REVIEW

Non-celiac Gluten Sensitivity. Is it in the Gluten or the Grain?

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ABSTRACT

Celiac disease is an immune-mediated inflammatory disorder of the small intestine caused by sensitivity to dietary gluten and related proteins in genetically predisposed individuals. Over the past several years, the concept of non-celiac gluten sensitivity (NCGS) has gained significant interest from the scientific community and mass media and the number of individuals embracing a gluten-free diet is rapidly growing. This condition is characterized by gastrointestinal or extraintestinal symptoms that respond to gluten withdrawal without evidence for underlying celiac disease or wheat allergy. Symptoms display significant overlap with the irritable bowel syndrome. Many important factors regarding this relatively novel condition remain to be elucidated; no discriminative markers to support a diagnosis of gluten sensitivity have been identified yet and its pathogenesis remains obscure. Here we review the current knowledge on NCGS, and outline potential pathogenic pathways of different gluten related disorders in order to gain clues about the pathophysiology of this novel condition.

Key words: gluten sensitivity – non-celiac gluten sensitivity - NCGS - celiac disease – wheat allergy - irritable bowel syndrome – IBS - gluten free diet – grain – wheat

Abbreviations: anti-DGP: anti-deamidated gliadin antibodies; anti-EMA: anti-endomysial antibodies; anti-TTG: anti-transglutaminase antibodies; ATIs: α-amylase/trypsin inhibitors; CD: celiac disease; FODMAPs: fermentable, oligo-, di-, monosaccharides, and polyols; GCD: gluten-containing diet; GFD: gluten-free diet; GM-CSF: granulocyte-macrophage colony-stimulating factor; IBS: irritable bowel syndrome; IELs: intraepithelial lymphocytes; IFN-γ: interferon gamma; NCGS: non-celiac gluten sensitivity; PBMC: peripheral blood mononuclear cell; TCR-γδ: gamma delta T-cell antigen receptor; TLR2: toll-like receptor 2; TLR4-MD2-CD14: lipopolysaccharide receptor complex; TNF-α: tumor necrosis factor-alpha; VAS: Visual Analogue Score; WGA: Wheat Germ Agglutinin

INTRODUCTION

Celiac disease (CD) is a chronic enteropathy caused by a state of heightened immunological responsiveness to ingested gluten or related proteins which results in small intestinal villous atrophy and increased intestinal permeability and, as a result, malabsorption in the small intestine[1]. The cornerstone of treatment for CD is lifelong adherence to a strict gluten-free diet (GFD) which usually leads to typical rapid clinical and histological improvement [2]. Another form of immunologic reactivity against gluten and other wheat proteins is wheat allergy. This disorder is characterized by an IgE mediated response against a variety of wheat components resulting in respiratory symptoms or gastrointestinal symptoms, the latter usually in children [3].

The majority of individuals seeking medical attention for gastrointestinal symptoms that benefit from gluten withdrawal, however, cannot be classified as either CD or wheat allergy [4]. The possibility of a causal relationship between the ingestion of gluten and the occurrence of symptoms in the absence of CD or wheat allergy has long been ignored but more recently, this relationship has gained significant interest. This novel entity is known as non-celiac gluten sensitivity (NCGS) and manifests as intestinal (diarrhea, abdominal discomfort or pain, bloating and flatulence) and/or extraintestinal symptoms (including fatigue, headache, lethargy) that occur after the ingestion of gluten and improve after gluten withdrawal [5]. Symptoms of NCGS display significant overlap with the irritable bowel syndrome (IBS), the latter being one of the most common disorders in today's society [6, 7].

