Beyond gluten: role of FODMAPs and other wheat proteins as triggers of symptoms in food intolerance

Umberto Volta
Mauro Serra
Giacomo Caio
Elisa Boschetti
Fiorella Giancola
Roberto De Giorgio

Department of Medical and Surgical Sciences, St. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy

Address for correspondence:
Roberto De Giorgio
Department of Medical and Surgical Sciences
University of Bologna
St. Orsola-Malpighi Hospital, Building #5
Via Massarenti 9
40138 Bologna, Italy
Phone: +390512143558; Fax: +39051345864
E-mail: roberto.degiorgio@unibo.it

Summary

Foods are known to be symptom trigger in a large number of patients. Although the underlying mechanisms are still far from being elucidated, the increasing number of patients presenting with a clinical picture suggestive of food intolerance has recently caught physicians’ attention. This review is intended to focus on clinical, diagnostic and therapeutic aspects of food intolerance such as those elicited by wheat/gluten (non celiac wheat/gluten sensitivity, NCW/GS) and fermentable oligo-, di-, mono- and polyols (FODMAPs). NCW/GS is a syndrome characterized by gastrointestinal (e.g., bloating, abdominal pain and bowel habit changes) and extraintestinal (e.g., headache, skin rashes and fibromyalgia-like) symptoms related to the ingestion of gluten-containing foods in subjects testing negative for celiac disease and/or wheat allergy. Symptoms improve/disappear after gluten-free diet and recur with gluten challenge. Functional bowel symptoms overlapping those of NCW/GS are also evoked by FODMAPs and wheat proteins (e.g., amylase trypsin inhibitors). So far, there are no biomarkers for NCW/GS, although 50% of patients display IgG anti-gliadin antibodies. A double-blind, placebo-controlled food challenge is currently the only way to confirm the diagnosis of NCW/GS. There are no controlled trials to prove actual efficacy of low-FODMAPs diet vs placebo. Studies are eagerly awaited to shed light on dietary changes as measure to be used in patients with food sensitivity and related gut symptoms.

KEY WORDS: anti-gliadin antibodies, amylase trypsin inhibitors, fermentable oligo-di- and monosaccharides and polyols, non celiac wheat/gluten sensitivity.

Introduction

Food intolerance or sensitivity has long been known in the clinical practice since patients attribute their digestive symptoms to certain alimentary components (1). These symptoms are exactly identical to those referred to as “functional” (i.e. non-organic) origin, including bloating, abdominal pain/discomfort and bowel habit abnormalities, which are cornerstone of conditions definable as functional bowel disorders (FBD) (2). Various mechanisms such as altered motility, visceral hypersensitivity, gut-brain axis impairment and neuroimmune changes, increased intestinal permeability along with perturbation of the gut microbiota, have been shown to play a role in symptom generation in patients with FBD (3). Among the myriad of factors eliciting gut pathophysiology, foods certainly represent one of the main trigger via the release of a wide array of mediators from enterococrine cells, neurons and immunocytes (e.g., mast cells) (4, 5).

Emerging evidence indicates that commonly consumed dietary components, such as wheat and gluten, are the main culprit of what is meant for...
food intolerance (6). The best example of such conditions is given by celiac disease (CD) defined as an immune-mediated enteropathy characterized by severe mucosal damage (villous atrophy) occurring in genetically predisposed individuals (7, 8). CD shows well-established biomarkers, i.e. anti-tissue transglutaminase (tTGA), endomysial (EmA) and deamidated gliadin peptide (DGP) antibodies. From a clinical standpoint, CD displays a variable clinical picture ranging from classical cases, presenting early in life with chronic diarrhea, growth faltering and other signs of malnutrition, to atypical cases characterized by extraintestinal, e.g. anemia, osteoporosis or short stature, or even minimal, e.g. chronic fatigue, manifestations. In addition, some patients are fully asymptomatic and the identification of CD is due to accidental serological tests (9). An increased frequency of CD (5-10%) is found in at-risk groups, e.g. first-degree relatives of CD patients, subjects with other autoimmune diseases, e.g. type 1 diabetes, autoimmune thyroiditis, patients with Down or Turner syndrome, and subjects with IgA deficiency. Finally, many cases escape diagnosis and are exposed to the risk of long-term complications, such as infertility, neurological disturbances or intestinal lymphoma. These complications can also occur as a consequence of a poor compliance to gluten free diet, the therapeutic mainstay of CD (10).

