Nutrition 118 (2024) 112293

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Case report

A possible unexpected link: Could wheat elimination trigger food protein-induced enterocolitis syndrome in a celiac disease patient?

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ARTICLE INFO

Article History:
Received 9 July 2023
Received in revised form 9 October 2023
Accepted 30 October 2023

Keywords:
FPIES
Celiac Disease
IgE
Food Allergy
Oral Food Challenge

ABSTRACT

Cases of association between celiac disease and wheat allergy have been described in the literature. However, to date, no reported cases have linked celiac disease with wheat food protein-induced enterocolitis syndrome (FPIES). We report a case of this association. A child diagnosed with celiac disease at the age of 2 years, following a gluten-free diet, experienced uncontrollable vomiting, and subsequent hypotension within 2 h of accidental ingestion of wheat flour. As a result, the child required hospitalization for fluid therapy. A similar episode occurred when the child turned 5 y, again resulting from accidental gluten ingestion. This time, the symptoms included vomiting, hypotension, and a loss of consciousness, leading to hospitalization for rehydration treatment. After this second episode, on suspicion of FPIES, the patient was referred to the pediatric allergists, who confirmed the diagnosis. To our knowledge, this is the first case of an association between celiac disease and FPIES.

It has been hypothesized that exclusion diets in food-allergic children may lead to an increase in specific immunoglobulin E levels for those foods and, consequently, the risk of anaphylaxis. However, FPIES is not an immunoglobulin E–mediated condition. Hence, further investigations are warranted to elucidate the underlying mechanisms linking these 2 disorders.

Case report

We report the case of a 6-year-old girl who experienced 2 characteristic episodes of food protein-induced enterocolitis syndrome (FPIES). These episodes occurred after inadvertent wheat ingestion, following its exclusion from her diet because of a confirmed diagnosis of celiac disease (CD).

The girl was born to allergic parents (father: childhood allergic asthma; mother: pollen-induced allergic rhinoconjunctivitis). In the context of an uneventful introduction of solid foods, the girl was introduced to wheat at the age of 6 mo, with tolerance. At 18 mo of age, the patient began experiencing bloating, weakness, anemia, and growth issues. Suspecting CD, laboratory screening tests were conducted. The results revealed a competent total immunoglobulin A (IgA) level, antihuman tissue transglutaminase IgG at 90.00 U/mL (negative threshold <7), and antihuman tissue transglutaminase IgA at 128.99 U/mL (negative threshold <7), along with a positive antiendomysial antibody result.

Considering that the antibody levels were more than 10 times the normal value, in accordance with the latest guidelines, an endoscopy with biopsy was not deemed necessary [1]. Thus, a diagnosis of CD was established, and the patient started a gluten-free diet.

During subsequent follow-up visits, CD was clinically and serologically well-controlled, indicating adherence to the gluten-free diet.

However, at the age of 4 y, after 2 h from accidental ingestion of wheat flour, she developed uncontrollable vomiting (20 episodes) followed by hypotension, requiring hospitalization for fluid therapy. In this instance, blood tests were performed, which showed leukocytosis and an increase in neutrophils.

A similar episode occurred when the child turned 5 y, again resulting from accidental gluten ingestion. This time, the symptoms included vomiting, hypotension, and a loss of consciousness, leading to hospitalization for rehydration treatment.

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https://doi.org/10.1016/j.nut.2023.112293

Table 1
Patient's allergometric tests

Skin prick test for wheat	Negative
Total immunoglobulin E	18.59 IU/mL
Specific immunoglobulin E for wheat (Triticum aestivum)	<0.10 IU/mL

After this second episode, on suspicion of FPIES, she was consequently referred to pediatric allergists for further investigation. The conducted tests, including the skin prick test, yielded negative results. Furthermore, the specific IgE for wheat also returned negative results (Table 1).

These results effectively ruled out the existence of an IgE-mediated wheat allergy but maintained the ongoing clinical suspicion of FPIES in the context of a patient with CD.