The current interest from the general public and mass media in this topic is overwhelming. NCGS is a trendy topic in forums and patient groups [7] and the number of hits on Google is a factor 4000 higher than the number of Pubmed hits. Although official data are lacking, the number of patients embracing a GFD is rapidly growing and fuel a global market of gluten-free products [8, 9]. It is estimated that 20% of the US population is currently buying gluten-free products, which is an order of magnitude greater than the number of actual CD patients. In 2011 the US gluten-free market accounted for $1.31 billion and it is projected to rise to $1.68 billion by 2015 [10]. Increased awareness and knowledge about CD can only explain a small fraction of this market rise and so does probably NCGS. The discussion whether or not gluten can cause symptoms in the absence of CD is confused by a popular theory that grains, by means of their composition, are unhealthy. This theory is based on the fact that grains were only introduced 10,000 years (or some 300 generations) ago in our diet. From an evolutionary point of view this is too short to adapt to the specific contents of wheat. The high carbohydrate content of wheat is being held responsible for many negative health aspects of grain products, in particular the current obesity epidemic. Recent wheat modifications have further increased immunogenicity and carbohydrate content. This hypothesis, outlined in a best-selling book has spread at a dramatic pace in the lay press and among social media [11]. Many celebrities have embraced this theory as a means to lose weight, further fueling the popularity of this hypothesis. This theory should be clearly distinguished from the question as to whether gluten, or in a wider perspective, products derived from grains, can cause symptoms in the absence of CD or wheat allergy. In the remainder of this review, we shall only focus on the scientific basis for the latter [8,12,13].

DEFINITIONS

There is no established definition of NCGS. According to the recently published Oslo definitions for CD and related terms [14] NCGS is defined as a condition in which ingestion of foods containing wheat, rye, and barley leads to one or more of a variety of immunological, morphological or symptomatic manifestations in people in whom CD has been excluded [14]. This definition is rather broad and based on expert consensus [15]. A more precise definition was proposed in the London definitions [8]. Here, the term 'gluten-related disorder' is proposed as an umbrella term for all diseases triggered by gluten and further divided into 3 main forms. These include autoimmune (which includes all forms of CD), wheat allergy and immune-mediated NCGS. NCGS is proposed as a definition for those cases where there is a symptomatic reaction on gluten, without appearance of allergic or autoimmune mechanisms. Thus, according to the London criteria, the diagnosis of NCGS is made in cases with negative immuno-allergy tests to wheat, negative CD serology (anti-EMA and/or anti-TTG), with normal duodenal histopathology and resolution of symptoms when started on a GFD [8]. Although not in the London definitions, it has been proposed to add the recurrence of symptoms after gluten reintroduction as a final step in the diagnostic process of NCGS [13] [Fig. 1].

OVERLAP WITH IBS

The majority of symptoms associated with NCGS are to a certain extent subjective, and may include both gastrointestinal as well as extra-intestinal symptoms: abdominal pain, diarrhea, nausea, headache, "brain fog," tingling and/or numbness in hands and feet, fatigue, and musculoskeletal pain. More severe neurologic and psychiatric conditions including schizophrenia and cerebellar ataxia have also been claimed to be associated with NCGS [16, 17].

Many of both the gastrointestinal and extraintestinal NCGS symptoms are reminiscent of those that may occur in individuals with IBS. Indeed many NCGS-patients fulfill the diagnostic criteria of IBS. This entity is defined as recurrent abdominal pain or discomfort for at least 3 days per month in the last 3 months associated with two or more of the following: improvement with defecation, onset associated with a change in stool frequency, or onset associated with a change in form (appearance) of stool [6, 18]. In addition to intestinal symptoms IBS may be associated with extraintestinal symptoms including fatigue, headache, lethargy [19]. The pathological process of IBS is currently not well understood and regarded as an interaction of important biological and psychosocial factors [6, 12]. It has been postulated that abnormal immune responses to dietary components might trigger symptoms in IBS and a persistent low-grade inflammation may favour development of IBS although formal evidence for this thesis is lacking [20]. Irritable bowel syndrome is a common problem; using the Rome III criteria, prevalence of IBS in adults and adolescents throughout the world is around 5-10% which is relatively similar across Europe and the USA [18, 19]. At this point it is unknown what percentage of these patients fulfils the criteria for NCGS.

