An Overview of Spectrum of Gluten-related Disorders

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INGRESS

The market for gluten-free food is increasing in Norway as in the whole western world. The reason for choosing this diet varies, but everything cannot be explained by an increase in celiac disease.

Avoidance of wheat-containing products is a worldwide phenomenon. People avoid wheat because of supposed health benefits, and gluten has been linked to a wide range of disorders, including gastrointestinal disorders, various skin problems, fatigue, migraines and weight gain. Complaints from gluten in people without celiac disease have received considerable attention in recent years, and therefore an increasing number of patients start gluten-free diet for their unexplained gastrointestinal complaints. In the US market for gluten-free diet is about USD 3 billion. It is also seen a similar development in Norway.

Mainly three disorders are related with gluten intake, where to apply to cover the expenses of gluten-free diet in Norway. They are celiac disease, wheat allergy and non-celiac gluten sensitivity (Figure 1). Here, a brief overview of these disorders and coherence with irritable bowel (Irritable bowel syndrome: IBS) will be given.

CELIAC DISEASE

The incidence increases in the same way as allergy, asthma and other auto-immune diseases. Celiac disease occurs in all ages and one study showed that up to 19% of patients with celiac disease diagnosed after they age 60 (1). Previously celiac disease considered as a childhood disease with diarrhea, malabsorption, cachexia and growth disturbance, but now are discovered most celiac patients in adulthood and perhaps earlier in the disease progression. Therefore, now we don't see the classical celiac symptoms and signs so often as earlier. Most have normal weight. Moreover, they have often diffuse complaints causing delayed diagnosis. Untreated celiac disease involves a number of sequelae and provides an increased risk of carcinomas and lymphomas of the gastrointestinal system (2).

Celiac disease classifications and diagnostic criteria should not be discussed thoroughly here, but the diagnosis is made by small intestinal biopsy, supported by clinic, serological tests, human lymphocyte antibody (HLA) typing and treatment efficacy. Guidelines for the diagnosis of celiac disease may also vary in children and adult. Treatment is strictly gluten-free diet.