The diagnosis of FPIES poses significant challenges, primarily because of the absence of specific biomarkers that can definitively confirm or exclude the condition [2]. Consequently, there is a prevalent diagnostic delay in many cases [2]. FPIES is primarily diagnosed based on clinical features, which, although not exclusive, consistently manifest whenever the patient consumes the triggering food. Several diagnostic criteria for FPIES have been described in the literature; however, ongoing discussions persist [2]. Currently, the most widely used diagnostic criteria are those proposed by the International Consensus on FPIES. According to these criteria, the diagnosis of acute FPIES requires the fulfillment of the major criterion (vomiting occurring 1–4 h after ingestion of the implicated food, without IgE-mediated allergic skin or respiratory symptoms) along with at least 3 minor criteria.

Clinical history is often enough to diagnose FPIES with particular attention to timing of symptoms after ingestion and the triggering food; however, when history alone is not enough, especially in the setting of chronic FPIES, supervised oral food challenges are warranted and considered the gold standard for diagnosis.

We can therefore observe how our patient presented with the major criterion and 6 minor criteria (Table 2).

We report on 2 episodes triggered by the same food. In our patient, in addition to repeated episodes of vomiting approximately 2 h after consuming wheat, exhibited pallor, hypotension, lethargy, and required a visit to the emergency room for fluid therapy.

After diagnosis FPIES, the family, school, and relatives were alerted about the danger of possible contaminations. In the subsequent follow-up, the child is in good clinical condition and has not experienced similar events again. Fortunately, in our specific case, the clinical criteria were sufficient to make a diagnosis of FPIES. It is not possible to perform an Oral Food Challenge with wheat in a child with celiac disease because of the potential consequences.

Table 2
Acute FPIES diagnostic criteria in comparison with our patient

Major criterion
✔ Vomiting in the 1- to 4-h period after ingestion of the suspect food and the absence of classic immunoglobulin E-mediated allergic skin or respiratory symptoms

Minor criteria
✔ A second (or more) episode of repetitive vomiting after eating the same suspect food
✖ Repetitive vomiting episode 1–4 h after eating a different food
✔ Extreme lethargy with any suspected reaction
✔ Marked pallor with any suspected reaction
✔ Need for emergency room visit with any suspected reaction
✔ Need for intravenous fluid support with any suspected reaction
✖ Diarrhea in 24 h (usually 5–10 h)
✔ Hypotension
✖ Hypothermia

Discussion

The pathogenesis of CD revolves around the pivotal role of T lymphocytes.

Wheat, as a member of the Poaceae family, primarily contains gliadins and glutenins, which serve as the key storage proteins in the wheat kernel, rendering wheat flour suitable for baking [3].

In CD, antibodies of the IgA and IgG classes, specifically targeting gliadin, bind to HLA-DQ2 or DQ8 molecules on antigen-presenting cells. This binding event subsequently triggers the activation of CD4+ T lymphocytes located in the lamina propria of the intestinal mucosa. Activated by gliadin, these T lymphocytes migrate from the lamina propria to the subepithelial region, initiating the production of various cytokines, including interferon gamma, interleukin 2, interleukin 4, and tumor necrosis factor-α [3]. The release of these cytokines leads to apoptosis (cell detachment and death) and lymphocytic hyperproliferation, resulting in the characteristic flattening of the intestinal mucosa.

Specifically, it has been shown that α-2 gliadin is a site located within the "33-mer" T-cell reactive peptide presented by DQ2.5. The 33-mer peptide, a 33-residue peptide fragment resulting from the normal gastrointestinal proteolysis of gluten, is a high-affinity substrate for tissue transglutaminase 2, the enzyme that deamidates three glutamines to glutamic acid [4]. Deamidated 33-mer has been found to be an extremely potent stimulator of T cells, many times more potent than any other known gluten peptide. It emerges as a central player in the pathogenesis of this autoimmune disease [5].

FPIES is classified as a non–IgE-mediated food allergy, primarily driven by cell-mediated immune responses. However, the precise underlying mechanism by which trigger foods in FPIES elicit symptoms and disease remains unclear. The timing of symptom occurrence in FPIES (typically 1–4 h) falls between IgE-mediated reactions (usually <2 h) and cell-mediated food reactions (often several hours or days). The involvement of both the adaptive and innate arms of the immune system has been proposed. It is hypothesized that exposure to a food induces inflammation in the gut, predominantly in the colon, leading to increased intestinal permeability and fluid shift into the gastrointestinal lumen. Nonetheless, the exact immune mechanism remains unknown, although several cellular elements and cytokines are believed to play a role.