PROVIDED EVIDENCE

In 1978 the Lancet published a case report of a patient with diarrhea and intermittent abdominal pain, without abnormalities on biopsy and with improvement on a GFD. This case is one of the first to be described as NCGS [21]. This observation was followed by a study in 8 adult female patients suffering from abdominal pain and chronic diarrhea who had dramatic relief on a gluten-free diet and return of symptoms after gluten challenge. Jejunal biopsies in these patients showed minor, but significant, changes in cellularity which returned to normal on the GFD. Apart from a slight increase in jejunal cellularity, no other clinical or immunological abnormalities reminiscent of CD were found [22]. Similarly in two more recent reports among non-celiac patients with IBS-like symptoms, gastrointestinal symptoms improved after exclusion of gluten from the diet [23, 24]. Recently, a randomized controlled trial of a gluten-containing diet (GCD) versus GFD in patients with diarrhea predominant IBS was performed [25]. Herein, 22 patients were placed on a GCD and 23 patients were placed on a GFD for 4 weeks. Participants showed no evidence of CD and were excluded if there was a history of previous response to gluten restriction. Quite surprisingly, patients on the GFD showed less bowel movements per day and in addition small bowel permeability was significantly higher in individuals on the GCD, in

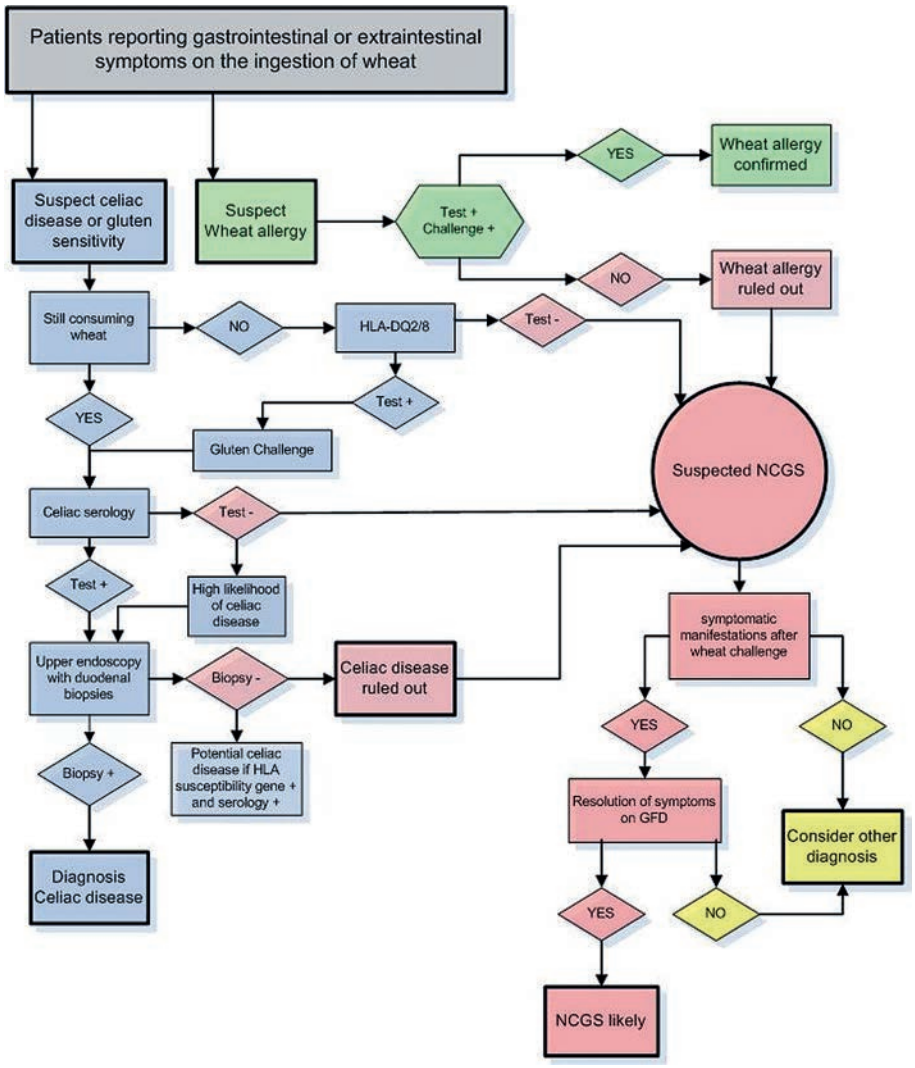

Fig. 1. Proposed algorithm for the differential diagnosis of gluten-related disorders [adapted from Boettcher E, Crowe SE: Dietary proteins and functional gastrointestinal disorders. Am J Gastroenterol 2013].

particular in those who were HLA-DQ2/8 positive. In this study, a GFD was not associated with significant effects on intraepithelial lymphocytes or villous atrophy.

More compelling evidence for the notion that gluten can cause symptoms in the absence of CD or wheat allergy comes from two recent double blind placebo-controlled studies.

