Chapter 13

Non-Celiac Gluten Sensitivity

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Abstract

Non-celiac gluten sensitivity (NCGS) is a resurfaced emerging disorder characterized by intestinal and extra-intestinal symptoms related to the ingestion of gluten-containing food in subjects not affected with either celiac disease (CD) or wheat allergy. Despite lacking solid epidemiological data, its prevalence has been estimated five to ten-times higher than that of CD and sells from gluten-free food market have rocketed three-fold lately. Unlike CD, NCGS seems to be associated with activation of the innate immune response. NCGS remains a diagnosis of exclusion of CD, due to the absence of diagnostic specific biomarkers. Evolving evidence has pointed the possibility of a relevant proportion of NGCS in literature actually suffering from overlooked minor forms of CD, the so-called "celiac lite" disease. The efficacy of a gluten-free diet for NCGS is controversial and other components in wheat, specially low-fermentable, poorly-absorbed, short-chain carbohydrates have been lately postulated as major contributors to symptoms, instead of gluten. This review updates evidence on epidemiology, pathophysiology, diagnosis and dietary interventions in NCGS, stressing the need of thorough screening for CD before a diagnosis of NCGS is given, considering that natural history and dietary restriction for both entities are radically different.

Keywords

Non-celiac gluten sensitivity, celiac disease, FODMAP, gluten-free diet, wheat, irritable bowel syndrome.

Abbreviations

CD: celiac disease,

FODMAPs: Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols,

GFD: gluten-free diet,

HLA-DQ2/DQ8: human leukocyte antigen DQ2/DQ8,

LE: lymphocytic enteritis,

NCGS: non-celiac gluten sensitivity.

1. Introduction

Non-celiac gluten sensitivity (NCGS) was originally described in 1976 and 1978[1,2] and the first series dates back to 1980[3], but only since 2010 a rapidly increasing number of papers have called our attention to an apparently novel syndrome entity, which has challenged physicians and researchers involved in gluten-related disorders. NCGS is characterized by intestinal and extraintestinal symptoms related to the ingestion of gluten-containing food, in subjects that are not affected with either celiac disease (CD) or wheat allergy. NGCS currently lacks diagnostic criteria and remains mostly a diagnosis of exclusion of CD. Additionally, many aspects of epidemiology, pathophysiology, clinical spectrum, and treatment are still unclear. In spite of these limitations, NCGS has been reported to presumably affect up to 5-10% of western population and gluten-free foods among non-celiac patients have grown in popularity[4]. As a matter of fact, sells from gluten-free food US market rocketed three-fold from 2006 to 2010 and another three-fold increase is expected by 2015[5]. A recent report revealed that about a third of U.S. adults (the highest percentage ever) expressed their willingness of avoiding gluten from their diets[6]. Therefore, NCGS has definitely settled down among gluten related disorders as a clinical, social and economical relevant entity.

The proposed diagnostic criteria for NCGS are displayed in Table 1[7-9], whereas the main pathogenic and clinical differences between CD and NCGS are summarized in Table 2[8]. The present review aims to critically overview available evidence on NCGS, focusing on epidemiology, adequate distinction of CD before a diagnosis of NCGS, pathogenesis and the efficacy of different dietary interventions for NCGS patients.

Table 1. Current proposed diagnostic criteria for NCGS[7-9].

1. Gluten ingestion elicits the rapid occurrence of intestinal and extraintestinal symptoms, which rapidly disappear after gluten withdrawal and recur upon reintroduction of gluten. 2. Specific IgE to gluten and wheat and skin prick tests results are negative (*exclusion of wheat allergy*). 3. Celiac disease serology (IgA endomysial antibodies, IgA tissue transglutaminase antibodies, IgG deamidated gliadin antibodies) results are negative and no villous atrophy is found on duodenal histology (*exclusion of CD*).
Observations: – HLA-DQ2 and/or HLA-DQ8 positive in 40-50% of NCGS patients. – Normal mucosa or increase in the number of intraepithelial lymphocytes can be found at histopathology. – Antigliadin antibodies (mainly of IgG class) are positive in about 50% of NCGS patients.

Table 2. Pathogenetic, clinical and prognostic differences between CD and NCGS[8-11].

