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EDITORIAL

Non-celiac gluten sensitivity: Time for sifting the grain

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Abstract

In the last few years, a new nomenclature has been proposed for the disease induced by the ingestion of gluten, a protein present in wheat, rice, barley and oats. Besides celiac disease and wheat allergy, the most studied forms of gluten-related disorders characterized by an evident immune mechanism (autoimmune in celiac disease and IgE-mediated in wheat allergy), a new entity has been included, apparently not driven by an aberrant immune response: the non-celiac gluten sensitivity (NCGS). NCGS is characterized by a heterogeneous clinical picture with intestinal and extraintestinal symptoms arising after gluten ingestion and rapidly improving after its withdrawal from the diet. The pathogenesis of NCGS is largely unknown, but a mixture of factors such as the stimulation of the innate immune system, the direct cytotoxic effects of gluten, and probably the synergy with other wheat molecules, are clues for the complicated puzzle. In addition, the diagnostic procedures still remain problematic due to the absence of efficient diagnostic markers; thus, diagnosis is based upon the symptomatic response to a gluten-free diet and the recurrence of symptoms after gluten reintroduction with the possibility of an important involvement of a placebo effect. The temporary withdrawal of gluten seems a reasonable therapy, but the timing of gluten reintroduction and the correct patient management approach are have not yet been determined.

Key words: Celiac disease; Gluten; Gluten-related disorders; Gluten sensitivity; Non-celiac gluten sensitivity

Core tip: Gluten-related disorders are extremely relevant in gastroenterologic practice, and their prevalence has increased in recent decades. Besides celiac disease and allergy, the newly born non-celiac gluten sensitivity is still an obscure syndrome with an unknown pathogenesis and important clinical concerns regarding diagnosis and patient management.

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INTRODUCTION

Wheat is a basic staple of the human diet, especially in Western countries where wheat-containing food dominates the menu. Since the start of agriculture in Mesopotamia about 10000 years ago, wheat has sustained mankind's development and health up to the present day[1]. This apparently contrasts with the selection of a genetic background susceptible to immune reactions against gluten [*i.e.*, celiac disease (CD)], the HLA DQ2 haplotype[2]. The development of adverse reactions against wheat and, in particular, against gluten, is supposed to be concomitant with the very moment humans started its ingestion. The first description of a patient affected by CD is ascribed to Areteus of Cappadocia, who in the 2nd century AD reported a case of chronic diarrhea and malabsorption. However, only at the end of the 19th century, Samuel Gee scientifically described the celiac syndrome in childhood and in the 1950s, Willem Dicke identified gluten as the environmental agent of CD[3]. Since then, the scientific community's interest concerning the effects of gluten on humans and the mechanisms underpinning gluten-induced intestinal and systemic damage has increased[4-6]. Nowadays, CD is considered an autoimmune disorder affecting about 1% of the worldwide population[7,8]. A different mechanism is involved in the allergic reaction to wheat (wheat allergy): a condition affecting 4% of the population with heterogeneous intestinal, respiratory, and cutaneous symptoms[6]. In addition to the food allergy against wheat, the other major forms of wheat allergy are baker's asthma and wheat-dependent exercise-induced anaphylaxis, which can lead to important anaphylactic reactions[9].

Recently, a third clinical syndrome has been introduced under the generic umbrella of gluten-related disorder, or non-celiac gluten sensitivity (NCGS), which apparently involves neither the allergic nor autoimmune mechanisms or a specific genetic background, as in CD[4]. Thus, gluten or other wheat components are supposedly the environmental factors that induce a wide range of gluten-related diseases with different pathogenic pathways, which globally affect a large proportion of the population[4,10].

NCGS AND ITS POSSIBLE PATHOMECHANISMS

NCGS is a clinical syndrome characterized by both intestinal and extraintestinal symptoms, which are responsive to gluten (wheat) withdrawal from the diet. The mechanisms by which gluten induces symptoms in NCGS are largely unknown, but their difference from those present in CD and wheat allergy appears clear. Although data is scant and conflicting, one can hypothesize that a multifactorial process is at the base of the NCGS symptomatic onset. The involvement of the innate immune system, a direct cytotoxic effect of gluten and gliadin, and the involvement of different target organs and other proteic components of wheat can be all implicated.