In the first study, IBS patients in whom CD was excluded and who were symptomatically controlled on a GFD, were challenged with either placebo or gluten in the form of two bread slices plus one muffin per day. In the gluten challenged group, 68% reported that symptoms were not adequately controlled compared with 40 % on placebo (P = 0.0001) [26].

In another recent retrospective study carried out by Carroccio et al [27], 920 patients with IBS diagnosis underwent an elimination diet of wheat, cow's milk, eggs, tomato, and chocolate and subsequent double-blind, placebo-controlled rechallenge with wheat capsules. Among these, as many as 276 (30%) became asymptomatic (Visual Analogue Score, VAS score < 10) on an elimination diet and showed symptoms again (increase in VAS score > 30) during a double blind placebo controlled gluten challenge. A significant percentage of these patients responded also to other food allergens and only a small percentage (~7%) responded to wheat only. Symptoms developed within a mean of 3 days of wheat reintroduction [27]. Intriguingly, anemia, weight loss, and a history of food allergy in infancy and of coexistent atopic diseases were more frequent in these wheat sensitive patients than in IBS controls. Moreover, the number of patients with positive gliadin antibodies was significantly higher when compared to IBS controls, as was the frequency of HLA-DQ2/8.

IS IT IN THE GLUTEN OR THE GRAIN?

Whilst these initial positive observations lend strong support to the notion that gluten may induce symptoms in individuals without CD, these findings need careful consideration. First of all, in the study by Carroccio et al, wheat capsules and not gluten capsules were used. Similarly, Vazquez-Roque et al used wheat-flour in their GCD and did not specifically address the effects of gluten-protein *per se*. It must be considered that the induction of symptoms by gluten in this study might be a wheat-specific rather than a gluten-

specific phenomenon and may in fact have been triggered by other constituents than gluten. Indeed as will be discussed later in detail, other proteins than gluten in wheat may activate the innate immune system and be held responsible for the development of symptoms.

