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Nonceliac Gluten Sensitivity: Sense or Sensibility?

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Recent studies support the existence of a new condition, nonceliac gluten sensitivity, which manifests as intestinal or extraintestinal symptoms that improve or disappear after gluten withdrawal in individuals with normal small-bowel mucosa and negative results on serum antitransglutaminase and antiendomysial antibody testing. Although the clinical value of this concept is under debate, the prevalence of nonceliac gluten sensitivity in the general population is supposed to be many times higher than that of celiac disease. The lack of an unambiguous definition of nonceliac gluten sensitivity, a major pitfall, is primarily related to the heterogeneous cause of this condition, whose symptoms are presumed to be caused by different mechanisms. If nonceliac gluten sensitivity is an etiologically heterogeneous syndrome, then management options should vary according to the predominant or concomitant underlying pathogenic pathways.

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An emerging problem in clinical practice is how to manage patients who experience wheat- or gluten-dependent symptoms in the absence of the main stigmata of celiac disease, such as positive results on serum antitransglutaminase or antiendomysial antibody testing and small-bowel villous flattening (1). This syndrome has been called by various names, including *gluten sensitivity*; *gluten hypersensitivity*; *nonceliac gluten intolerance*; and our preferred term, *nonceliac gluten sensitivity*. Nonceliac gluten sensitivity can be characterized by intestinal symptoms (such as diarrhea, abdominal discomfort or pain, bloating, and flatulence) or extraintestinal symptoms (such as headache, lethargy, attention-deficit/hyperactivity disorder, ataxia, or recurrent oral ulceration) (2), which improve or disappear after gluten withdrawal in individuals in whom celiac disease has been ruled out on the basis of negative serologic results or demonstration of normal small-bowel mucosa (**Table 1**).

The concept of nonceliac gluten sensitivity is not new. Apart from sporadic case reports in children and adults, a double-blind, crossover trial more than 30 years ago (3) showed that 6 of 8 adult patients who had abdominal pain and chronic diarrhea were gluten-sensitive in the absence of celiac disease. Since then, no systematic research has been done, probably because of the difficulty of objectively demonstrating nonceliac gluten sensitivity.

Nevertheless, considerable debate about nonceliac gluten sensitivity has recently surfaced on the Internet, with a sharp increase in forums, patients or patient groups, manufacturers, and physicians advocating a gluten-free diet. Claims seem to increase daily, with no adequate scientific support to back them up. At present, the ratio between Google and PubMed citations for nonceliac gluten sensitivity is 4598:1, more than 10-fold higher than that for breast cancer, Alzheimer disease, lung cancer, or celiac disease itself. This clamor has increased and moved from the Internet to the popular press, where gluten has become "the new diet villain" (4); marketers have estimated that in the United States, "15% to 25% of consumers want gluten-free foods" (5) and it has been suggested that "17 million Americans are gluten-sensitive" (6), although official data on the prevalence of nonceliac gluten sensitivity are not available. Of note, general public awareness of nonceliac gluten sensitivity in the United States has been shown to be higher than that of celiac disease (7).

What sort of evidence do we have for the existence of a condition presumed to be so widespread? Apart from an uncontrolled, unblinded study (8), which identified a subgroup of patients with diarrhea-predominant irritable bowel syndrome whose symptoms improved after gluten withdrawal, the first study to confirm the existence of nonceliac gluten sensitivity was a randomized, double-blind, placebo-controlled rechallenge trial (9) that showed that gluten worsened functional symptoms in patients who did not have celiac disease.

Parallel to this, interest has grown in the mechanisms at the base of this new condition. One hypothesis is that unlike celiac disease, which is characterized by a predominant adaptive immune pathway (1), nonceliac gluten sensitivity is characterized by an activation of the innate stress response (10, 11). It is hard to accept this concept in view of the presumed etiologic heterogeneity of this syndrome, and if we acknowledge that nonceliac gluten sensitivity is an etiologically heterogeneous syndrome rather than a distinct nosographic entity, management options should vary according to the predominant or concomitant underlying pathogenic pathways.