In addition to CD, physicians have become progressively aware of a new clinical challenge in the field of gluten-related disorders, i.e. a condition referred to as non-coeliac wheat / gluten sensitivity (NCW/GS) (11-13). Patients with such syndrome complain of symptoms related to gluten ingestion in the absence of CD and wheat allergy (WA). In addition to gluten, other dietary components either inherent to or extra wheat, i.e. amylase trypsin inhibitors (ATIs) and fermentable oligo-, di-, monosaccharides and polyols (FODMAPs), are now emerging as new triggering factors for symptoms in food sensitivity (14, 15). Both ATIs and FODMAPs, which can also be responsible for triggering symptoms. However, the current impact in the general population exerted by ATIs and FODMAPs remains largely unsettled. Future epidemiological studies are eagerly awaited to shed light on the epidemiology of these two other food sensitivities.

Epidemiology

The prevalence of NCW/GS is undefined and largely variable according to the different clinical setting, i.e. primary care or tertiary referral centres (12, 22, 23). Data from the National Health and Nutrition Examination Survey (NHANES), a United States primary care program, showed an estimated rate of 0.6% NCW/GS over 7,762 patients (22), whereas in the tertiary care Center for Celiac Research, University of Maryland, the prevalence of this syndrome was around 6% (12). The reason for this 10-fold difference between primary and tertiary care remains unclear, although it may be possible that such patients are more commonly seen in highly specialized clinics. Furthermore, about 1/3 of patients with irritable bowel syndrome (IBS, the prototype of all FBD) displays clinical features matching the diagnosis of NCW/GS (24). Since it is well established that IBS is a very common condition found in up to 25% of the general population (25, 26), it is very much likely that also NCW/GS is characterized by a high prevalence in the general population. In an Italian multicentre study, the prevalence of NCW/GS resulted to be 3.2% in more than 12,000 patients with a 1.15:1 ratio between NCW/GS and CD (23).