In a follow-up study on their original observation, Biesiekierski et al [28] conducted a placebo-controlled, cross-over rechallenge study in 37 subjects with NCGS and IBS (based on Rome III criteria). In order to control other potential triggers of gut symptoms, all diets had a reduced content of fermentable, poorly absorbed short-chain carbohydrates (ie, fermentable, oligo-, di-, monosaccharides, and polyols [FODMAPs])[28]. It has been hypothesized that FODMAPs, that are found widely in grains, trigger gastrointestinal symptoms by inducing luminal distension via a combination of osmotic effects and gas production because they provide a substrate for bacterial fermentation in the small and large intestine [28, 29]. After a two week run-in on a gluten-free and low FODMAP diet test subjects were then randomly assigned to diets containing either high-gluten, low-gluten or control (whey protein). Quite surprisingly, gastrointestinal symptoms consistently and significantly improved during reduced FODMAP intake in all participants, but significantly worsened to a similar degree when their diets included protein, regardless whether it was gluten or whey. In only 8% of participants gluten-specific effects were observed. Participants were then rechallenged for 3 days with diets containing either high-gluten, low-gluten or control (whey protein), and during this rechallenge symptoms increased by similar levels among groups, again regardless of the protein source. Based on these observations it was concluded that no evidence had been found for specific or dose-dependent effects of gluten in patients with NCGS placed on a GFD low in FODMAPs. This study calls into question the very existence of NCGS as a discrete entity.

POTENTIAL PATHOGENIC MECHANISMS

In CD, incomplete degradation of gluten proteins and subsequent preferential T-cell recognition of these proteins seem to favour the immunostimulatory and toxic effects of gluten epitopes in the gastrointestinal system. This results in a high intraepithelial lymphocyte count, typical tissue damage and the production of antibodies against transglutaminase (anti-TTG), anti-endomysium (EMA) and/or anti-deamidated gliadin antibodies (DGP) [5]. In NCGS these typical changes found in biopsy and serum cannot be observed. However, different studies suggest a rise in intraepithelial lymphocytes without characteristic villous atrophy (Marsh I) and also a rise in anti-gliadin antibody has been observed [4, 20, 22, 26, 27, 30, 31]. Similarly, different studies have shown that the HLA-DQ2 allele was significantly more frequent in diarrhea predominant IBS patients and NCGS patients compared to healthy controls [20, 30, 32]. Although such observations have not been consistently reproduced in the studies performed so far, these may point towards an, albeit mild, immune activation in NCGS. Such mechanisms may involve adaptive immune responses but more recently, there is an increasing interest in the role of the innate immune system in NCGS. This is based on the observation that intake of wheat-based products may provoke immediate reactions, which is too short to be mediated by an adaptive immune response. Circumstantial evidence comes from observations that markers of innate immunity, including TLR2, are upregulated in patients with NCGS [33]. In addition, adaptive immune markers including IFN-γ, IL-17 and IL-21 were expressed at increased levels in the small intestine mucosa of patients with CD, but not in those with NCGS [33]. Finally, the number of TCR-γδ IELs were only elevated in CD subjects, while in NCGS patients the number of γδ IELs were similar to those in controls [33, 34]. More compelling evidence for the role of innate immunity came from Vazquez-Roque et al who showed an increased production of TNF-α, IL-10 and GM-CSF in the absence of IFN-γ production after in vitro PBMC stimulation with gluten fragments in non-celiac patients with diarrhea predominant IBS [25].

Another potential pathogenic mechanism that has gained recent significant interest is the role of intestinal permeability in the pathogenesis of NCGS. While CD is consistently associated with increased small intestinal permeability [35], it is not known whether patients with NCGS present similar alterations. Two recent studies found no evidence for a difference in intestinal permeability in these patients [26, 33], whilst another recent study found a higher small bowel permeability in non-celiac IBS-patients on a GCD compared to a GFD [25].

