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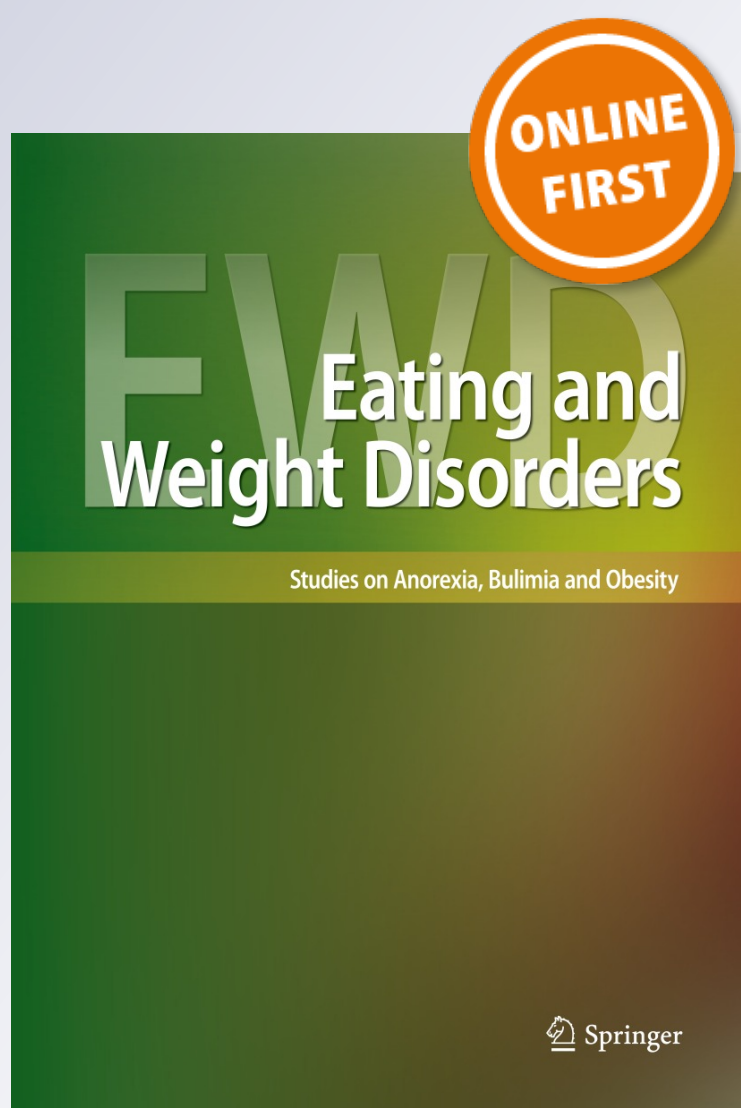
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Wheat-dependent exercise-induced anaphylaxis following laparoscopic adjustable gastric banding procedure associated with *Helicobacter pylori* infection

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Abstract Wheat-dependent exercise-induced anaphylaxis (WDEIA) is a special form of adult food allergy when allergic symptoms are elicited when triggering factor such as exercise is added after ingestion of wheat. Besides the molecular characteristics of wheat proteins, the gastric function is decisive for the allergenic potential. Alterations in the gastric milieu are frequently experienced during a lifetime either physiologically or as a result of gastrointestinal pathologies. *Helicobacter pylori* infection can lead to hypoacidity and enhance the sensitization risk for food allergens in adults. Gastric transit of food proteins and alterations in the gastric secretion can be disturbed after bariatric surgery such as the laparoscopic adjustable gastric banding (LAGB) procedure used commonly as therapy for morbid obesity. We report a case of WDEIA in a 42-year-old man with *H. pylori* positive gastritis, 2 years after bariatric surgery and no history of allergy previously. Our presented case strongly suggests that *H. pylori*-associated gastritis and gastric anatomy and functional changes after adjustable gastric banding lead to the alterations in gastric milieu and may contribute to a development of food allergy in previously non-sensitized patients.

