

Culprits in non-celiac gluten-sensitivity

Vasile D. Balaban^{1,2}, Alina Popp^{2,3}, Georgiana Robu¹, Bogdan Macadon¹, Mihăiță Pătrășescu¹, Săndica Bucurică^{1,2}, Raluca S. Costache^{1,2}, Petruț Nuță¹, Florentina Ioniță Radu^{1,4}, Mariana Jinga^{1,2}

INTRODUCTION

The growing interest for gluten-free diet (GFD) in the last decades has led 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 report⁴. NCGS describes the individuals whose symptoms get better on a GFD, in the absence of CD or wheat allergy⁵. 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 Sabatino¹¹, 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.

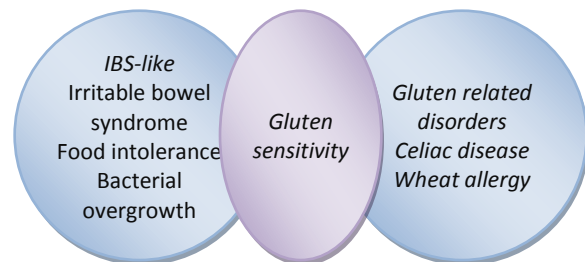
The main issues of NCGS are^{12,13,14}:

1. most of the times, NCGS is self-diagnosed or 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. approximately 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 CD¹⁶. 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 enterobioscopy. A diagnostic algorithm was recently proposed, which includes proof of both gluten responsiveness and

¹ Carol Davila Central Emergency Military Hospital, Bucharest

² Carol Davila University of Medicine and Pharmacy, Bucharest

³ Alfred Rusescu Institute for Mother and Child Care, Bucharest, Romania

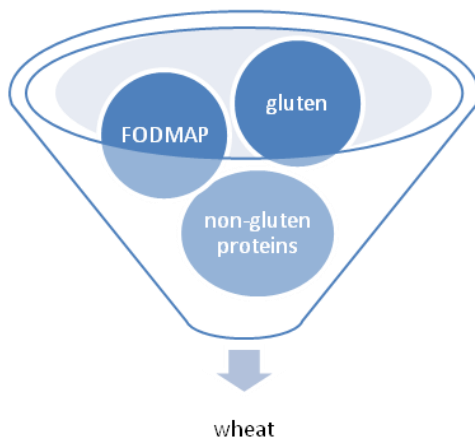
⁴ Titu Maiorescu University, Faculty of Medicine, Bucharest

relapse on gluten challenge (Salerno criteria)¹⁷.

ROLE OF GLUTEN AND OTHER TRIGGERS IN NCGS

The pathogenesis of NCGS is not completely 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 GFD¹⁸ – 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 interest 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 agglutinin – WGA)

ii) Carbohydrates

- Oligosaccharides, lactose, fructose, polyols (sorbitol, mannitol) – they osmotically draw water and are easily 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 carbohydrates, 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 IBS²⁴, has also been theorized 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 diet²⁵.

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 week²⁶. 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 patients²⁷.

References:

1. Verdu EF, Armstrong D, Murray JA. Between celiac disease and irritable bowel syndrome: the "no man's land" of gluten sensitivity. *Am J Gastroenterol* 2009; 104:1587–94.
2. Verdu EF. Editorial: Can gluten contribute to irritable bowel syndrome? *Am J Gastroenterol*. 2011;106(3):516-8. doi: 10.1038/ajg.2010.490.
3. Vazquez-Roque MI, Camilleri M, et al. A controlled trial of gluten-free diet in patients with irritable bowel syndrome-diarrhea: effects on bowel frequency and intestinal function. *Gastroenterology* 2013; 144(5):903-911.e3.
4. Ludvigsson JF, Leffler DA, Bai JC, et al. The Oslo definitions for coeliac disease and related terms. *Gut* 2013; 62: 43–52.
5. Catassi C, Bai JC, Bonaz B, et al. Non-celiac gluten sensitivity: the new frontier of gluten related disorders. *Nutrients* 2013; 5:3839-3853.
6. Ellis A, Linaker BD. Non-celiac gluten sensitivity? *Lancet* 1978; 1:1358- 1359.
7. Jonas A. Wheat sensitive - but not coeliac. *Lancet* 1978; 1:1047.
8. Cooper BT, Holmes GK, Ferguson R, Thompson RA, Allan RN, Cooke WT. Gluten-sensitive diarrhea without evidence of celiac disease. *Gastroenterology* 1980; 79(5 Pt 1): 801-806.
9. Lebwohl B, Ludvigsson JF, Green PH. Celiac disease and non-celiac gluten sensitivity. *BMJ* 2015; 351:h4347.
10. Biesiekierski JR, Newnham ED, Irving PM, et al. Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. *Am J Gastroenterol* 2011; 106: 508–514.
11. Di Sabatino A, Volta U, Salvatore C, et al. Small amounts of gluten in subjects with suspected nonceliac gluten sensitivity: a randomized, double-blind, placebo-controlled, cross-over trial. *Clin Gastroenterol Hepatol* 2015; 13(9):1604-1612.e3.
12. Volta U, Bardella MT, Calabro A, et al. An Italian prospective multicenter survey on patients suspected of having non-celiac gluten sensitivity. *BMC Med* 2014; 12:85.

