Nonceliac Gluten Sensitivity or Wheat Intolerance Syndrome?

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The increase in world-wide consumption of a Mediterranean diet, which includes a wide range of wheat-based foods, has possibly contributed to an alarming rise in the incidence of wheat (gluten?)-related disorders.1,2 Gluten, the main protein complex in wheat, barley, and rye, is a mixture of alcohol-insoluble (“glutenins”) and alcohol-soluble (“gliadins”) proteins.3 Gliadins are a group of proline and glutamine-rich proteins resistant to digestion in the gastrointestinal tract.

Gluten consumption has been linked to a wide range of disorders, including celiac disease (CD), wheat allergy, dermatitis herpetiformis, gluten ataxia, peripheral neuropathy, and possibly a “new” entity called “nonceliac gluten sensitivity.”4-6

In fact, in recent years there has been a resurgent interest in an entity first described in 19787 a so-called “nonceliac gluten sensitivity” (NCGS). This concept now applies to patients who do not meet the criteria for CD, but who report experiencing a number of intestinal and/or extra-intestinal symptoms after consuming gluten-containing foods. These patients by definition present neither the autoantibodies nor the enteropathy characteristic of CD.

We propose here that NCGS is a misnomer and probably an umbrella term including various clinical entities.

The Clinical Spectrum of NCGS

NCGS is characterized by a various combination of intestinal and extra-intestinal symptoms, mostly occurring soon after ingestion of gluten-containing foods and disappearing quickly with a strict gluten-free diet.8 By definition, these patients do not present with CD-specific autoantibodies or enteropathy.

Upon reintroduction of gluten, rapid relapse typically occurs. The clinical manifestations are mostly, but not exclusively, gastrointestinal, and are similar to those of irritable bowel syndrome (IBS).9,10

In a recent prospective survey11 conducted in 38 Italian centers on 486 patients with suspected NCGS, the clinical picture was characterized by combined gastrointestinal and systemic symptoms (Figures 1 and 2). Among the most common gastrointestinal manifestations were abdominal pain, bloating, diarrhea and/or constipation, nausea, epigastric pain, gastroesophageal reflux, and aphthous stomatitis. The systemic manifestations were most commonly tiredness, headache, fibromyalgia-like joint/muscle pain, leg or arm numbness, ‘foggy mind,’ dermatitis or skin rash, depression, anxiety, and anemia. Of note, in this study, 95% of patients reported the appearance of symptoms every time or often after the ingestion of gluten containing food. In more than one-half of these patients, the symptoms occurred within 6 hours after gluten ingestion; in about 40%, between 6 and 24 hours after ingestion; and only in less than 10%, more than 24 hours after ingestion. Similar data had been published by Carroccio et al12 on reviewing the clinical features of 276 patients with NCGS. In a double-blind placebo-controlled trial, which included 34 patients with IBS,13 with CD ruled out and symptoms controlled with a gluten-free diet, it was found that upon reintroduction of gluten, intestinal symptoms and fatigue reappeared more frequently than in the control group (68% and 40%, respectively). Additional extra-intestinal clinical manifestations described include neurologic disorders such as attention deficit and hyperactivity, sleep problems, and cerebellar ataxia14; psychiatric disorders such as autism, depression, bipolar disorder, and schizophrenia15-18; muscular problems,17 and even autoimmune diseases such as psoriasis.19

Although the natural history of NCGS is far from being known, available published evidence would suggest that the prevalence of autoimmune conditions in NCGS is not higher than that of the general population.9 In the study by Sapone et al20 on 26 patients with NCGS, none had autoimmune disorders. However, in the large series recently reported by Volta et al11 an associated autoimmune disease was detected in 14% of cases.

How common is NCGS? Estimating the prevalence of NCGS is impossible. In fact, the lack of objective diagnostic criteria (see below) impedes an assessment of the prevalence. As a result, various estimates ranging from 0.6% based on rigorous national US surveys21,22 to around 6% (6 patients with NCGS for each patient with CD)6 to a whopping 50% of the general population in some popular websites. NCGS would seem to be more common among adults than children, with an average age at onset of 40 years (17-63 years age range). There is limited evidence of the existence of NCGS in children, as few studies are available, and conducted on small numbers of patients.23,24

ATI Amylase/trypsin inhibitor
CD Celiac disease
FODMAP Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols
IBS Irritable bowel syndrome
NCGS Nonceliac gluten sensitivity

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Like CD, NCGS appears to be more prevalent among women than men, with a male to female ratio of 1:2.5.\textsuperscript{10,25} It also seems to be more common in first degree relatives of patients with CD, because according to the results of a retrospective study by Volta et al,\textsuperscript{25} 12.8\% of patients with NCGS were first degree relatives of patients with CD. Some old studies\textsuperscript{26,27} had shown that local instillation of gluten in the rectum of relatives of patients with CD who did not have CD resulted in mucosal evidence of sensitization (a significant increment in the absolute number of intraepithelial lymphocytes). Whether this could be related to NCGS remains, however, to be demonstrated.

