EDITORIAL

Exploring the Strange New World of Non-Celiac Gluten Sensitivity

In critical moments, men sometimes see exactly what they wish to see.

Spock: Star Trek, the Original Series

This month's issue of *Clinical Gastroenterology and Hepatology* features the latest clinical trial investigating the phenomenon of non-celiac gluten sensitivity (NCGS). Although NCGS has been reported for at least 35 years,[1] clinical trials to rigorously investigate this syndrome are still in their infancy. To date, only a few prospective randomized clinical trials on the role of gluten in inducing symptoms in individuals without celiac disease have been published,[2–4] each with its own strengths and limitations. This is to be expected in a relatively young area of investigation, but it has resulted in a significant, and perhaps undue, degree of skepticism regarding the nature and even the existence of NCGS. To better understand where the current study fits into the NCGS literature, we will review the pertinent features of prior studies.

In 2007, Wahnschaffe et al[5] published "Predictors of Clinical Response to the Gluten Free Diet in Patients with Diarrhea-Predominant Irritable Bowel Syndrome." Although not a randomized trial, this study was among the first rigorous prospective studies to begin to investigate responses to gluten in individuals without celiac disease. In this study, 41 patients with diarrhea-predominant irritable bowel syndrome (IBS-D) and normal or increased intraepithelial lymphocytes on duodenal biopsy were placed on a gluten-free diet (GFD). The authors reported a statistically significant 30% improvement in an IBS patient-reported outcome score, decrease in mean bowel frequency from 4 to 2 per day, and that nearly half of subjects normalized symptoms. Participants more likely to respond well to the GFD were DQ2 and/or immunoglobulin G antigliadin antibody/immunoglobulin G tissue transglutaminase positive. Although the lack of a control group limited interpretation, this study set the stage for future investigation and suggested some pathophysiologic mechanisms.

The modern age of NCGS began in 2011 with the publication of "Gluten Causes Gastrointestinal Symptoms in Subjects Without Celiac Disease: A Double-Blind Randomized Placebo-Controlled Trial."[3] This study firmly established the double-blind randomized controlled trial as feasible and thus the optimal design of NCGS clinical studies. Key to the success and influence of this study was that the primary aim "to determine whether gluten ingestion can induce symptoms in non-celiac individuals" and design were both laudably simple. In this study, the authors took 34 patients with preexisting suspected NCGS (without celiac disease but with irritable bowel syndrome [IBS] symptoms that were controlled on a GFD) and randomized them to gluten or placebo in the form of a muffin for 6 weeks. During the treatment phase, 68% of participants receiving gluten experienced symptomatic exacerbation compared with 40% on placebo. Symptoms occurred quickly, generally within the first 2 weeks, and included both standard gastrointestinal symptoms and fatigue. Predictive measures that were based on the data from Wahnschaffe et al[5] including HLA type and antigliadin antibody titer did not appear to select for response. This study provided compelling evidence that symptoms could be elicited by gluten in non-celiac subjects, leaving questions of prevalence and pathophysiology to future studies.

The 2012 article "Non-Celiac Wheat Sensitivity Diagnosed by Double-Blind Placebo-Controlled Challenge: Exploring a New Clinical Entity"[6] provided additional important data. This trial also had the primary aim of confirming the existence of NCGS, but unlike the previous articles, self-initiation of a GFD was an exclusion criterion for the trial that drew from a population of patients with IBS-like symptoms and normal celiac serologies, duodenal, histology, and negative skin prick test and serum-specific immunoglobulin E to wheat. Although this report focuses on the patients with NCGS, one of the important findings was that of 920 consecutive IBS patients, 276 had dramatic improvement in symptoms on a GFD with exacerbation during double-blind gluten challenge, suggesting that up to one-third of IBS patients may improve with gluten restriction. Furthermore, most also appeared to have more diffuse food sensitivity, with reactions to cow's milk protein and/or a history of other food allergy/intolerance. These data suggested both that NCGS may be common in patients with functional-type gastrointestinal symptoms and also that food intolerances tend to travel in packs.

The next report, published in 2013, was reminiscent of the article by Wahnshaffe et al[5] in that it enrolled 45 otherwise typical IBS-D patients with no history of gluten avoidance and randomized them to a GFD or a regular diet.[4] The study focused on mechanisms and potential biomarkers including intestinal permeability, HLA type, and tight junction proteins, as well as confirming that a GFD did result in improved stool frequency.

The last addition to the NCGS clinical trial was a follow-up study by Biesiekierski et al[2] titled "No Effects of Gluten in Patients With Self-reported Non-Celiac Gluten Sensitivity After Dietary Reduction of Fermentable, Poorly Absorbed, Short-chain Carbohydrates." This study was more ambitious than prior studies, with multiple gluten doses, a partial crossover design, and evaluation of other dietary components including

fermentable oligo-di-monosaccharides and polyols (FODMAPs) and whey protein. Complex studies tend to yield complex results. This study is interpretable in multiple ways but appeared to show in a population with suspected NCGS very similar to the earlier study from this group that people who were in theory feeling well on a GFD improved further on a low FODMAP diet and then failed to worsen with gluten exposure. These results cast significant doubt on whether NCGS was a distinct clinical entity and whether intolerance to FODMAPs was being misinterpreted as NCGS by patients and physicians.[7]