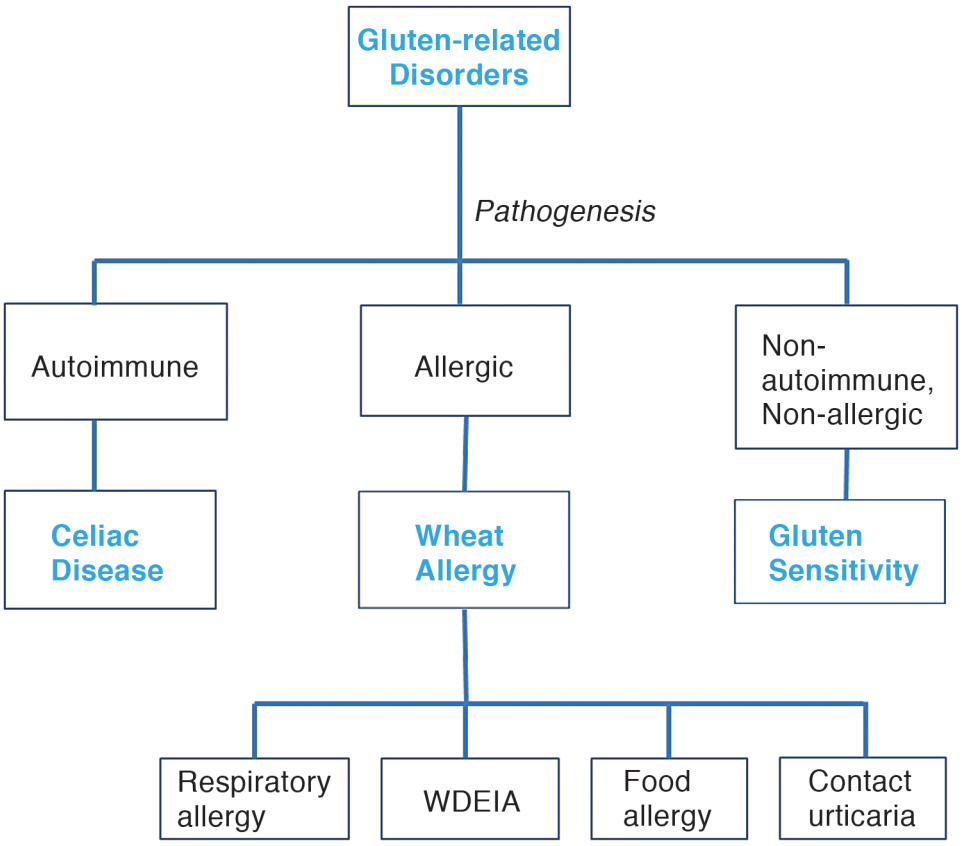

Figure 1. Classification of gluten-related disorders.

WHEAT ALLERGY

Wheat proteins cause allergic reactions (IgE-mediated) in patients with wheat allergy. Clinic and precipitating factors may vary from typical classical food allergy, baker asthma- and rhinitis, contact urticaria to wheat-dependent exercise induced anaphylaxis (WDEIA). The latter is a special form of wheat allergy where gluten intake alone did not induce any symptoms, but allergic reactions are occurred when triggering factors such as physical exercise or nonsteroidal anti-inflammatory drugs (NSAIDs) intake comes after ingestion of gluten (3). Both exercise and NSAIDs intake can facilitate allergen absorption from the gastrointestinal tract such that allergic symptoms may occur. Exercise mobilizes and activates intestinal immune cells, which disrupts the normal balance between pro-inflammatory and anti-inflammatory responses (4). Dysregulation of this process in patients with food-sensitized immune cells could be involved in exercise-induced reactions. Approximately 80% of patients with WDEIA have IgE reacts in omega-5 gliadin, and the remaining patients to high molecular weight glutenin (HMW-glutenin). Simultaneous measurement of specific IgE against omega-5 gliadin and HMW-glutenin were found to be very useful components in the diagnosis of WDEIA. Soybean is also the second most frequent causative food item after wheat, and WDEIA is often seen in Japan.

Symptoms of classic wheat allergy can be from skin, gastrointestinal tract and/or respiratory tract, and severity can vary from mild to life threatening (anaphylaxis). Baker asthma- and rhinitis are triggered by the inhalation of flour, while contact urticaria caused by hydrolyzed wheat protein in cosmetic products. Wheat allergy diagnosed using blood tests (increased specific Ig E levels to wheat), prick test and/or provocation tests. It is also important to distinguish wheat allergy from grass (timothy) allergy. Slightly elevated levels of specific Ig E to wheat may be cross-reaction with timothy, and in this condition, timothy levels (specific IgE levels)

in blood are higher than wheat. But "real" wheat allergy patients usually have negative timothy levels or higher wheat levels than timothy. The disorder is treated with the same diet as in celiac disease, and they will get the support to cover expenses for gluten-free diet.

NON-CELIAC GLUTEN SENSITIVITY

Non-celiac gluten sensitivity can also be called gluten sensitivity, gliadin hypersensitivity, gluten intolerance or gluten intolerance without celiac disease. The characteristic criteria for these patients are that they get symptoms triggered by gluten, and relief after gluten-free diet after having excluded celiac disease and wheat allergy.

The concept of non-celiac gluten sensitivity was first introduced in 1978 with a case report of a patient with abdominal pain and diarrhea who exhibited no abnormalities on small-intestine biopsy samples, whose symptoms improved when they changed to a gluten-free diet (5). A study of eight adult females with abdominal pain, diarrhea, and small-intestine biopsy findings with no significant changes published in 1980 found that symptoms were relieved when the patients adhered to a gluten-free diet, and returned after a gluten challenge (6). Similar results have been reported in patients with non-celiac IBS-like symptoms (7). The withdrawal of wheat products was found to improve these symptoms in double-blind randomized, placebo-controlled studies involving patients with IBS-like symptoms (8).

