

Celiac Disease and Wheat Allergy: A Growing Association?

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Established Facts

- Celiac disease and wheat allergy (WA) are uncommon diseases, whose association is exceptional currently.
- In both entities, a gluten-free diet is mandatory.

Novel Insights

- The gluten content in gluten-free food could exercise as a source of sensitization.
- The increasing diagnosis of celiac disease could raise the association between celiac disease and WA.

Keywords

Wheat allergy · Celiac disease · Wheat sensitization · Gluten

Abstract

Introduction: Celiac disease and wheat allergy (WA) are infrequent diseases in the general population, and a combination of the 2 is particularly rare. Celiac disease occurs in around 1% of the general population and WA in around 1% of all children. **Case Report:** We report 2 patients with celiac disease and a gluten-free diet who developed WA consistent in anaphylaxis and an eyelid angioedema, respectively, through accidental wheat exposure. A serum study and an intestinal biopsy confirmed celiac disease. Both patients were studied with a skin prick test and serum-specific IgE,

with a diagnosis of WA. **Discussion:** In patients with celiac disease, the trace amounts of cereals present in gluten-free food could act as a sensitization factor, and probably patients with persistent symptoms (despite a gluten-free diet) are experiencing WA symptoms rather than celiac disease symptoms. The number of patients diagnosed with celiac disease has increased in the recent decades: the association between celiac disease and WA, exceedingly rare to date, could increase as well, prompting special attention to the possibility of inadvertent intake of cereals.

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Introduction

Gluten-related disorders (celiac disease [CD], IgE-mediated wheat allergy (WA), and non-celiac gluten sensitivity) have an estimated global prevalence of approximately 5% overall [1], with CD occurring in around 1% of the general population [1, 2] and WA in around 1% of all children [2].

Case Report

We report 2 cases of children with CD who subsequently developed WA.

The first case is a 12-month-old child with hen’s egg and cow milk allergy who started with vomiting, diarrhea, delayed growth, and hypertransaminasemia. Laboratory tests revealed antitransglutaminase IgA antibody (tTG) 47.47 U/mL (reference range, 0.0–10.0) and anti gliadin IgA antibody >100 U/mL (reference range, 0.0–12.0L), normal total IgA (38.4 U/mL), and severe subtotal villous atrophy on duodenal biopsy (stage 3B of the Marsh-Oberhuber classification).

Given the suspicion of CD, the patient was started on a gluten-free diet. Subsequent serologies were negative, including deamidated gliadin peptide antibody.

Due to persistent delayed growth, a challenge test was performed. After reintroducing gluten to the patient’s diet, positive anti-tTG and anti-PDG antibodies were measured (15.94 and 110 U/mL, respectively). A genetic study was consistent with CD susceptibility: the patient expressed HLA DQA1*05 cis HLA DQB1*02.

The rise in specific antibodies after gluten rechallenge and the results of molecular testing and biopsy confirmed the diagnosis of CD. The child started a gluten-free diet once again.

In the second case, a 6-month-old child with hen’s egg and cow milk allergy also presented with delayed growth.

The serological study results were: anti-tTG IgA antibody 0.27 U/mL (reference range 0.0–10.0), anti-gliadin antibody >100 U/mL (reference range 0.0–12.0), and normal total IgA. The duodenal biopsy showed villous atrophy (stage 3A of the Marsh-Oberhuber classification). Anti-endomysium antibodies were also positive, and genetic analysis showed a predisposition to CD (HLA DQA1*05 cis HLA DQB1*02). Thus, a diagnosis of CD was made, and the patient started on a gluten-free diet.

In both patients, at the age of 6 and 7 years, respectively, a diagnosis of rhinoconjunctivitis/asthma due to *Phleum pratense*, *Cynodon dactylon*, and *Olea* sp. pollen sensitization was made.

Subsequently, the first patient developed abdominal pain, vomiting, sneezing, and lacrimation after the accidental intake of gluten-containing bread, and the second patient developed eyelid angioedema after touching wheat flour.

In light of these symptoms of IgE-mediated allergy (anaphylaxis and angioedema, respectively), an allergy panel was performed, including skin prick tests (Alk-Abelló Laboratories) and specific IgE (ImmunoCAP; Phadia) to the most important aeroallergens and cereals. The skin prick test was positive if the wheal diameter was >3 mm to the negative control, and the IgE was considered positive if >0.35 KU/L. The study results confirmed a diagnosis of IgE-mediated WA (Table 1).

