ORIGINAL ARTICLES

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Culprits in non-celiac gluten-sensitivity

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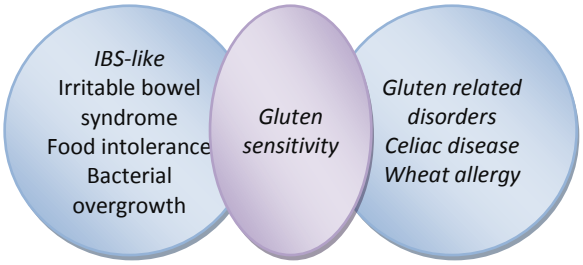
INTRODUCTION

The growing interest for gluten-free diet (GFD) in the last decades has lead to a significant number of people going for this diet, in the absence of a diagnosis of celiac disease (CD). Owing to the perception that dietary gluten could be responsible for some of the symptoms in patients with irritable bowel syndrome (IBS)[1,2,3] (*Figure 1*), a new concept emerged, that of non-celiac gluten-sensitivity (NCGS), as it was named in an international consensus report[4]. NCGS describes the individuals whose symptoms get better on a GFD, in the absence of CD or wheat allergy[5]. The first reports about this condition date back to the late 1970s (two case reports) and the early 1980s (the Birmingham study)[6,7,8], and recently, some authors consider more appropriately to term it "people who avoid gluten"[9]. Biesiekierski et al.[10] were the first to publish a randomized clinical trial that proved the existence of NCGS; confirmation later came from the italian study of Di Sabatino[11], who showed in a randomized, placebo-controlled, cross-over design, a small, but statistically significant, alteration of symptoms in NCGS patients when they were gluten challenged.

The main issues of NCGS are[12,13,14]:

1. most of the times, NCGS is self-diagnosed of diagnosed by alternative health care practitioners
2. people who decide to go gluten-free rarely exclude CD before starting the diet, and when they address the doctor for evaluation, alternative diagnoses such as bacterial overgrowth or food intolerances (lactose, fructose) are found
3. aproximately one in four people with NCGS have persistent symptoms despite dietary gluten restriction

Figure 1: Spectrum of IBS-like syndromes (modified after Verdu AF, Am J Gastro 2009)



The prevalence of NCGS is variable, with reported values between 0.5 and 13%[15]. It is estimated that nowadays more people are following a GFD after a self-diagnosis of gluten-sensitivity than patients with CD[16]. Unlike the other gluten-related disorders, the diagnosis of NCGS is purely clinical, considering that there is no specific biomarker or characteristic histopathological changes on enterobiopsy. A diagnostic algorithm was recently proposed, which includes proof of both gluten responsiveness and

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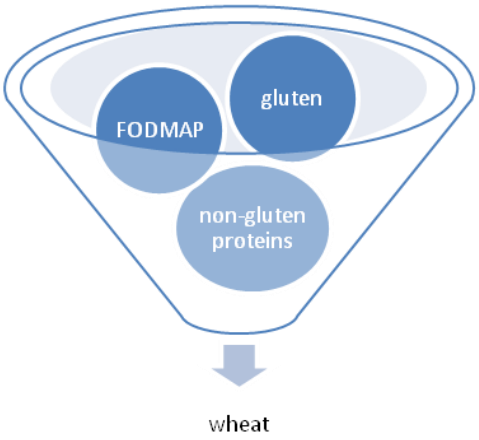
relapse on gluten challenge (Salerno criteria)[17].

ROLE OF GLUTEN AND OTHER TRIGGERS IN NCGS

The pathogenesis of NCGS is not completeley understood. The name NCGS implies that gluten is the culprit for the symptoms associated with this condition. However, recently there has been some questioning about gluten being the real trigger in NCGS, while considering other components which are also found in the cereals avoided in the GFD[18] – Figure 2.

Figure 2. Wheat components as possible triggers for NCGS



In this setting a "gluten conspiracy"[19] was described, which comprises two main ideas: if wheat is causing the symptoms, it must be the gluten in wheat responsible for them, and if the GFD improves the symptoms, this benefit is due to withdrawal of gluten. The pitfall of proving this misconception, that gluten is not the (only) one responsible, is that most of the challenges in clinical trials are performed with wheat (slices of bread, wheat flour capsules), and wheat contains not only gluten, but non-gluten proteins and non-protein components such as FODMAPs.