Introduction

The rising number of food-induced severe adverse reactions accounts for the importance of food allergy in adults in Western society [1]. Food-dependent exercise-induced anaphylaxis (FDEIA) is a special form of food allergy in adults where allergic symptoms are elicited when triggering factors such as exercise or concomitant drugs are added after ingestion of the causative food, most often wheat [1–4]. Besides molecular characteristics of the wheat proteins, the stomach function is decisive for the allergenic potential. Alterations in the gastric milieu are frequently experienced during a lifetime either physiologically or as a result of *Helicobacter pylori* infection or after bariatric surgery [5, 6]. Laparoscopic adjustable gastric banding (LAGB) commonly is the procedure of choice in Europe for morbid obesity, but the long-term outcomes and quality of life, have been questioned [7]. We report the case of the patient with wheat-dependent exercise-induced anaphylaxis (WDEIA) and possible causal relationship with *H. pylori* infection following LAGB.

Case presentation

A 42-year-old male was admitted to the emergency unit from gym club because of generalized anaphylaxis. During the strenuous physical exercise, he developed skin itching, generalized urticaria, pharyngeal and labial pruritus, angioedema, hypotension, dyspnea and short-term loss of consciousness. Symptoms were relieved rapidly by treatment with epinephrine, antihistamines, and dexamethasone. This episode of anaphylaxis grade III was the first in his life. Five weeks later the patient was consulted by an allergist-clinical immunologist at the university centre. It

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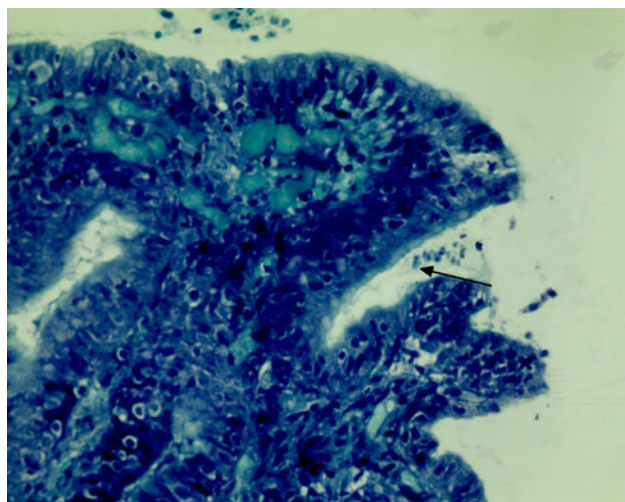


Fig. 1 High-magnification of gastric mucosa demonstrating inflammatory infiltrate with neutrophils, mononuclear cells and eosinophils

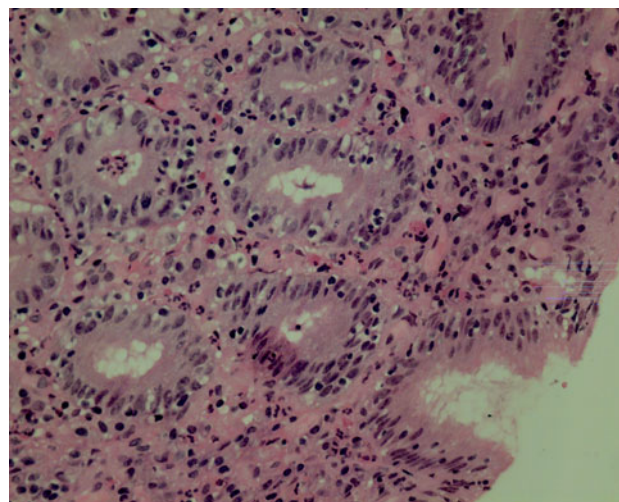


Fig. 2 High-magnification of gastric mucosa demonstrating *Helicobacter pylori* infection

was revealed that exercise-induced anaphylaxis developed several hours after eating vegetable soup with bread. Three weeks later he developed urticaria during mild physical exertion (jogging) after eating “kūčiukai” (a traditional Lithuanian Christmas dish made from wheat flour, leavened dough and poppy seeds).