Initially, a T-cell–mediated response was suggested, as evidenced by in vitro proliferation of peripheral blood mononuclear cells in FPIES patients compared with controls on exposure to food antigens [6,7]. This activation was associated with the release of high levels of proinflammatory cytokines, including tumor necrosis factor-α and TH-2 cytokines (IL-10, IL-4) [8–10]. However, more recent studies have not consistently supported these findings. For instance, Caubet et al. found no difference in T-cell proliferation or Th2 cytokine production in children with cow's milk FPIES on casein challenge [11]. However, they did identify a significant systemic innate immune activation in children with FPIES, primarily observed in CD14+ monocytes, neutrophils, eosinophils, and CD56 natural killer cells. In acute FPIES reactions, patients may have elevated peripheral neutrophil counts, making an increase in circulating neutrophils, peaking approximately 6 h after oral food challenge, part of the diagnostic criteria. Stool examination may also reveal the presence of neutrophils and eosinophils in both acute and chronic FPIES cases.

A reduced expression of the transforming growth factor-β type I receptor was found in epithelial and mononuclear cells in duodenal biopsies of children with FPIES [12]. Because transforming growth factor-β has various effects that enhance cell–protein

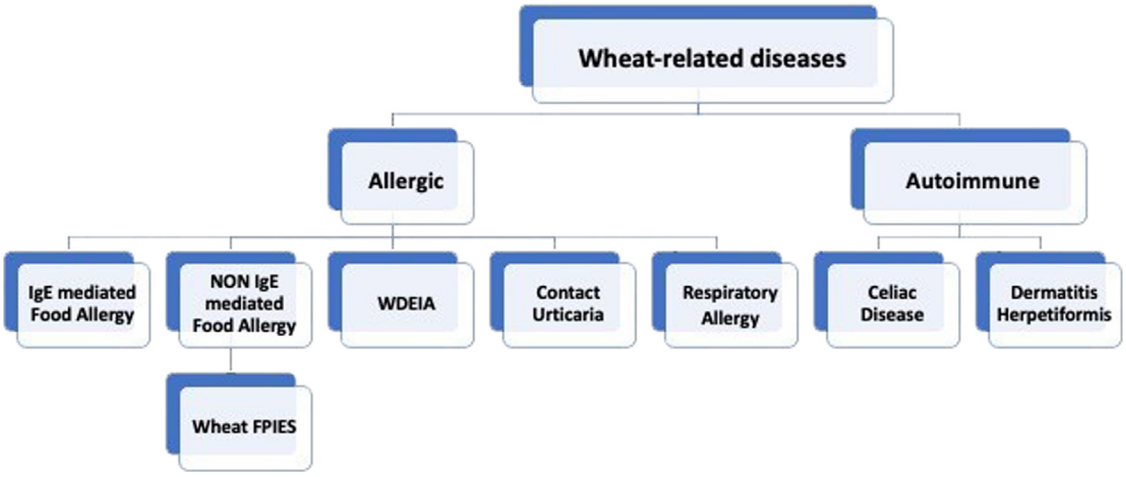

Figure 1. Overview of possibile Wheat-related diseases

matrix interactions, its reduced activity could contribute to the barrier-disrupting effect of T-cell cytokines, potentially leading to increased penetration of food antigens and contributing to the pathogenesis of FPIES. What we can see, however, is that in these patients there may be a strong immune system reaction toward the same element, wheat, triggering underlying immune-mediate responses that causes different symptoms.

The remarkable aspect of this case extends beyond the mere coincidence of 2 distinct food-related reactions. What is truly intriguing is the onset of FPIES in this girl, who had been tolerant of the food for a year before her CD diagnosis. Typically, FPIES manifests on initial exposure to the offending food, making this a unique case of secondary FPIES. FPIES is classified into acute and chronic forms, with the latter often presenting progressively but still triggered by the first ingestion of the responsible food. Amid the current ambiguous understanding of FPIES pathogenesis, our case raises suspicions that either prolonged food abstinence, celiac-type immunologic reactions in the intestine, or possibly both, can serve as pathogenic factors in FPIES.