Firstly, the study by Sapone *et al*[11] demonstrated in a series of NCGS subjects reporting different gastrointestinal symptoms that intestinal permeability and adaptive immune responses are not involved in the process. In fact, by using the lactulose/mannitol test and investigating the main components of tight junctions (zonulin and claudins), the authors found no alterations, this fact excluding the presence of a "leaky gut" as in CD or other intestinal inflammatory conditions. The concomitant duodenal increase of toll-like receptor-2 and the significant reduction of the T-regulatory cell marker FOXP3 compared to healthy subjects and CD patients suggested a stimulation of the innate immune system that does not involve the interferon γ pathway. In the duodenal histology of NCGS, a slight increase of γ and δ intraepithelial lymphocytes was reported. The data collected on the absence of an adaptive immune response stimulation seems to be confirmed by another study that investigated the effect of a gluten-containing diet in patients affected by a diarrhea-type irritable bowel syndrome (IBS)[12]. In contrast with the previous studies, an alteration of gut permeability was reported in these patients, especially in subjects carrying a CD-compatible genetic background (*i.e.*, HLA DQ2). However, the definitive exclusion of the adaptive immune system is not possible. Based on the findings published by Brottveit *et al*[13], who explored and compared the initial mucosal immunologic events in CD and NCGS subjects before and after a gluten challenge, an increase of interferon γ and heat shock protein 27 levels after gluten challenge was evidenced together with an increased density of intraepithelial lymphocytes, this latter independent from the gluten challenge. Differently, other authors failed to identify any gliadin-related immunologic alteration in the duodenal mucosa of NCGS patients[14].

Besides the possible alteration of the immune system, gluten presents some peculiar biologic properties that induce intestinal damage[15]. Different *in vitro* studies on two- and three-dimensional cell cultures (mainly enterocytes) demonstrated that the treatment with gluten and gliadin induces alterations of the main cellular homeostatic processes. Cellular morphology and motility[16,17] and cytoskeleton organization and intercellular contact through the tight junction proteins are all altered[18,19]. Treated cells present a reduced viability due to the stimulation of apoptosis and a reduction of synthesis of nucleic acids (DNA and RNA) and proteins[20]. Moreover, the oxidative balance is disrupted by a decrease of reduced glutathione and thiols[18,21].

While the researchers' attention is focused on gluten, other molecules also contained in wheat may be involved in the NCGS symptoms. Among them, the amylase trypsin inhibitor enzymatic family is a known trigger of the toll-like receptor-4 pathway of the innate immune system, stimulating the release of pro-inflammatory cytokines in cells from CD and non-CD patients and biopsies[22]. Other authors have indicated that the fermentable oligosaccharides, disaccharides, monosaccharides and polyols-present in wheat (fructans) and other foods and known as FODMAPs-are important factors in causing unspecific gastrointestinal symptoms (especially bloating). These poorly absorbed short-chain carbohydrates are fermented in the colon with gas release, the resulting intestinal distension being at the base of reported symptoms. In a placebo-controlled, crossover rechallenge study, Biesiekierski *et al*[23] found no evidence of a specific dose-dependent effect of gluten in patients with suspected NCGS undergoing a low FODMAPs diet. Although graved by an important nocebo effect, their data suggest that NCGS might be confused with FODMAP sensitivity, and gluten might be only a cofactor (or a confounder) when looking for the origin of gastrointestinal symptoms. In a recent study, a low FODMAP diet was effective in controlling gastrointestinal symptoms in patients with intestinal bowel disease[24], thus supporting its use as a first-line therapy. However, the data from the reported studies are extremely heterogeneous and even scant in the case of amylase trypsin inhibitor, thus making their interpretation difficult. The main bias is caused by the absence of a clear diagnostic flowchart for NCGS as all the studies simply enrolled patients clinically responding to a period of gluten-free dieting without excluding the placebo effect.