Clinical picture

NCW/GS is characterized by a wide array of gastrointestinal and extra-intestinal symptoms, occurring shortly after gluten ingestion, improving or completely vanishing in a few hours/days when gluten is withdrawn from the diet and recurring rapidly when gluten is reintroduced (11-13, 18). A mandatory pre-requisite for suspecting this condition is to rule out the diagnosis of both CD and WA when patients are on a gluten-containing diet. In the last years the experts of
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gluten related disorders have started to work intensively on this condition as shown by three Consensus Conferences: one held in London (2011) (12); the other in Munich (2012) (13); and, finally, the third one in Salerno (2015) (27). Furthermore a remarkable number of peer-review papers and reviews on this topic have been published (11, 18, 28-32). Although there is a general agreement that NCW/GS does exist, our knowledge on this syndrome is still lacking with many unsettled aspects. Moreover, whether NCW/GS is a transient or a permanent disorder still remains an open issue. Because of its clinical picture NCW/GS can be regarded as a syndrome rather than an unique disorder, being characterized by a variety of gluten-related gastrointestinal and extra-intestinal symptoms. In a previous work from our group the clinical and serological features of NCW/GS were investigated in seventy-eight non-consecutive patients diagnosed in our center in a two-year frame (January 2009 - June 2011) (33). In all of them NCW/GS was suspected on the basis of symptoms elicited by gluten ingestion after the exclusion of CD and WA. NCW/GS diagnosis was confirmed by a trial of GFD for 6 months with a quick disappearance of symptoms, followed by an open gluten challenge of one month with an immediate relapse of the clinical picture. All NCW/GS patients showed both gastrointestinal and extra-intestinal symptoms occurring in a few hours or days after gluten ingestion. Among gastrointestinal symptoms the most frequent manifestations were abdominal pain and bloating, followed by diarrhea and, less frequently, constipation. Among extra-intestinal signs the most frequent symptoms were mental confusion (or “foggy mind”), followed by fatigue, skin rash, headache, joint and muscle pain (fibromyalgia-like syndrome), numbness, depression / anxiety and anemia. Similarly to CD, NCW/GS resulted to be more frequent in females than in males. Clinical features of NCW/GS emerged from this study showed that this syndrome is more frequent in middle-aged adults, while is less frequent in adolescents and elderly people (33) and even rare in children (34). In particular, in children it has been reported that gastrointestinal symptoms (abdominal pain 80%, diarrhea 73%, bloating 26%) were more frequent than extra-intestinal signs (mainly tiredness and headache, found in 33 and 20% of cases, respectively). Along with gluten, FODMAPs can evoke gastrointestinal symptoms similar or even overlapping those reported by NCW/GS patients (6). Due to their small molecular size and rapid fermentability, these molecules cause the intestinal distension due to liquid and gas production eliciting functional gastrointestinal symptoms. Common food sources of FODMAPs are grains and cereals (e.g., wheat, rye and barley), milk, legumes, honey, fruits (e.g., watermelon, cherry, mango, pear) and vegetables (e.g., chicory, fennel, beetroot and leek). A proof of concept that FODMAPs play a role in symptom generation is indicated by the evidence that a low-FODMAPs diet significantly improves functional gastrointestinal symptoms (15). Other wheat proteins, i.e. ATIs, are thought to evoke both gastrointestinal and extra-intestinal symptoms similar to NCW/GS, thus introducing a further confounding factor in the vast array of dietary components triggering functional symptoms (35). Future research will be directed to dissect out the three major components, i.e. gluten, FODMAPs and ATIs, in order to address specific dietary manipulation effective for appropriate patient management. Among the several unsettled issues in the field of food sensitivity, it remains still unclear whether NCW/GS patients are more prone to autoimmune disorders and complications like CD patients. A few published studies suggested that the finding of autoimmune disorders in NCW/GS is a rare event (11, 12, 33). However, recent data report that patients with NCW/GS display a high prevalence of serum autoantibodies (antinuclear antibodies, ANA) and a frequent association with autoimmune disorders (i.e., Hashimoto’s thyroiditis) in the same guise of CD (36, 37). Another relevant point that needs to be explored is whether patients with NCW/GS can develop well-known CD-associated complications, such as ulcerative jejuno-ileitis, collagenous sprue, small intestinal lymphoma and other gastrointestinal neoplasms (7-9). Since NCW/GS has been only recently identified, its follow-up is still too short to have solid information on the outcome of this condition (11-13, 27).

Diagnosis

The diagnosis of NCW/GS is based on the thorough evaluation of the clinical features according to the indications illustrated by the Consensus Conferences on this syndrome (12, 13, 27). However, since it is impossible to rule out a placebo effect simply related to gluten withdrawal, double-blind, placebo-controlled (DBPC) trials are recom
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mended to prove that a given patient actually has NCW/GS. So far, few trials have been performed and most of them included IBS patients (with a few extraintestinal symptoms) rather than true NCW/GS cases (38-40). Clearly, this evident bias in patient selection contributed to generate inconsistent results. In fact, two studies performed by the same group initially confirmed that a number of IBS patients matches criteria for NCW/GS showing symptom recurrence following gluten reintroduction (38). The second trial, however, showed that gluten evoked neurological, but not intestinal, symptoms in a very few patients with IBS, whereas most of them improved after a low-FODMAPs diet (40). This latter finding suggests that FODMAPs intolerance can be predominant in a subset of patients with IBS-like phenotype. Carroccio et al. demonstrated that IBS patients, randomized to receive whole wheat vs placebo, showed a significant worsening of their intestinal and extra-intestinal symptoms after wheat ingestion (39). A recently published DBPC trial used pure gluten- vs rice starch-(control) containing capsules to clarify the exact role played by gluten in symptom generation in patients with highly suspected NCW/GS. The results showed that gluten ingestion induced the significant recurrence of a variety of symptoms including bloating, abdominal pain, foggy mind, aphthous stomatitis, headache and depression. However, the analysis of the single patient response disclosed that a subset of NCW/GS did not worsen after gluten ingestion raising the possibility that other dietary factors, i.e. FODMAPs and ATIs, can be a major trigger of food sensitivity (41). Regarding FODMAPs seven studies have been so far published showing efficacy of a low-FODMAPs diet vs free diet. However, none of these trials has a placebo group as a comparator, thus introducing a possible bias hampering the actual value of a low-FODMAPs diet both in terms of diagnosis and as a therapeutic measure (42).