The patient had no history of atopy, food, drug or pollen allergy, and no digestive complaints. The patient had laparoscopic obesity surgery (Swedish adjustable gastric banding, SAGB) 2 years ago. After that, his body mass index (BMI) dropped from 42.6 to 29.2 kg/m², and status of inflation was partially filled. Skin prick tests (SPTs) were positive to wheat flour (6 mm), yeast compound (4 mm) and oat (3 mm), negative to house dust mites, cat, dog, Alternaria mold, Betulaceae tree mixture, grass mixture, cereals, Compositae weed mixture, mugwort allergens, codfish, soja, hen's egg, buckwheat, positive control histamine (5 mm). Total serum IgE was elevated 772.1 kU/l (normal value <150 kU/l). Allergen-specific IgE in serum is strongly positive for crab, wheat, barley, rye (>300 LU, MAST-CLA 4 class), oat and carrot allergens (1 class). No specific IgE to 35 inhalant allergens was detected. Video esophagogastroduodenoscopy was performed, no changes of esophagus and duodenum were detected, erosive gastritis was diagnosed and biopsy from antrum of stomach was taken. Histology revealed marked infiltration of gastric mucosa with neutrophils, moderate with mononuclear cells and mild with eosinophils, and no villous atrophy was found (Fig. 1). *H. pylori* density on the surface of gastric mucosa was high (Fig. 2). The diagnosis of WDEIA was made according to clinical criteria of anaphylaxis grade III (generalized urticaria, itching, angioedema, hypotension, dyspnea, short-term loss of consciousness after the consumption of causative food allergens several hours prior

the physical exercise, symptoms relieved by injected epinephrine) and allergy confirmed by positive SPTs and food allergen-specific IgE in serum. Chronic active *H. pylori* (+) gastritis after LAGB was confirmed. Triple therapy for *H. pylori* eradication was initiated. Therapy consisted of omeprazole 20 mg twice daily, amoxicillin 1 g twice daily, and clarithromycin 500 mg twice daily for 7 days. The patient was recommended to avoid wheat and other cereals in his diet, and pursue exercise regime, avoidance of physical activity approximately 4 h after meal. The patient was provided with a written, personalized Anaphylaxis Emergency Action Plan, and epinephrine autoinjector, and antihistamines were prescribed. *H. pylori* eradication was confirmed by negative CLOtest* Rapid Urease Test during esophagogastroduodenoscopy 6 months later. Recommendations' compliance was effective preventive measure, and at the follow-up of 2 years period there were no episodes of repeated anaphylaxis.

Discussion

Wheat grain is the most widely consumed grain in the world. In adults, food allergy to ingested wheat seems to be infrequent and especially described as an anaphylactic reaction induced by exercise [1–4]. We presented the case of 42 years old man who developed sensitization to wheat allergens leading to WDEIA. We postulate that two triggering factors could be related—*H. pylori* infection and adjustable gastric banding procedure for obesity treatment.

Wheat allergens are present in the different fractions of wheat grains. A-amylase/trypsin inhibitor and lipid transfer protein are found in the water/salt-soluble fraction, and omega5-gliadins and LMWglutenins have been detected in