Prevalence rates of non-celiac gluten sensitivity differed widely from 0.5% to 13% in different countries, and in US the prevalence is about 6% (1). They may also have other extra-intestinale symptoms such as joint pain, fatigue, depression and eczema in addition to their gastrointestinal complaints (abdominal pain, bloating and irregular bowel movements). These patients have intolerance to gluten, but they do not get the same reaction in the intestine by celiac disease. They will not get the same reaction as seen in wheat allergy either. There are no clear mechanisms for non-celiac gluten sensitivity, and we do not know certain about other alternative explanations such as starch-gluten interaction and fermentation process, nocebo effect, or other substances in wheat (non-gluten proteins: α-amylase / trypsin inhibitor) can play role (9). Currently there is an absence of any reliable biomarkers to confirm or detect this condition and diagnosis is therefore based on exclusion. It is essential to exclude celiac disease (based on clinical, laboratory and histological findings), wheat allergy (negative wheat skin prick test and specific IgE levels in blood) and other organic causes which give these gastrointestinal complaints. Then, double-blind provocation tests with and without gluten is also required in some conditions.

The current clinical consensus is that the diagnostic criteria for non-celiac gluten sensitivity should include self-reported gluten intolerance, negative celiac disease serology (including Ig A endomysial antibodies, Ig A tissue transglutaminase antibodies and Ig G deamidated gliadin peptide antibodies) and the absence of villous atrophy on duodenal histology (whilst on a gluten containing diet). As such, it is accepted that non-celiac gluten sensitivity patients might have an increased number of duodenal (IELs) (>25 IEL/100EC), i.e., lymphocytic enteritis (LE), which represents Marsh 1 lesions (Marsh-Oberhuber) in the histological classification for coeliac disease. Intraepithelial lymphocytes are a nonspecific histological findings which may be associated not only with celiac disease but also to the use of anti-inflammatory drugs, *Helicobacter pylori* infection, small intestine bacterial overgrowth or other autoimmune disorders such as Sjogren's syndrome (10-13).

After organic gastrointestinal causes have been excluded, almost all of these patients get the diagnosis of IBS. Wheat mainly contains carbohydrate and protein (gluten and non-gluten protein), but also have lipid components. Wheat germ agglutinin and α-amylase/trypsin inhibitor are the non-gluten proteins in wheat. Wheat contains only 1-2% of lipids components and therefore, this part of the wheat did not get any attention in research.

Many IBS patients experience improvement in symptoms when they avoid gluten in their diet. Conversely tolerate gluten if they are already on low FODMAP (fermentable oligo-, di- and monosaccharides and polyols)-diet. A study in 2011 from Australia showed that gluten reproduces gastrointestinal complaints in patients with IBS (celiac disease was excluded in all) (14). However, there were many uncertain factors in the study and therefore it was performed a placebo-controlled double-blind study published in 2013 (15).

Then participants were first given a low FODMAP diet for two weeks and then they got to try the following three diets for three weeks: High gluten (16 grams gluten per day), low gluten (2 grams gluten per day and 14 grams whey protein) or placebo (16 grams whey protein). The results showed that gluten did not give such problems among participants. With other words, gluten did not reproduce the symptoms after low FODMAP diet. The study brought now a new discussion about non-celiac gluten sensitivity exists or not. However, these two studies showed different results and therefore it is early to conclude.

Here it is not the protein components, but the short-chain carbohydrate components (fructans) of wheat which is most likely responsible for the IBS symptoms. It is also the total amount of carbohydrates that are released over the colon and the fermentation capacity of gut microbiota which are crucial factors in symptom generation.

CONCLUSION

Celiac disease and wheat allergy can be diagnosed using objective diagnostic tests, while non-celiac gluten sensitivity does not have such tests currently. There are no reliable epidemiological data, no diagnostic biomarkers and no clear mechanisms for gluten intolerance. The condition is documented via provocation tests that are resource and time-consuming. Therefore better diagnostic methods are needed, and the relationship between gluten and IBS symptoms should be explored further.

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