**Diagnosing NCGS**

In spite of uncertainties on definition, a set of diagnostic criteria for NCGS has been proposed,\textsuperscript{6,10,28} largely based on the exclusion of CD and wheat allergy. Although the exclusion of CD is obviously crucial to entertain the possible diagnosis of NCGS, in reality often times a gluten-free diet is
initiated by the patients without having first ruled out the
diagnosis of CD. In a recent survey on 248 adults with self-
reported NCGS, this was found to be the case in as many as 62% of the respondents.29 The detection of normal levels of
specific IgE and/or of negative skin tests for gluten and
wheat is considered adequate to eliminate the quite rare occurrence of IgE-mediated wheat allergy causing symptoms
suggestive of NCGS (ie, exclusion of immediate type allergy
to wheat). Typically, clinical symptoms because of NCGS are
described as occurring soon after ingestion of gluten, and
regressing also quite rapidly after its withdrawal (ie, rapid
induction of intestinal and extra-intestinal symptoms by
 gluten containing foods). Normal intestinal mucosa or “lym-
phocytic enteritis” (an increase in the number of intraepithe-

dial lymphocytes) is also part of the NCGS diagnostic criteria.

The need to rule out CD before labeling a patient with
NCGS cannot be overemphasized. In fact, beginning a
 gluten-free diet without having first gone through an
adequate diagnostic work-up for CD would evidently result
in a number of missed or at least delayed diagnoses of CD.
Individuals believing to be affected by a gluten-related disor-
der should be advised to seek medical guidance, and be
screened for CD while on a gluten-containing diet.30 An
adequate work-up for CD is, therefore, mandatory, including
in most cases an intestinal biopsy while on a gluten-
containing diet. It has been reported that about 60% of pa-
tients with NCGS have a completely normal mucosa (<25%
of intraepithelial lymphocytes, grade 0 of the modi-

cified Marsh-Oberhuber classification). The remaining 40%
may have a modest increase in intraepithelial lymphocytes
up to 40% (grade 1).4,10,20,25 Grade 1 intestinal lesion has
traditionally been considered of a very low specificity for
CD, as it is also common in a number of other conditions,
such as intestinal infections, Helicobacter pylori infections,
nonsteroidal anti-inflammatory drugs use, recurrent abdom-
inal pain, common variable immunodeficiency, etc.31-34

Still, as also reiterated by a consensus of the European Soci-
ety of Pediatric Gastroenterology and Nutrition,35 Marsh
grade 1 lesion is part of the spectrum of CD. Therefore, in pa-
tients showing Marsh 1 changes, it becomes important to
make a proper differential diagnosis between CD and NCGS.
In this regard, the levels of γδ T-cell receptors in intraepithelial
lymphocytes can be very helpful because these appear to be
extremely specific for CD.35 The detection of deposits of IgA
anti-tissue transglutaminase antibodies in intestinal mucosa
has an additional discriminatory diagnostic value.36

Supportive but unspecific diagnostic criteria are consid-
ered positive antigliadin antibodies, mainly IgG and only occa-
sionally IgA class, found to be between 25% and 56% of
NCGS cases.4,10-12,25,38 This prevalence, although lower
than in CD (around 85%), is clearly higher than of the
healthy population (2%-8%) but only marginally higher
than what found in other entities such as IBS (20%) or auto-
immune hepatitis (21.5%). The titers of these antibodies are
generally higher than in patients with CD,25,26 and they
appear to regress to normal in the vast majority of patients
with NCGS 6 months on a gluten-free diet,29 unlike what
happens in CD, where they appear to persist longer.10,39
However, it remains unclear if these antibodies have a path-
ogenic significance at all; and certainly, given their partial
but substantial overlapping with controls and other disor-
ders, they lack a meaningful diagnostic value.

HLA-DQ2 and/or HLA-DQ8 genotypes are positive in
about 40% of patients with NCGS.4,20,25 This prevalence is,
thus, much lower than that of CD (where is nearly 100%) and
does not differ from that of the general population
(around 30%). Thus, genetic testing for HLA haplotypes is
not useful for diagnostic purposes.