In recent years, we can find various wheat-related disorders in the literature. These include celiac disease, wheat-induced anaphylaxis reactions, and, now, as we describe, FPIES [13]. This element causes many different reactions with different immunopathological mechanisms that certainly need further investigation (Fig. 1). As described in our case, these disorders can also coexist and this causes 2 important issues.

The first is that, with this clinical case, we aim to draw attention to this association to prevent potentially dangerous diagnostic delays for our patients because of the necessity of strictly avoiding certain foods. It is crucial to strictly avoid contaminations or accidental ingestions in this patient. Apart from the complications associated with the underlying condition (CD), such incidents can lead to the patient seeking emergency care and necessitate immediate treatment and support. The second important issue is we need to increase and specify clinical diagnostic criteria for FPIES, because in these patients, with FPIES coexisting with CD, it would be unethical to perform an oral food challenge for the risks that the introduction of wheat can pose in a patient with CD.

Further investigation is warranted to explore the relationship between FPIES and CD, considering both the severity of acute events and the challenges.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Husby S, Koletzko S, Korponay-Szabó I, Kurppa K, Mearin ML, Ribes-Koninckx C, et al. European Society paediatric gastroenterology, hepatology and nutrition guidelines for diagnosing coeliac disease 2020. J Pediatr Gastroenterol Nutr 2020;70:141–56.

[2] Nowak-Węgrzyn A, Chehade M, Groetch ME, et al. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: Executive summary-Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol 2017;139:1111–26. e4.

[3] Sollid LM. Molecular basis of celiac disease. Annu Rev Immunol 2000;18:53–81.

[4] Qiao SW, Bergseng E, Molberg Ø, et al. Antigen presentation to celiac lesion-derived T cells of a 33-mer gliadin peptide naturally formed by gastrointestinal digestion. J Immunol 2004;173:1757–62.

[5] 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;53:1274–8.

[6] Hoffman KM, Ho DG, Sampson HA. Evaluation of the usefulness of lymphocyte proliferation assays in the diagnosis of allergy to cow's milk. J Allergy Clin Immunol 1997;99:360–6.

[7] Van Sickle GJ, Powell GK, McDonald PJ, Goldblum RM. Milk- and soy protein-induced enterocolitis: evidence for lymphocyte sensitization to specific food proteins. Gastroenterology 1985;88:1915–21.

[8] Mori F, Barni S, Cianferoni A, Pucci N, de Martino M, Novembre E. Cytokine expression in CD3+ cells in an infant with food protein-induced enterocolitis syndrome (FPIES): case report. Clin Dev Immunol 2009:679381. 2009.

[9] Petrosino MI, Scaparrotta A, Di Filippo P, et al. Food protein-induced enterocolitis syndrome in children: what's known? What's new? Eur Ann Allergy Clin Immunol 2018;50:99–107.

[10] Caubet JC, Bencharitiwong R, Ross A, Sampson HA, Berin MC, Nowak-Węgrzyn A. Humoral and cellular responses to casein in patients with food protein-induced enterocolitis to cow's milk. J Allergy Clin Immunol 2017;139:572–83.

[11] Goswami R, Blazquez AB, Kosoy R, Rahman A, Nowak-Węgrzyn A, Berin MC. Systemic innate immune activation in food protein-induced enterocolitis syndrome. J Allergy Clin Immunol 2017;139:1885–96. e9.

[12] Konstantinou GN, Bencharitiwong R, Grishin A, et al. The role of casein-specific IgA and TGF-β in children with food protein-induced enterocolitis syndrome to milk. Pediatr Allergy Immunol 2014:25651–6.

[13] Mennini M, Fiocchi A, Trovato CM, et al. Anaphylaxis after wheat ingestion in a patient with coeliac disease: two kinds of reactions and the same culprit food. Eur J Gastroenterol Hepatol 2019;31:893–5.