/L), nTri a aA\_TI (alpha-amylase) (3.0 kU/L), Mal d 1 (0.5 kU/L), Pru p 1 (0.3 kU/L), Api g 1 (0.2 kU/L), Cor a 1 (0.5 kU/L), Ara h8 (0.5 KU/L). Cor a 8, Ara h 9, and Pru p 3 were negative. No specific IgE against Tri a 19 (omega 5 gliadin) were detected. A detailed education, including a strict dietary conduct, avoided further episodes.

Celiac disease is a gluten-induced immune-mediated condition, characterized by a specific genetic genotype (HLA-DQ2 and HLA-DQ8) with the production of tissue-specific autoantibodies (transglutaminase and endomysium). The inflammatory process specifically targets the intestinal mucosa, but various also non-specific symptoms may be also present, suggesting the systemic nature of the disease [4]. We describe herein, two cases of an exceptional association of celiac disease and documented allergic IgE-

mediated disease (anaphylaxis). There is, indeed another similar case report, but without the molecular diagnosis [5]. The relationship between allergy and autoimmune disorders is complex and poorly understood, especially in wheat allergy-celiac disease, although some hypotheses can be made [6].

Kreiner et al identified shared susceptibility loci and similarities in pathways between allergy and autoimmune diseases, suggesting partially shared mechanisms [7]. The presence of IgE autoantibodies in autoimmune patients is recognized since more than 40 years, but autoantibodies are not associated with a higher rate of atopy. However, recently, IgE were suggested to be active triggers of autoimmunity through mechanisms involving the secretion of Type I interferons by plasmacytoid dendritic cells, recruitment of basophils to lymph nodes, and activation of adaptive immune responses through B and T cells. There is also evidence supporting the role of IgE receptors in the function of dendritic cells. The activation of these cells by the immune complexes of DNA-specific IgE antibodies also can induce the B-cell differentiation and plasma cell formation [8]. The involvement of B cells has also been hypothesized. CD5+ B cells can have a negative regulatory function and their deficiency can worsen both allergic and autoimmune diseases (such as experimental autoimmune encephalomyelitis, chronic colitis and lupus-like models of autoimmunity) [9].

In conclusion, the two clinical cases herein described, would support the possible coexistence of autoimmune and IgE-mediated diseases. The assessment of Tri a 14, gluten, gliadin and omega 5 gliadin specific IgE should be taken into account as a diagnostic marker in patients with ascertained celiac disease, and anaphylaxis [10] after wheat-containing food ingestion. It is reasonable to hypothesize that the occasional consumption of wheat flour-containing proteins could trigger an Ig-E mediated sensitization, superimposed to the pre-existing autoimmune disease.

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## REFERENCES

1. Longo G, Berti I, Burks AW, Krauss B, Barbi E. IgE-mediated food allergy in children. *Lancet*. 2013;382:1656–64.
2. Nilsson N, Sjölander S, Baar A, Berthold M, Pahr S, Vrtala S, et al. Wheat allergy in children evaluated with challenge and IgE antibodies to wheat components. *Pediatr Allergy Immunol*. 2015;26:119-25.
3. Sander I, Rihs H-P, Doekes G, Quirce S, Krop E, Rozynek P et al. Component-resolved diagnosis of baker's allergy based on specific IgE to recombinant wheat flour proteins. *J Allergy Clin Immunol*. 2015;135:1529-37.
4. Leonard MM, Sapone A, Catassi C, Fasano A. Celiac Disease and Nonceliac Gluten Sensitivity: A Review. *JAMA*. 2017;318:647-56.
5. Borghini R, Donato G, Marino M, Casale R, Tola MD, Picarelli A. In extremis diagnosis of celiac disease and concomitant wheat allergy. *Turk J Gastroenterol*. 2018;29:515-17
6. Torres JA, Sastre J, de las Heras M, Cuesta J, Lombardero M, Ledesma A IgE-mediated cereal allergy and latent celiac disease. *J Invest Allergol Clin Immunol*. 2008;18: 407-14
7. Kreiner E, Waage J, Standl M, Brix S, Pers TH, Alves AC, et al. Shared genetic variants suggest common pathways in allergy and autoimmune diseases. *J Allergy Clin Immunol*. 2017;140:771-81
8. Ettinger R, Karnell JL, Henault J, Panda SK, Riggs JM, Kolbeck R, et al. Pathogenic mechanisms of IgE-mediated inflammation in self-destructive autoimmune responses. *Autoimmunity*. 2017;50:25-36.
9. Noh G, Lee JH. Regulatory B cells and allergic diseases. *Allergy Asthma Immunol Res*. 2011;3:168-77.
10. Kennard B, Thomas L, Rutkowski I, Azzu K, Yong PFK, Kastemow B, et al. A multicenter evaluation of diagnosis and management of omega 5-gliadin allergy (also known as wheat-dependent exercise induced anaphylaxis) in 132 adults. *J Allergy Clin Immunol Pract*. 2018;6: 1892-97.