Nonceliac Gluten Sensitivity or Wheat Intolerance Syndrome?

Stefano Guandalini, MD[1], and Isabel Polanco, MD[2]

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 1978[7] 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 survey[11] 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 al[12] 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 ataxia[14]; psychiatric disorders such as autism, depression, bipolar disorder, and schizophrenia,[15-18] 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 al[20] on 26 patients with NCGS, none had autoimmune disorders. However, in the large series recently reported by Volta et al[11] 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 surveys[21,22] 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

From the [1]Section of Pediatric Gastroenterology, Hepatology, and Nutrition, University of Chicago, Chicago, IL; and [2]Autonomous University, La Paz Children's University Hospital, Madrid, Spain

The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2014.12.039

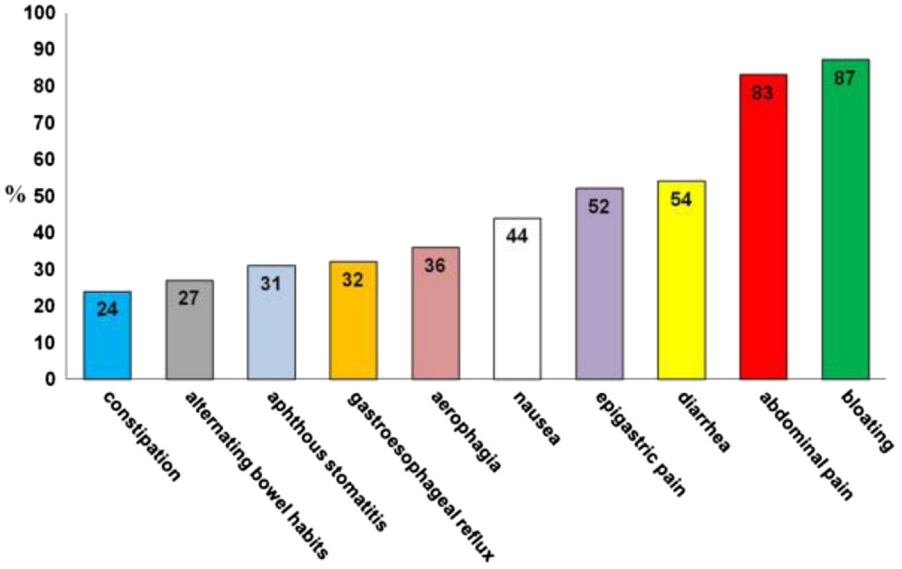

Figure 1. Gastrointestinal manifestations of NCGS (from reference[11]).

Like CD, NCGS appears to be more prevalent among women than men, with a male to female ratio of 1:2.5.[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,[25] 12.8% of patients with NCGS were first degree relatives of patients with CD. Some old studies[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,[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

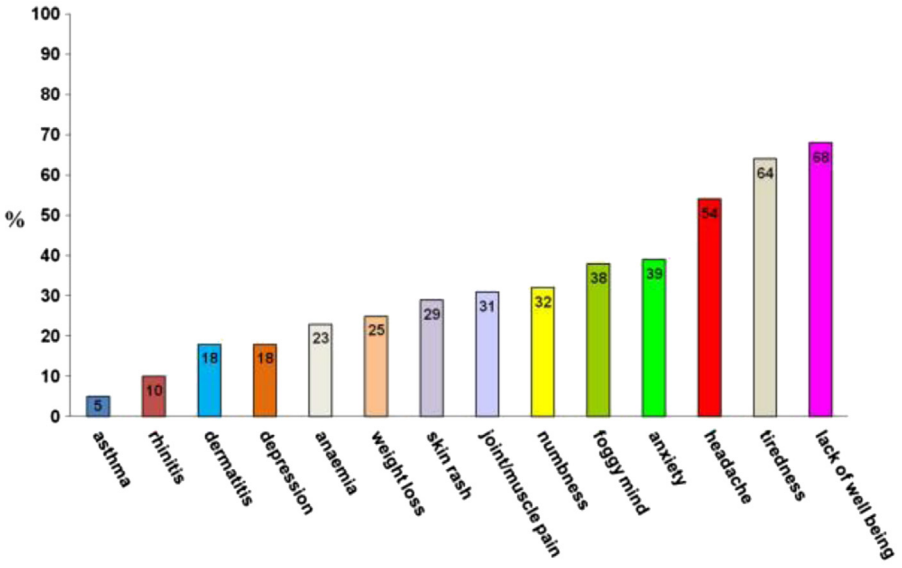

Figure 2. Extra intestinal manifestations of NCGS (from reference[11]).