HOW MANY PATIENTS WITH NCGS ARE THERE AND WHICH SYMPTOMS DO THEY REPORT?

Subjects with NCGS claim a variety of intestinal and/or extra-intestinal symptoms, similar to those occurring in patients affected by CD or IBS[25]. Symptoms occur after gluten ingestion; they improve/disappear when gluten is withdrawn from the diet or recur within a few hours or days on gluten challenge.

In a recent Italian, multicenter prospective survey of 486 subjects with symptomatic benefit from a gluten-free diet (62% of these subjects underwent intestinal biopsy to exclude CD), the large majority of patients reported more than two associated gastrointestinal or extraintestinal symptoms[10]. The most frequent intestinal symptoms (> 80%) were bloating and abdominal pain, while more than 50% of patients reported diarrhea, 27% alternating bowel habits, and 24% constipation. Also, epigastric pain was frequent and followed, with decreasing prevalence, by nausea, aerophagia, gastroesophageal reflux disease, and aphthous stomatitis. In this study, as in many other studies on NCGS, systemic extraintestinal symptoms were frequently present: tiredness, lack of well-being, and neuropsychiatric symptoms such as headache, anxiety, "foggy mind", arm/leg numbness, and depression. Additional extraintestinal manifestations were as reported: muscle or joint pain, weight loss, dermatitis, and skin rash. Looking at the data regarding gluten withdrawal, NCGS is suspected in children (with fatigue apparently as their most frequent systemic symptom) and in adults, with a higher prevalence in females than in males[6,26]. Additionally, there are reports that NCGS is more common in families with a history of CD[26-29].

There is some overlap between IBS and NCGS. In fact, in patients fulfilling the Rome Ⅲ criteria for IBS, mainly in those with diarrhea, both predominant and in mixed form, NCGS has been diagnosed in a high percentage of cases: these have been sub-grouped as having gluten-sensitive IBS[30-32]. Similarly, in patients affected by allergic disorders, a high prevalence of NCGS has been reported (77/262 patients), thus confirming the need for a clearer definition of both the syndrome and the effects of gluten on the gastrointestinal tract[33].

An objective approach to NCGS diagnosis is not available to date, as significant serologic and histologic markers are lacking; thus, the epidemiology of the NCGS disorder is quite approximate and not based on powerful studies. The reported prevalence of NCGS in the current literature varies between 0.6% and 6%. The former prevalence rate results from the National Health and Nutrition Examination Survey program, based on interviews and medical examinations carried out by general practitioners[34], while the latter rate is the outcome of the experience by the Tertiary Center for Celiac Research at the University of Maryland[6]. At present, we should consider as affected by NCGS only those subjects who have been extensively studied to exclude CD or wheat allergy and have responded to a blind placebo-controlled gluten challenge, therefore excluding self-diagnosed self-treated subjects.

HOW CAN WE DIAGNOSE AND TREAT NCGS?

The main problem concerning NCGS is the absence of a set of standardized diagnostic criteria. The clinical picture of NCGS seems very unspecific. Although some allergic manifestations (urticaria, asthma, labial edema, *etc*.) strongly suggest the presence of an IgE-mediated disorder, the presence of abdominal discomfort, evacuation disturbances, foggy mind, chronic fatigue, and unspecific skin manifestations do not help clinicians in any differential diagnosis. As a result, when NCGS is suspected, the first step is represented by the exclusion of other disorders, especially CD and wheat allergy. Serologic negativity to anti-transglutaminase IgA and anti-wheat component IgE antibodies and/or the absence of a duodenal atrophy at duodenal histology and skin reaction during

Table 1 Non-celiac gluten sensitivity identikit

Name and definition	Pathogenesis	Prevalence	Diagnosis	Treatment
Non-celiac gluten/wheat sensitivity is an intestinal/extraintestinal syndrome responsive to gluten withdrawal in absence of CD and WA	Multi-factorial, including innate immunity and direct cytotoxic effects of gluten	Ranging from 3% to 5%, though specific studies are lacking	*Via* placebo-controlled blind gluten challenge	No data are available for guidance
	Other molecules are potentially involved: Amylase trypsin inhibitor, FODMAPs		Prior exclusion of celiac disease and allergy	An on-demand gluten-free regimen should be considered
			AGA IgG, IELs, basophil activation and eosinophil duodenal/colon infiltration are potential biomarkers	

AGA: Anti-gliadin antibodies; CD: Celiac disease; FODMAP: Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IELs: Intraepithelial lymphocytes; WA: Wheat allergy.

a prick test, are necessary pre-requisites.