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 agglutinin) are considered as possible triggers for NCGS-like symptoms³⁰. 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 sensitivity³².

-
13. Biesiekierski JR, Newnham ED, Shepherd SJ, et al. Characterization of adults with a self-diagnosis of nonceliac gluten sensitivity. *Nutr Clin Pract* 2014; 29:504-509.
 14. Tavakkoli A, Lewis SK, Tennyson CA, et al. Characteristics of patients who avoid wheat and/or gluten in the absence of celiac disease. *Dig Dis Sci* 2014; 59:1255-1261.
 15. Molina-Infante J, Santolaria S, Sanders DS, Fernandez-Banares F. Systematic review: nonceliac gluten sensitivity. *Aliment Pharmacol Ther* 2015; 41:807-820.
 16. Rubio-Tapia A, Ludvigsson JF, Brantner TL, Murray JA, Everhart JE. The prevalence of celiac disease in the United States. *Am J Gastroenterol*. 2012; 107(10):1538-1544.
 17. Catassi C, Elli L, Bonaz B, et al. How the diagnosis of non celiac gluten sensitivity (NCGS) should be confirmed: The Salerno experts' criteria. *Nutrients* 2015; 7(6):4966-4977.
 18. Fasano A, Sapone A, Zevallos V, Schuppan D. Nonceliac gluten sensitivity. *Gastroenterology* 2015; 148 (6):1195-1204.
 19. Gibson P. Food intolerance. Oral presentation, "Clinical nutrition: What's new in 2014?" Session at UEG Week 2014, October 18-22, Vienna, Austria.
 20. Gibson PR, Shepherd SJ. Food choice as a key management strategy for functional gastrointestinal symptoms. *Am J Gastroenterol*. 2012; 107(5):657-66.
 21. Murray K, Wilkinson-Smith V, Hoad C, et al. Differential effects of FODMAPs (fermentable oligo-, di-, mono-saccharides and polyols) on small and large intestinal contents in healthy subjects shown by MRI. *Am J Gastroenterol*. 2014; 109(1):110-119.
 22. Ontiveros N, Hardy MY, Cabrera-Chavez F. Assessing of Celiac Disease and Nonceliac Gluten Sensitivity. *Gastroenterol. Res. Pract.* 2015:723954.
 23. Volta U, Caio G, Tovoli F, De Giorgio R. Non-celiac gluten sensitivity: questions still to be answered despite increasing awareness. *Cell Mol Immunol* 2013, 10:383-392.
 24. Halmos EP, Power VA, Shepherd SJ, et al. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. *Gastroenterology*. 2014; 146(1):67-75.e5.
 25. Biesiekierski JR, Rosella O, Rose R, et al. Quantification of fructans, galacto-oligosaccharides and other short-chain carbohydrates in processed grains and cereals. *J Hum Nutr Diet* 2011; 24: 154-76
 26. Biesiekierski JR, Peters SL, Newnham ED, Rosella O, Muir JG, Gibson PR. No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates. *Gastroenterology* 2013; 145: 320-328.
 27. Zanini B, Baschè R, Ferraresi A, et al. Randomised clinical study: gluten challenge induces symptom recurrence in only a minority of patients who meet clinical criteria for non-coeliac gluten sensitivity. *Aliment Pharmacol Ther* 2015; 42: 968-976.
 28. Schuppan D, Pickert G, Ashfaq-Khan M, Zevallos V. Non-celiac wheat sensitivity: differential diagnosis, triggers and implications. *Best Pract Res Clin Gastroenterol*. 2015; 29(3):469-476.
 29. Junker Y, Zeissig S, Kim SJ, et al. Wheat amylase trypsin inhibitors drive intestinal inflammation via activation of toll-like receptor 4. *J Exp Med*. 2012; 209(13):2395-2408.
 30. Aziz I, Hadjivassiliou M, Sanders DS. The spectrum of noncoeliac gluten sensitivity. *Nat Rev Gastroenterol Hepatol*. 2015; 12(9):516-526.
 31. Dalla Pellegrina C, Perbellini O, Scupoli MT, et al. Effects of wheat germ agglutinin on human gastrointestinal epithelium: insights from an experimental model of immune/epithelial cell interaction. *Toxicol Appl Pharmacol* 2009;237:146-153.
 32. Carroccio A, Rini G, Mansueto P. Non-Celiac Wheat Sensitivity Is a More Appropriate Label Than Non-Celiac Gluten Sensitivity. *Gastroenterology* 2014; 146(1):320-321.