Gluten Challenge for NCGS Diagnosis
The lack of a specific biomarker requires as the only reliable
standard for diagnosis a double blind, placebo-controlled chal-
lenge. However, this is seldom used even in published studies,
and rarely in clinical practice, where the diagnosis is almost
invariably made on patient’s report and often times even
without having properly excluded CD. It can immediately be
seen as this represents a major problem for any progress in un-
derstanding this entity. Moreover, there is no agreement on
what would constitute a proper gluten challenge, as modalities
and amount of gluten used in clinical trials have been varied.
For example, Biesiekierski et al13 conducted a double-blind
placebo-controlled trial using either gluten (bread and muffins
containing 16 g of gluten) or placebo (the same foods, indistin-

uounguishable to the eye and taste, but gluten-free). Carroccio
et al11 conducted a crossover trial challenge using capsules
containing xylose or wheat. Francavilla et al23 in their open-

label trial in children used a dose of “at least 5 g” per day.
Clearly, there is urgent need for a standardization of a diag-
nostic protocol for any clinical trial. As it stands, the diagnosis
is largely relying on patients’ report, with all the amount of un-
certainty that this carries.

A Critical Reassessment of NCGS
The Unproven Role of Gluten in NCGS
An important point to be noted at this juncture is that even
when a double blind placebo-controlled challenge is per-
formed, there is no proof that gluten is responsible for the
symptoms unless chemically purified gluten is used. Instead,
wheat is commonly used to conduct such challenges, and pa-
tients thought to have NCGS may in reality react to compo-
nents of wheat that have nothing to do with gluten. Alternative
options include, but are not limited to: (1) starch and other carbohydrates such as fructans (see below for more

ight into the carbohydrates that may be responsible for a
vast portion of patients with NCGS16); and (2) amylase/
trypsin inhibitors (ATIs)—a series of proteins found in
some experimental systems to have a proinflammatory effect
in the intestine. Alternative possibilities are detailed below.

Fermentable Oligosaccharides, Disaccharides,
Monosaccharides, and Polyols
The same Australian group that reported a study widely
quoted as the first and arguably the best documentation of

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the existence of NCGS, subsequently produced a strong evidence that some patients with NCGS patients, defined exactly as those who were investigated in the first report, were indeed affected not by gluten, but by eating large amounts of a series of carbohydrates, collectively known under the acronym of “FODMAP” (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols). In fact, when patients enrolled as NCGS were first put on a diet devoid of FODMAP, their IBS-like symptoms significantly improved; and when they were then allocated under double-blind circumstances to 3 groups (eating no gluten; 2 g of gluten per day; or 16 g of gluten per day, in a cross-over type of investigation), there was no difference between these 3 regimens in terms of symptoms, thus, clearly demonstrating no role for gluten at least in these patients with IBS-like NCGS. In fact, eliminating “gluten” in practical terms may mean eliminating FODMAP, as wheat, rye, and barley-derived products carry the highest FODMAP content, predominantly fructans (fructo-oligosaccharides) and galacto-oligosaccharides, and reintroducing “gluten” implies reintroducing substantial amounts of these poorly digested carbohydrates.

Of course, especially at the light of the fact that the population enrolled in this study was selected based on showing IBS-like symptoms and patients with Marsh 1 lesions were by definition excluded, it remains to be seen what portion of the larger population of patients with NCGS these patients with FODMAP-sensitivity represent. It is indeed unlikely that all subjects with NCGS are FODMAP-sensitive, as this condition could hardly explain the occurrence of extra-intestinal manifestations such as depression.

ATIs

Many modern as well as ancient wheat cultivars possess a variety of low molecular weight proteins that are inhibitors of alpha-amylases and proteases. Such proteins, first described by an Italian group in 1973, play an important protective role in the grain. In 2012, Junker et al identified 2 such proteins (alpha-ATIs or ATIs): CM3 and 0.19, that are potent activators of various innate immune cells such as dendritic cells and macrophages. ATIs engage the TLR4–MD2–CD14 complex and lead to upregulation of maturation markers eliciting release of proinflammatory cytokines in cells from patients with and without CD and in biopsies from patients with CD. Could these effects be also responsible for some of the wheat-related gastrointestinal symptoms experienced by patients with NCGS? It is entirely possible, though at the moment only speculative.