Despite the absence of reliable NCGS biomarkers, some serologic and/or histologic alterations have been reported: (1) anti-gliadin antibodies IgG class could be present in 50% of patients with suspected NCGS[27]; (2) cytometric basophil activation is positive in 66% of patients responding to a wheat blind challenge associated to duodenal intraepithelial lymphocytosis and eosinophil infiltration of duodenum and colon[35,36]; and (3) mild duodenal intraepithelial lymphocytosis could be present in about 50% of NCGS cases, suggesting a microscopic enteritis[10,36,37].

Once alternative causes of a patient's clinical status have been excluded, the second step is to focus on a link between symptoms and gluten ingestion with an on/off mechanism. Typically, symptoms would arise rapidly or at least after a few hours from the ingestion of gluten-containing food and would disappear "instantly" once gluten is withdrawn from the diet. This passage meets some criticism. Firstly, the period of gluten exclusion to ascertain the symptomatic response is not standardized, therefore, it is not clear how long the gluten-free diet should be maintained in absence of any clinical response. Secondly, the gluten-free dietary regimen during the proof period (if you pardon the pun) should be kept absolutely strict-the same way as for CD-to facilitate nutritional control. Thirdly, how should a gluten-free diet response be checked and measured, and how great should the symptomatic improvement be in order to define a patient responsive to gluten exclusion? Because of the absence of reliable biomarkers altered by gluten ingestion, a symptomatic trend can be measured using scores (as the gastrointestinal symptom rating scale) validated for functional diseases or visual analogue scales[38]. The quantification of symptomatic improvement is at the base of a common definition of "gluten-free diet response". Although necessary, a response to a gluten-free diet would be insufficient to define a patient as gluten sensitive, due to the possibility of a placebo effect, which is known to be present in functional diseases[39]. Thus, a third step is required in order to eliminate or reduce the impact of the placebo effect in the diagnostic process. To reach this goal, a double- or at least single-blind challenge should be proposed to patients while they are on their gluten-free diet, to make evident the symptomatic onset during the blind assumption of gluten in a sort of n-of-1 process[40]. The problems to be solved here are: What dosage of gluten? Which vehicle should be used? How long should the challenge last? Which method to use for symptoms quantification?

POTENTIAL MANAGEMENT OPTIONS AND CONCLUSIONS

Once the diagnosis of NCGS is reasonably reached, the management and follow-up of patients is completely obscure. A logical approach is to undertake a gluten-free dietary regimen for a limited period (*e.g.*, six months), followed by the gradual reintroduction of gluten. During the gluten-free diet, the ingestion of prolamine peptide (gliadin)-derived from wheat, rye, barley, oats, bulgur, and hybrids of these cereal grains-should be avoided. Rice, corn, and potatoes have been the typical substitutes, but nowadays other different cereals and pseudocereals, such as amaranth, buckwheat, manioc, fonio, teff, millet, quinoa, and sorghum, can be used. After some period on a gluten-free diet, the reintroduction of gluten can start with cereals of low gluten content (*e.g.*, oats). In addition, einkorn farro (*Triticum monococcum*) can be used, having no direct *in vitro* or *ex vivo* toxicity and low (7%) gluten content[41].

Chronically, gluten-free-diet periods can be administered during symptomatic relapses as a sort of "on-demand" therapy. NCGS is a clinical syndrome hampered by many obscure sides (summarized in Table 1). Its pathogenesis and clinical presentation are not clear, and the diagnostic flowchart and patient management are not standardized. However, in the

epidemiologic dimension, the possibility to spare a large number of patients undergoing a drug-based therapy with side effects and costs is intriguing and makes NCGS a hot topic in gastroenterology.

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