Gluten is a component of the more complex protein mixture contained in wheat flour. As a consequence, it cannot be considered the sole agent responsible for functional symptoms in persons who eat bread and pasta, and other proteins, such as α-amylase/trypsin inhibitors or even yeast, may be involved in IgE-mediated allergic reactions to wheat flour (12). In addition, some of the carbohydrates contained in bread and pasta were

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Table 1. **Main Characteristics Distinguishing Celiac Disease From Nonceliac Gluten Sensitivity**

Characteristic	Celiac Disease	Nonceliac Gluten Sensitivity
Synonyms	Celiac sprue, gluten-sensitive enteropathy	Nonceliac gluten intolerance, nonceliac wheat intolerance, gluten sensitivity, gluten hypersensitivity
Prevalence	About 1% of the general population	Unknown, but suspected to be higher than that of celiac disease
Genetics	Related to *HLA-DQ2* or *HLA-DQ8*	Unrelated to a specific HLA haplotype
Mechanisms	Predominant adaptive immune reaction to gluten peptides restricted by *HLA-DQ2* or *HLA-DQ8*	Unknown but multiple mechanisms are suspected, including innate immune reaction to gluten; IgE-mediated wheat allergy; starch carbohydrate malabsorption; opioid-like activity of gluten; gluten-induced, low-grade inflammation; and nocebo effect of gluten-containing food
Serum antibodies	Positive results on TTA, EMA, or AGA testing	Negative results on TTA and anti-EMA testing, sometimes positive results on IgG AGA testing
Villous flattening	Present	Absent
Symptoms	Intestinal and extraintestinal	Intestinal and extraintestinal
Morbidity	Increased	No data
Mortality	Increased	No data

AGA = antigliadin antibodies; EMA = endomysial antibodies; TTA = antitransglutaminase antibodies.

shown to escape small-bowel absorption, possibly because of an interaction between the starch and the protein moieties of wheat flour, and to cause abdominal discomfort and diarrhea (13). Thus, starch malabsorption may represent an additional cause of functional gastrointestinal distress in otherwise healthy persons who eat wheat flour. Gluten, on the other hand, can mimic some of the effect of opiates, and it has been shown to alter intestinal transit times in healthy volunteers in a naloxone-reversible manner (14). Gluten has also been shown to induce low-grade intestinal inflammation in experimental models, although this still needs to be confirmed in humans (15). Last but not least, nonceliac gluten sensitivity may only be apparent and caused by the nocebo effect of wheat or gluten ingestion. The relevance of this phenomenon in patients who believe themselves to be food-sensitive has already been shown in double-blind studies (16). Of note, many of these patients were formerly on highly restrictive diets, had already withdrawn gluten from their diet, and were convinced that it had helped to limit their irritable bowel syndrome–like symptoms.

As a result, it seems that nonceliac gluten sensitivity should be the subject of more in-depth clinical research, and that "sense" should prevail over "sensibility" to prevent a gluten preoccupation from evolving into the conviction that gluten is toxic for most of the population. We must prevent a possible health problem from becoming a social health problem. Self-prescription of gluten withdrawal by a growing number of patients inevitably leads to a series of problems: subsequent inability to correctly diagnose or exclude celiac disease, deleterious health effects from the probably suboptimal adherence to a gluten-free diet in the case of patients with undiscovered celiac disease, and the high economic burden related to an unjustified gluten-free diet (17).

In conclusion, we believe that nonceliac gluten sensitivity may exist in patients in whom celiac disease has been properly excluded. However, the optimal diagnostic algorithm necessary to define the patient with nonceliac gluten sensitivity is still under debate. Because the condition has been confirmed by means of appropriate diagnostic tools, such as oral food challenge, in only a few patients with putative food sensitivity (18), we believe that an individualized approach should be used to recognize nonceliac gluten sensitivity. Double-blind, placebo-controlled, gluten challenge testing is the method with the highest diagnostic accuracy, but its use is limited to a research setting because it is expensive and time-consuming (19). Until a valuable biomarker of nonceliac gluten sensitivity is identified, a reasonable approach in day-to-day clinical practice would be to perform cheaper and easier open or single-blind gluten challenge tests (20), depending on whether objective or subjective symptoms, respectively, were present (**Table 2**).

Table 2. **Characteristics and Indications of Oral Gluten Challenge Tests in Diagnosing Nonceliac Gluten Sensitivity**

Challenge Test	Characteristics	Indications
Open	Unmasked gluten; neither patients nor physicians are blinded	Objective gluten-dependent symptoms, such as rash, urticaria, or episodes of vomiting and diarrhea
Single-blind, placebo-controlled*	Vehicle-masked gluten and placebo administered in a crossover fashion; patients but not physicians are blinded	Subjective gluten-dependent symptoms, such as abdominal discomfort, nausea, fatigue, or headache
Double-blind, placebo-controlled*	Vehicle-masked gluten and placebo administered in a crossover fashion; both patients and physicians are blinded	Selected patients who manifest subjective symptoms or inconclusive results in a single-blind test or participants in research studies

* Placebo-controlled testing requires that the challenge be done sequentially by administering capsules that contain purified gluten or placebo.

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