

## Nonceliac Gluten Sensitivity. Where is the Missing Piece of the Puzzle? Short Review

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Wheat is the most widely consumed food grain in the world. Gluten is the main structural protein complex of wheat with equivalent toxic proteins found in other cereals, including rye and barley. The toxic protein fractions of gluten include gliadins and glutenins. The syntagm “gluten-related disorders” represents an umbrella-term used to describe the conditions related to ingestion of gluten-containing food [1]. Celiac disease (CD) is an immune-mediated enteropathy caused by exposure to dietary gluten and related prolamines in genetically susceptible individuals (DQ2 and/or DQ8 HLA). It occurs in symptomatic subjects with gastrointestinal and non-gastrointestinal symptoms and in some asymptomatic individuals, including subjects affected by: type I diabetes, autoimmune disorders and first degree relatives of individuals with celiac disease. CD is characterized by specific autoantibodies against tissue transglutaminase 2 (anti-TTG2) and anti-endomysium (EMA). Wheat allergy (WA) is an adverse immunologic reaction to wheat proteins. In both conditions the reaction to gluten is mediated by T-cell activation in the gastrointestinal mucosa. In the pathogenesis of WA, wheat specific IgE antibodies play a central role, triggering the release of chemical mediators, such as histamine from basophils and mast cells [2]. In contrast, CD is an autoimmune disorder, as demonstrated by specific serologic auto-antibodies TTG and EMA. Besides CD and WA, there are cases of gluten reactions in which neither allergic nor autoimmune mechanisms are involved. These are generally defined as non celiac gluten sensitivity (NCGS) [3]. The definition of NCGS includes those cases of gluten reaction in which both allergic and autoimmune mechanisms have been ruled out (diagnosis by exclusion criteria). More specifically, these are cases with negative immuno-allergy tests to wheat or negative CD serology, with normal duodenal histopathology and clinical symptoms that can overlap with CD or WA. These patients show resolution of symptoms when started on a gluten free diet, implemented in a blinded fashion to avoid a possible placebo effect of the dietary intervention [3]. An overlap between the irritable bowel syndrome (IBS) and NCGS has been detected, requiring even more stringent diagnostic criteria. Epidemiological surveys in Europe and USA showed that the prevalence of CD in the general population is 1% [1]. Wheat is one of the 10 foods that most frequently produce allergy in childhood and the results of challenge testing show that wheat allergy affects up to 1% of the population [4]. NCGS frequency is still unclear, a few epidemiological data on adult population have been generated and further studies are required to help establishing the magnitude of the problem among adult as well as pediatric population. Following the landmark paper of Sapone [3], describing clinical and diagnostic features of adults with NCGS in 2012, an increasing number of papers have been published, confirming that NCGS should be included in the spectrum of gluten-related disorders. However, many aspects of NCGS epidemiology, patho-physiology, clinical spectrum and treatment are still unclear. Further studies are required in those directions especially among children with unresolved digestive symptoms. Also, future researches should be performed to identify reliable biomarkers for NCGS diagnosis and to better define different NCGS subgroups. Total gluten exclusion is difficult to achieve in childhood, so researches should establish if NCGS patients should exclude gluten or only to reduce the amount of daily intake. Also, the length of time for gluten elimination should be defined in cases with NCGS. The vast majority of celiac experts initially reacted with a great deal of skepticism to the concept of NCGS existence and the fact that it was a separate entity from CD. We are now with NCGS where we probably were with CD forty years ago. In the 1980s we knew that CD existed, but we had little information on the mechanisms involved in the pathogenesis of the enteropathy, the genetic background and its complication. Given the limited literature on the topic, it should not be a surprise that there are still numerous questions about NCGS that should be addressed [1].

A number of *in vitro* studies have confirmed the cytotoxicity of gluten's main antigen, gliadin. Gliadin has agglutinating activity, reduces F-actin content, inhibits cell growth, induces apoptosis, alters redox equilibrium and causes a rearrangement of the cytoskeleton through the zonulin pathway and the loss of tight junction competence in the gastrointestinal mucosa [5-7]. The diversity of gluten-induced conditions is in agreement with the idea that the immune system reacts to the triggering environmental factor, gliadin, in distinct ways.

In the latest years, there was an impressive number of papers published regarding the definition, diagnosis and treatment of CD. A lot of pediatric studies described a high number of asymptomatic (silent, latent/potential) or atypical form of CD. In many cases, this condition was indicated by intestinal morphology alterations observed after upper digestive endoscopy performed to evaluate an irritable bowel syndrome non-responsive to classic therapy [8]. The lack of awareness of some clinicians regarding pauci-symptomatic forms of CD contributed to the under-diagnosed status of several patients with mild digestive discomfort, exposing them to the risk of complications. Although it was proved that 12% of IBS patients might have CD [9], it still exists clinical confusion between functional intestinal disorders and atypical forms of CD. And to add to the confusion, there's also growing evidence that a subset of patients with IBS who definitely don't have CD may in fact have NCGS, and therefore will still benefit from a gluten-free diet. Although NCGS is thought to be present in a large part of patients affected by gastrointestinal functional diseases, the lack of diagnostic criteria represents a relevant problem. As a result, they were left in a no man's land, unrecognized by either allergists or gastroenterologists. Due to poor physician's awareness of this disease, NCGS patients were commonly referred to psychiatrists because they were believed to have an underlying mental illness [10].

In recent decades, the role of dietary components in inducing IBS symptoms has been explored. There is evidence that certain food components can contribute to symptoms through the effects of malabsorption of carbohydrates [11]. A lot of evidence were building for the role of poorly absorbed, short-chain carbohydrates (lactose, fructose and sorbitol) in the induction of IBS symptoms, with dietary restriction providing symptomatic relief [12].

However, the diagnosis in all IBS patients should be reconsidered regarding the increasing number of newly recognised cases with NCGS thought to be so far IBS or psycho-somatic diseases triggered by emotional distress. The quality of life of all these patients will be improved after reconsidering the conditions and started the gluten free diet.

### Conflict of Interest

I have no conflict of interest.

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