Wheat Allergy

Although “classic” IgE-mediated allergy to wheat is well described, there is no evidence that it may manifest itself with IBS-like symptoms. Hence, this entity is quite unlikely to be part of the spectrum of NCGS. However, there is good evidence that at least a subset of patients with NCGS may have a non-IgE-mediated food allergy. In fact, Carroccio et al reported a series of adults with self-reported nonceliac wheat intolerance causing IBS-like symptoms who had a personal history of food allergy in pediatric age, coexistent atopic diseases, positive anti-gliadin, and anti-beta-lactoglobulin antibodies, and eosinophils in the small intestinal mucosa, suggesting they might be suffering from a non-IgE-mediated allergy to wheat. In their prior study on a similar population sample, about one-third of patients with IBS improved on elimination diet and worsened on DBPC challenge with wheat and cow’s milk proteins, suggesting again that a percentage of them could suffer from non-IgE-mediated food allergy. Of interest, the great majority of the patients they studied showed lymphocytic enteritis in the duodenal mucosa (Marsh 1 lesion). Clearly more investigations are needed in this regard.

Early-Stage CD

Although the diagnosis of CD follows a well-standardized process and is clearly defined, there are instances where the disease cannot be recognized as the process has not yet reached the point of being detectable neither by serum antibody testing nor by pathology. Yet, culture supernatants from duodenal biopsies or tissue sections of duodenal biopsies may be able to detect the highly specific autoantibodies in patients who are symptomatic but have a normal histology and negative serum markers for CD. Thus, one can speculate that a portion of patients labeled with NCGS may indeed be patients with seronegative CD still lacking an overt intestinal damage.

A Placebo/Nocebo Effect

The profound effect of placebo is well recognized in a variety of functional gastrointestinal disorders, and even in organic and severe conditions such as fistulizing Crohn’s disease where about 15% of patients experience improvement on placebo. The existence of a relevant phenomenon of placebo/nocebo effect has in fact been reported in double-blind-controlled trials in adult patients with self-reported food intolerances, and the likelihood of a placebo effect of gluten withdrawal has been suggested. In a study on patients with IBS-like symptoms claiming to suffer from various food intolerances, only 12 of the 32 (37.5%) patients self-reporting such symptoms improved on elimination diet and reacted to the DBPC challenges, indicating that almost two-thirds of such patients did indeed present a typical placebo/nocebo effect. Thus, it is quite conceivable that a portion of patients with NCGS, and arguably a substantial one, fall in this category. Given the lack of any objective diagnostic marker, this appears quite likely.

Discussion

We believe that this fascinating area is in a state of fluid transition, with little still known and much to be discovered. However, we also believe that some admittedly provocative conclusions, at the light of what illustrated above, can be drawn. There is no proof that gluten is causing NCGS. Indeed, had it not been for the fact that the role of gluten is well known in CD, we suggest that no one would have thought of it as...
responsible for the self-reported symptoms occurring in patients while eating wheat (absolutely no data are available for any untoward effect caused by rye and/or barley). The term “sensitivity” appears to imply an immune-mediated mechanism as responsible for this vague entity. This is not justified by any robust data, so the use of this term should be discouraged, and the noncommitting, generic term “intolerance” should be used. As we have seen, various different disorders are grouped under this umbrella term (Figure 3): some well identified (such as FODMAP reactivity, placebo/nocebo effect, or non-IgE wheat allergy), other still unclear (such as ATI-induced inflammation, early stage CD, and perhaps even gluten sensitivity).

As a result, we here propose to abandon the misleading term “nonceliac gluten sensitivity” and, in line with a similar proposal advanced by Carroccio et al., we recommend replacing it with the broader, more honest term of “wheat intolerance syndrome” to reflect the following objective elements: the causative role of wheat (not of gluten); the fact that the symptoms can be better described under the term of “intolerance,” a terminology not implying any specific underlying mechanism; and finally, the fact that we are undoubtedly dealing with a series of symptoms that may recognize various causes, hence, falling well under the definition of the term “syndrome.”

Clearly, when more studies will be able to progressively tease out the various components of the wheat intolerance syndrome and clarifying their pathogenesis, then we will abandon this umbrella term. This would be much like what happened for the syndrome of intractable diarrhea of infancy of the 1970s, another descriptive term that progressively “lost many pieces” to new entities such as microvillus inclusion disease, milk protein enteropathy, immune deficiencies, syndromic diarrhea/tricho-hepato-enteric syndrome, Na-losing diarrhea, congenital chloride diarrhea, etc, and eventually ceased to be used.

Until then, let us all humbly make a step backward: change the terminology to a more apt one, stop making diagnostic algorithms as we were dealing with a single entity, and go back to the drawing board to design rigorous prospective, randomized, double-blind placebo-controlled, studies with a well standardized approach to answer all the question marks.

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References