The latest trial is a double-blind, randomized crossover trial by Di Sabatino et al,[8] which is published in this issue of *Clinical Gastroenterology and Hepatology.* Eligible subjects were "strongly suspected" to have NCGS on the basis of the patient's self-report, ie, intestinal or extraintestinal symptoms believed to be worsened by exposure to even small amounts of gluten. As was the case in other series of patients with NCGS,[2,9,10] there was a strong female predominance (87%). All 61 patients were on a gluten-containing diet at the time of enrollment. Of note, patients with a known sensitivity to dietary FODMAPs were excluded. After a 1-week run-in period in which all subjects strictly adhered to a GFD, subjects were randomized to capsules containing 4.375 g of gluten or placebo containing the equivalent amount of rice starch. After exposure to gluten or placebo for 1 week, all subjects then spent 1 week without exposure (ie, washout) and then crossed over to the other arm for 1 more week. The primary outcome was a summary score of 15 intestinal and 13 extraintestinal symptoms on day 7 of gluten exposure compared with placebo exposure.

The investigators found that patients experienced more severe symptoms in the gluten arm compared with the placebo arm (mean score, 56.9 vs 43.7; $P = .034$). At first glance this is a positive trial, congruent with the first trial conducted by Biesiekierski et al[3] that concluded that gluten causes greater symptoms than placebo. But further analysis performed by the investigators reveals a complex story. With regard to individual patient responses to gluten compared with placebo, most subjects either had no significant difference in symptoms during gluten exposure compared with placebo or felt more severe symptoms during the placebo period. The overall positive finding was driven by large effects in 3 individuals whose symptoms were far more severe during gluten exposure compared with placebo. It is also notable that no baseline biomarkers (including fecal calprotectin, intraepithelial lymphocytosis, immunoglobulin G antigliadin antibodies, or HLA haplotype) correlated with a significant symptomatic worsening from gluten compared with placebo. But there was 1 objective predictor of symptoms; patients on average had more severe symptoms during the first week of exposure than during the second week of exposure, regardless of whether the exposure was gluten or placebo.

What are we to make of these mixed results? On the one hand, gluten caused more severe symptoms than placebo. But this overall positive result was driven by a minority of patients, whereas the rest had no (or at most a modest) worsening compared with placebo. These findings can be a Rorschach test of sorts, in which the viewer draws interpretations that are based on his or her prior beliefs about NCGS.[7,11] Some will conclude that more patients would have a symptomatic worsening in the gluten arm if the dose of gluten were higher; moreover, the positive finding after the exclusion of FODMAP-sensitive individuals may be a rebuttal to the negative follow-up trial by Biesiekierski et al.[2] Others would point out that the 3 patients who fared worse on gluten may be a product of chance; still others will question whether the use of 10 capsules daily in each arm will magnify the potential for nocebo effect (ie, a negative placebo effect), especially during the first week of exposure.[12]

These varying interpretations point to the difficulty of conducting dietary intervention trials, particularly when attempting to define an ill-understood clinical entity. Clinical trials that involve a change in diet (such as the GFD) are inherently more complicated and unpredictable than drug studies because foods are complex, and any prescribed dietary change inevitably leads to secondary diet changes. A pertinent example of inadvertent secondary dietary changes is the increase in fat content and decrease in fiber that occurs with adoption of the GFD.[13–15] In addition, symptoms themselves lead to dietary change because individuals naturally tend toward blander diets when they are experiencing gastrointestinal symptoms. Finally, all these studies rely at least in part on diet recall, which is subjective, especially as regards portion size, and subject to a significant Hawthorne effect.[16] These factors may account in part for the order effect observed in this trial, in which both groups had more severe symptoms during the first half of the trial before crossover.

It is therefore not surprising that this trial, like its predecessors, seems only to contribute to the uncertainty about NCGS. But from these results and those of previous trials, it is reasonable to draw several conclusions. First, NCGS is distinct from IBS in that extraintestinal symptoms are prominent and respond to dietary modification, unlike the extraintestinal symptoms that can be seen in IBS.[17] Indeed, half of the individual clinical components that worsened with gluten compared with placebo (aphthous stomatitis, depression, and foggy mind) related to non-intestinal symptoms, and this is certainly compatible with symptoms reported by NCGS patients in clinical practice. Second, there are no proven biomarkers for NCGS at this time, and studies focused on these have had, at best, conflicting results.[18,19] This is particularly important to emphasize in light of the fact that patients are looking for answers and may be offered testing for NCGS via non–evidence-based tests of blood, stool, or saliva. Third, it is undeniable that gluten exerts a large nocebo effect on a significant

number of patients in this study, which is consistent with that observed in previous trials. This needs to be accounted for in the design of future trials and acknowledged in our discussions with patients who are coming to us seeking an honest, evidence-based approach to improving their health. We also would posit that the great utility of blinded gluten challenge has led to overly ambitious studies that attempt to address NCGS symptom distribution and severity, pathomechanisms, biomarkers, and prevalence, often all in a single study. If nothing else, NCGS is a complex entity and will not give up its secrets easily. As such, studies with more limited but focused aims are likely to be more effective in providing important incremental knowledge.

Finally, it is counterproductive to debate whether NCGS is "real"; the patients are real and seeking our care. Some of these patients are in a great deal of distress, and we should try to help them. At the present time, this involves ruling out celiac disease, testing for additional food intolerances or gastrointestinal conditions, and providing the latest data regarding what we know—and what we do not know—about this evolving entity.

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Conflicts of interest
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