A potential explanation for the different immune activating mechanisms between CD and NCGS may relate to the fact that it is unclear whether it is the gluten that provokes symptoms in NCGS patients. In fact, as outlined in the previous section, other constituents of grains may be responsible. The protein contents of modern wheat varies between 7% and 22% and gluten proteins are the main proteins in wheat. Gluten proteins are classically divided into two groups, the monomeric gliadins and the polymeric glutenins. Gliadins are classified into three groups: α/β-gliadins, γ-gliadins, and ω-gliadins [3]. There are at least 50 gliadin epitopes that exert immunomodulatory, cytotoxic and gut-permeating activities. Where some immunomodulatory gliadin peptides activate specific T-cells, others are able to induce a pro-inflammatory innate immune response [5]. In addition, lectins also may exert immunostimulatory effects. Lectins are found in a variety of plants, especially in seeds, where they serve as defence mechanisms against other plants and fungi. Most lectins are very stable proteins and are resistant to the effects of digestive enzymes [36]. Among these, Wheat Germ Agglutinin (WGA) has been identified to directly stimulate the release of several pro-inflammatory cytokines from monocytes and macrophages through the binding to glycoconjugates [37, 38]. WGA may also increase intestinal permeability through yet unknown mechanisms [38]. So far, there are no human data on the effect of WGA on inflammatory responses.

Another category of proteins identified as strong activators of innate immune responses are pest resistance molecules in wheat known as α-amylase/trypsin inhibitors (ATIs). Members of the ATI family have been previously characterized as allergens in baker's asthma and gastrointestinal hypersensitivity to wheat [3]. In a very recent study it was found that ATIs elicit release of proinflammatory cytokines in monocytes, macrophages, and dendritic cells from celiac and non-celiac

patients and in celiac patients' biopsies through the engagement of the TLR4-MD2-CD14 complex [39]. These findings defined cereal ATIs as novel contributors to immune activation in CD. While not formally tested in this study, it was hypothesized that ATIs may fuel inflammation and immune reactions in other intestinal and nonintestinal immune disorders, in particular NCGS.

CLINICAL SPECTRUM AND DIAGNOSIS OF NCGS

As alluded to above, the majority of symptoms associated with NCGS are subjective, and may include both gastrointestinal as well as extraintestinal symptoms. More severe neurologic and psychiatric conditions including schizophrenia and cerebellar ataxia have also been ascribed to NCGS [16, 17]. However, formal evidence for this association is lacking and should be interpreted with great caution. More objective findings were described in the study by Carroccio et al including a more frequent presence of anemia, weight loss, a history of food allergy in infancy and coexisting atopic diseases in wheat sensitive patients compared to IBS controls [27]. It should be noted that a high amount (53%) of patients were HLA-DQ2 or DQ8 positive and therefore it cannot be excluded that some of these patients in fact had latent CD.

At this moment, there are no objective criteria for the diagnosis NCGS, and in our experience the diagnosis relies heavily on a detailed history taking with the help of a skilled dietician. In Figure 1 we purpose an algorithm for the differential diagnosis of gluten-related disorders. There is a desperate need for reliable biomarkers and/or an algorithm that include clinical, biochemical and histopathological findings which support the diagnosis of NCGS. Double-blind placebo controlled gluten challenge studies are cumbersome and generally not applicable in daily clinical practice. A possible potential marker for the future is intestinal deposits of IgA anti-TG2. In a recent study, these deposits were identified in 68% of potential NCGS patients negative for both serum anti-TG2 antibodies and intestinal abnormalities [40]. Values were significantly higher in symptomatic patients that responded to a GFD. These deposits may reflect a promising histopathological marker for NCGS, although latent CD in these patients has not been excluded.

CONCLUDING REMARKS

The observation that some patients respond with symptoms after ingestion of grains in the absence of CD or wheat allergy cannot be ignored. Symptoms are characterized by both gastrointestinal and extraintestinal symptoms that are reminiscent of those that occur in individuals with IBS. Whether it is the gluten or the grain that is responsible for these symptoms remains to be defined. NCGS patients may display a rise in epithelial cell count, a higher frequency of positive serum assays for anti-gliadin and a greater association with HLA-DQ2 of DQ8 haplotype than controls although these biomarkers seem to be non-specific and discrepancies have been reported. The question whether innate or adaptive immune responses are involved in the development of symptoms remains to be established. Similarly, whether NCGS belongs to the spectrum of CD with related immunology or to the spectrum of functional bowel disorders caused by other components of wheat, warrants further evaluation.

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