Among the possible non-gluten triggers, FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) and α-amylase/trypsin inhibitors (ATIs) have been studied in the literature.

The wheat kernel contains many components, among which the following are of interst for NCGS:
i) Proteins
- Storage proteins – represented by gluten (glutenins and prolamins – gliadin in wheat, and the equivalents secalin in barley and hordein in rye)
- Metabolic proteins – enzymes, enzyme inhibitors (eg. ATI – amylase-trypsin inhibitor), lectins (eg. wheat germ aglutinin – WGA)

ii) *Carbohydrates*
- Oligosaccharides, lactose, fructose, polyols (sorbitol, mannitol) – they osmotically draw water and are easly fermented by colonic bacteria (leading to gas formation in the gut lumen), which clinically translates into diarrhea, bloating and flatulence

FODMAPs

FODMAPs, an acronym for some osmotically-active, easily fermented carbohidrates, which are found also in gluten-containing cereals, have been described as a possible culprit of digestive symptoms in patients with NCGS[20,21,22,23]. A diet with reduced intake of FODMAPs (low-FODMAP), which has proven beneficial for IBS[24], has also been theoretized as being useful for NCGS patients.

In 2011, Biesiekierski showed that among cereal foods there is an overlap between the gluten-free and low-FODMAP ones, which could represent a confounder regarding the real culprit in NCGS: thus, the misconception that gluten is responsible for the digestive symptoms could be in fact explained by the presence of FODMAPs in the diet[25].

Another study performed by Biesiekierski on 37 NCGS patients (normal duodenal histology, negative HLA DQ 2/8) revealed that after 2 weeks on low-FODMAP (which lead to a significant relief of symptoms), there were no specific or dose-dependent effects upon dietary challenge in 3 randomized groups – high gluten (16 g gluten/day), low gluten (2 g gluten/day + 14 g whey protein/day) or control (16 g whey protein/day) diet for 1 week[26]. Gluten-specific effects were observed in only 3 out of 37 patients (8.1%). After a washout period of at least 2 weeks, 22 of the 37 patients crossed over to 3 groups which were given gluten (16 g/day), whey (16 g/day) or control (no additional protein) diet for 3 days. After the 3-day rechallenge, there were no differences between the three groups. Moreover, none of the 3 individuals

who had a previous gluten-specific response in the first part of the trial reported such a response upon crossover. However, this short exposure to gluten in the second part of the study was associated with higher depression scores, which could explain why NCGS patients feel better on a GFD despite the persistence of gastrointestinal symptoms.

In conclusion, this study proved that gluten had no effect in patients with NCGS placed on low FODMAPs diets, and these carbohydrates could be the true cause of symptoms. Thus, we can state that people who eat gluten-free could be in fact sensitive to FODMAP and not to gluten, and the benefits of the GFD could be explained by its overlap with the low-FODMAP diet.

Among the limits of this trial, we should consider the possible nocebo effect on reintroduction of gluten/whey in the study groups.

The questionable role of gluten in NCGS is also supported by the double blind, cross-over trial of Zanini, who showed that gluten challenge induces symptom recurrence in only one third of NCGS patients[27].

Amylase-trypsin inhibitors (ATIs)

Beside FODMAPs, Schuppan's group identified some non-gluten proteins as a possible trigger for NCGS, specifically amylase-trypsin inhibitors (ATIs)[28,29]. These have been shown to induce intestinal inflammation by activation of TLR4 (toll-like receptor 4), effect limited to gluten-containing cereals only (wheat,barley, rye)[18].

In addition to ATIs, other non-gluten proteins such as WGA (wheat germ aglutinin) are considered as possible triggers for NCGS-like symptoms[30]. Current data has shown that these lectins can increase intestinal permeability, through mechanisms still unknown.[31]

CONCLUSIONS

Current knowledge suggests that the symptomatic benefit of a GFD in NCGS patients could be in fact not the consequence of gluten elimination, but avoidance of other compounds found in cereals such as FODMAPs or ATIs. Considering the evidences that question the causative role of gluten in NCGS, some authors have proposed renaming of this condition to non-celiac wheat sensitivity[32].

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