the gluten fraction and are water/salt-insoluble [8]. Omega5-gliadins and glutenins are class 1 food allergens and are heat- and acid-stable glycoproteins that induce IgE sensitization and anaphylaxis [8]. Our patient became sensitized to wheat allergens, based on the positive skin prick test results and sIgE, there was no cross-sensitization to grass or cereal pollens. Wheat allergens cross-link IgE on mast cells and eosinophils and release of histamine and other mediators leads to allergic symptoms. In WDEIA, a wheat intake alone does not induce any symptoms and strenuous exercise, such as jogging, aerobics, basketball, tennis or running, bicycling, dancing and even walking induce anaphylaxis symptoms from 10 min to 4 h after meal [1–3]. The National Institutes of Health and the Food Allergy and Anaphylaxis Network proposed a definition and set criteria for diagnosing anaphylaxis [9]. These criteria require the presence of cutaneous signs or symptoms, in combination with respiratory symptoms, cardiovascular, gastrointestinal symptoms (or associated end-organ dysfunction due to low blood pressure), or both. A variant of food-induced anaphylaxis is food-dependent, exercise-induced anaphylaxis (FDEIA), which refers to an IgE-mediated food-induced anaphylactic reaction that develops only when exercise is undertaken within a few hours of ingesting a food [10, 11]. If the food is consumed without subsequent exercise or if exercise is performed without associated ingestion of the food, the patient does not develop allergic symptoms [10, 11]. The pathomechanisms of wheat-induced anaphylaxis are complex and remain incompletely understood. Increased permeability and protein absorption from gastrointestinal tract as undigested forms, and a decrease in blood pH associated with exercise may play some role. Gliadin appears in sera from FDEIA patients and healthy controls after exercise/food challenge, but not after ingestion alone [8]. Aspirin and NSAIDs increase gastrointestinal permeability and enhance mast cell degranulation [12]. Another mechanism is that an enzyme tissue transglutaminase in the intestinal mucosa is activated by exercise and aspirin, and catalyzes the formation of large gliadin peptide aggregates which facilitate greater IgE cross-linking [12]. The first step in the cascade of WDEIA events most likely depends on intestinal mast cell activation caused by increased osmolality of the microenvironment because of exercise-induced blood flow redistribution from inactive to active tissues, and displacement of ingested allergens from the gut to the skin and skeletal muscles [4].

Gastrointestinal mucosa is a barrier for alimentary antigens and most wheat proteins are hydrolyzed when subjected to gastrointestinal digestion. Low gastric acid pH is crucial for activation and liberation of gastric and pancreatic proteases which degrade proteins to small nutritionally valuable peptones and peptides, which

optimally are ignored by the immune system. By increasing the gastric pH, digestive function is interfered, leading to persistence of labile food protein during gastric transit and antiulcer medications such as H₂-receptor blockers or PPIs increase the risk of food allergy [5, 13]. Patients infected with *H. pylori* produce less acid and marked inflammation of the antrum and body of the stomach and the hypochlorhydria is assumed to be due to the bacteria and/or accompanying inflammation inhibiting parietal cell function and enhancing the risk of food allergy [14, 15]. A virulence factor of *H. pylori* is CagA, and anti-*H. pylori* and anti-CagA IgG titres have been determined in children with atopic dermatitis as the sole clinical manifestation of food allergy [16]. The enhanced mucosal and inflammatory lesions commonly found in individuals infected by CagA-positive *H. pylori* strains could alter the integrity of the gastric barrier, increase the epithelial permeability and render non-selective the passage of allergens in circulation which, in atopic persons, could directly stimulate an IgE response. We speculate that in our patient the gastric mucosa eosinophilic inflammation is a consequence of *H. pylori* infection and IgE allergy. Our patient became sensitized to wheat allergens after the LAGB. Although we have not found any published data about the incidence of food allergy after LAGB, we speculate that the mechanisms of eliciting food allergy could be that a limited amount of food entering the stomach and the lower rate of food passage through the digestive tract may create a low acid environment, decrease peristalsis, and leads to abnormal pyloric function. Development of gastritis in the corpus and fundus may significantly decrease acid secretion and enhance the risk of sensitization to food allergens [6]. We speculate that *H. pylori* infection and the LAGB were the important co-factors for the sensitization to food allergens to develop in the non-atopic patient previously non-sensitized to inhalant and food allergens.

Conclusion

Our presented case is an original case report and strongly suggests that *H. pylori*-associated gastritis and gastric anatomy and functional changes after adjustable gastric banding lead to the alterations in the gastric barrier, enhanced mucosal permeability and crossing of food antigens and may contribute to a development of food allergy in previously non-sensitized patients.

Conflict of interest The authors declare that they have no conflict of interest.

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