Since biomarkers are still unavailable for NCW/GS, the diagnosis of this syndrome remains questionable. So far, the only serological marker which has been identified in a significant number of patients with NCW/GS is represented by antibodies to native gliadin (AGAs) (12, 34, 39). AGAs have been found in the sera of about half of the NCW/GS patients being predominantly of the IgG class (34). Although AGAs are not specific for NCW/GS since they are detected in autoimmune disorders, IBS, connective tissue diseases, their positivity, especially at high titers, in patients with a clinical picture suggestive of NCW/GS can be confirmatory for this diagnosis. In parallel to symptom resolution, AGAs disappeared in almost all patients with NCW/GS within 6 months of GFD (43).

Regarding histopathology, a duodenal biopsy is recommended in cases with suspected NCW/GS on a gluten containing diet to rule out CD diagnosis even if the celiac serology is negative. NCW/GS patients show a normal duodenal mucosa histology, although an increased number of intraepithelial lymphocytes (IELs) ranging from 25 to 40 /100 epithelial cells suggests an accompanying low-grade inflammation (34). There is no increase of T-cell receptor γ/δ IELs in biopsies of patients with NCW/GS (16). No correlation exists as far as the histocompatibility leukocyte antigen (HLA) complex is concerned. Positivity for HLA-DQ2 and/or -DQ8 in NCW/GS patients is slightly higher than that detected in the general population (12, 34). Up to 20% of NCW/GS showed abnormalities of laboratory tests regarding changes such as low levels of ferritin, folic acid, vitamin D and B12, indicative of malabsorption (44). Evidence of osteopenia detected by bone densitometry has been found in about 50% of cases (45).

Treatment

No established guidelines are yet available for the treatment of patients with NCW/GS and FODMAPs intolerance. Concerning NCW/GS there is a general consensus that self-diagnosis of sensitivity to dietary gluten should be avoided and people should not stop gluten ingestion without a specific prescription given by a gastroenterologist with expertise in the field. Due to a presumed diagnosis of NCW/GS many subjects start GFD without ruling out CD (46). Sometimes, this turns out to be an inappropriate dietary restriction leading to nutritional deficiencies with clinical consequences (18). Therefore a diagnosis of NCW/GS should be always posed in a referral centre following a careful clinical evaluation (23). Patients recognized as gluten-sensitive will be advised to begin GFD. The new diet will include gluten-free cereals, such as rice, corn, buckwheat and millet and leguminosae, e.g. quinoa, amaranth and soybean (47). A growing availability of commercial gluten-free products helps patients with NCW/GS to adhere strictly to a gluten-free regimen which includes also meat, fish, fruit and vegetable consumption. It is not established yet whether NCW/GS patients must avoid inadvertent gluten contamination, as recommended.
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to CD patients. Moreover, it is noteworthy to underline that there is an individual level of tolerance in NCW/GS (12, 23).
The persistence of symptoms after a long period of GFD (6 weeks) suggests that other triggers such as FODMAPs and/or ATIs can be responsible for symptom generation. In these cases a low-FODMAPs diet can lead to a significant improvement of the clinical picture (6).

Conclusions

Foods are regarded as triggers of gastrointestinal and extraintestinal symptoms found in a large number of subjects. Inside the spectrum of food intolerance NCW/GS has been widely accepted as a newly identified gluten related syndrome (46). Along with gluten, other dietary components either inherent to or extra wheat, emerged to have a role in evoking functional digestive symptoms experienced by patients. The potential culprits of symptom generation have been identified in amylase-trypsin inhibitors (ATIs), present in the soluble protein fraction of wheat (14), and in FODMAPs, detectable not only in gluten-containing cereals (wheat, rye and barley), but also in milk, honey and legumes (15).

In conclusion, our review points to the impact of some dietary components related to wheat, gluten and FODMAPs (ATIs being still poorly investigated) as factors triggering functional digestive symptoms and, concerning NCW/GS, also extraintestinal manifestations. The mechanisms underlying food hypersensitivity are still poorly understood; thus, our review focused on clinical features with the intent to expand current knowledge in this area of gastroenterology. A better tailored understanding of food intolerance is expected to promote tailored dietary approaches as a valuable tool in the treatment of most food-related functional bowel disorders and inherent comorbidities.

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