Table 1. Allergological study results

	Patient 1		Patient 2	
	IgE kU/L	prick test	IgE kU/L	prick test
IgE total	1,842	/	418	/
<i>Phleum pratense</i>	75.4	+	15.9	+
<i>Cynodon dactylon</i>	N.R.	+	N.R.	+
<i>Olea europaea</i>	>100	+	7.63	+
<i>Triticum aestivum</i>	36.5	+	32	+
Gluten	45.2	+	41	+
Ph p 1, p 5b	75.4		14.2	
Ph p7, p 12	0.02		0.06	
Ole e 1	>100		N.R.	
rTri a 14 LTP	0.38		10.5	
rTri a 19 omega-5 gliadina	0.04		0.28	

The study was performed according to the Helsinki Declaration. A written informed consent was obtained from the parents of both patients. No animals were used for the study.

Discussion

CD and WA are infrequent diseases in the general population, and a combination of the 2 is particularly rare [3–5].

CD is a multi-symptom autoimmune disease, mediated by T and B cells, and its manifestations develop in patients with a genetic predisposition [1, 6], whereas WA is caused by a Th2 response, and its symptoms change according to exposure [2]. These may include asthma and/or rhinitis (Baker’s asthma), urticaria and/or angioedema, and anaphylaxis with or without exercise as a trigger.

More than 20 allergenic proteins have been identified in wheat, and links between these specific proteins and the specific symptoms of WA have been demonstrated in the literature. In our patients, the allergen responsible for WA was probably wheat-LTP (rTri a 14).

Wheat sensitization occurs in approximately 4.5% of the European population [7], probably due to the high prevalence of sensitization to grass pollen in many areas and its cross-reactivity with pollen from wheat and other cereals. However, in a study by Pastorello et al. [8], rTri a 14 was identified as the allergen in 9/22 children with WA, and no cross-reactions among rTri a 14 and grass, rice, peach (rPru p 3), or corn (rZea m 14) were found. In the study by Constantin et al. [9], it was demonstrated that rPh p 1 and 5 are specific markers of grass allergy.

This rules out the hypothesis that wheat sensitization in our patients could be secondary to cross-reactivity with grass pollen.

Other proteins could be involved in WA, such as α -amylase/trypsin inhibitor family and ω 5-gliadin, but these are linked specifically to Baker's asthma and wheat-dependent exercise-induced anaphylaxis [8].

There are 3 possible explanations for wheat sensitization in patients on a gluten-free diet: (1) wheat sensitization may be masked by the abdominal symptoms of CD. Thus, the abdominal symptoms, such as irritability, vomiting, and diarrhea, which are related to CD, could be an indicator of a WA too, although an IgE-mediated allergy is usually accompanied with skin lesions. Digestive symptoms only, as in these cases, could be related to a food protein-induced enterocolitis syndrome rather than to an IgE-mediated hypersensitivity. (2) Wheat sensitization may be lost after cessation of gluten intake in a previously sensitized patient. We do not have skin or blood tests about wheat sensitization before CD diagnosis. (3) Wheat sensitization may start during a gluten-free diet, caused by intermittent/inadvertent intake of trace amounts of cereals. In fact, gluten-free food has a minimal amount of gluten not dangerous for celiac patients but probably responsible for wheat sensitization. In our patients, the third hypothesis appears to be most reasonable.

Regarding the possible causal link between CD and WA, the epitopes recognized by B cells in CD are not the same epitopes recognized in WA or wheat-dependent exercise-induced anaphylaxis, as demonstrated in the literature [8]. This shows that CD and WA are 2 different immune responses to different wheat epitopes. This is not

the first attempt to search a link between CD and a Th2-mediated entity: the hypothesis of a relationship between CD and eosinophilic esophagitis was suggested, but there are no consistent studies supporting this hypothesis [10].

On the other hand, the increased permeability of the bowel mucosa in CD facilitates the passage of allergens and, consequently, sensitization to intermittent intake even of small amounts of cereals.

In our patients, the cause of sensitization may have been the dietary gluten challenge in the first case and the intermittent/inadvertent intake of trace cereals in the second.

This raises 2 questions: first, if the trace amounts of cereals present in gluten-free food could act as a sensitization factor, being the cause of the WA development in patients with a gluten-free diet; and second, if patients with a diagnosis of CD who have persistent symptoms (especially extragastrointestinal ones) despite very little cereal intake could actually experience symptoms of WA and not of CD.

In conclusion, we report 2 cases of patients with CD who developed WA. The number of patients diagnosed with CD has increased in the recent decades [1]. The association between CD and WA, exceedingly rare to date, could increase as well, prompting special attention to the possibility of inadvertent intake of cereals.

Disclosure Statement

None of the authors has conflicts of interest or has received payment regarding this article.

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