	Celiac disease (CD)	**Non celiac gluten sensitivity (NCGS)**
Interval between exposure to gluten and onset of symptoms	Week to years	Hours to days
Pathogenesis	Adaptative immunity	Innate immunity
HLA	HLA-DQ2/DQ8 positive in 97% of cases	HLA-DQ2/DQ8 positive in 40-50% of cases
Symptoms	Gastrointestinal and extraintestinal symptoms; undistinguishable from NCGS and wheat allergy	Gastrointestinal and extraintestinal symptoms; undistinguishable from CD and wheat allergy
Autoantibodies *(including IgA endomysial and tissue transglutaminase antibodies)*	Almost always present*	Always absent

	Celiac disease (CD)	Non celiac gluten sensitivity (NCGS)
Histopathology	Villous atrophy almost always present**	Villous atrophy always absent
Natural history	Coexisting conditions Long-term complications	Absence of coexisting conditions and long-term complications
Gluten-free diet (GFD)	A strict GFD modifies the natural history of the disease	A strict GFD does not seem mandatory on account of its natural history

***** According to ESPGHAN updated guidelines[10], CD antibodies are not detectable in the blood of all patients with CD; in seronegative cases for anti-TG2, EMA, and anti-DGP but with severe symptoms and a strong clinical suspicion of CD, small intestinal biopsies and HLA-DQ testing are recommended. According to Catassi and Fassano´s diagnostic rules[11], response to a GFD supporting a diagnosis of CD could be assessed histologically in patients with seronegativity.
****** According to ESPGHAN updated guidelines[10], LE without villous atrophy might be specific for CD upon high count of $\gamma\delta$ cells (or $\gamma\delta$/CD3 ratio) in immunohistochemical assessment of biopsies or the presence of IgA anti-TG2 intestinal deposits. According to Catassi and Fassano´s diagnostic rules[11], celiac enteropathy in the small intestine biopsy could be LE without villous atrophy associated with IgA subepithelial deposits.

2. Epidemiology

The overall prevalence of NCGS in the general population is still unknown, mainly because many patients are currently self-diagnosed and start a gluten-free diet (GFD) without medical advice or consultation. Besides, NCGS lacks diagnostic biomarkers. Despite no solid epidemiological study on NCGS is available, it has been reported to be five to ten times more common than CD[4,9]. Recent studies have shown variable rates of self-reported NCGS (0.55% in the USA[12], 5% in children in New Zealand[13], 13% in adults in UK[14]). In patients with self-reported gluten sensitivity, gluten avoidance is associated with improvement of nonspecific behavioral and gastrointestinal complaints[13,15]. However, the vast majority of the NCGS children involved in one of the aforementioned studies were not tested for CD nor underwent an intestinal biopsy[16]. In the study from the UK, 7% of patients were reclassified

as having CD during the study[14], whereas a more recent study conducted in Australia pointed out that just over 1 in 4 self-reporting improvement on a GFD fulfilled strict criteria for a diagnosis of NCGS[17]. Furthermore, initiation of a GFD without adequate exclusion of CD occurred in 62% of patients. As such, an inadequate exclusion of CD in patients with self-reported improvement on a GFD (not performing HLA genotyping and serology combined with small bowel biopsy if positive haplotypes), might lead to an overestimation of both the prevalence of NCGS and the response to a GFD in patients with NCGS.

Although risk factors for NCGS have not yet been identified, the disorder seems to be more common in females and in young/middle age adults. The prevalence of NCGS in children is still unknown, although the first series has been recently described[18].

3. Clinical Picture and Natural History

NCGS is characterized by symptoms that usually occur soon after gluten ingestion, disappear with gluten withdrawal and relapse following gluten challenge, within hours or few days. The "classical" presentation of NCGS is a combination of irritable bowel syndrome-like symptoms, including abdominal pain, bloating, bowel habit abnormalities (either diarrhea or constipation), and systemic manifestations such as "foggy mind", headache, fatigue, joint and muscle pain, leg or arm numbness, dermatitis (eczema or skin rash), depression[7-9]. It is also quite common that many NCGS patients self-report the causal relationship between the ingestion of gluten-containing food and worsening of symptoms. In children, extra-intestinal manifestations seem to be less frequent, the most common symptom being tiredness[18].

No familiar aggregation or major complication of untreated NCGS has so far been described, especially malabsorption-related and autoimmune comorbidities[7-9]. Interestingly, several studies have reported a remarkable prevalence of malabsorption symptoms, familiar history of CD and

autoimmune disorders among NCGS patients[3,19-24]. Yet again, concerns arise about the possibility of having labelled CD patients as having NCGS.

4. NCGS: How Many Patients are Really Suffering "C*eliac-lite*" Disease?

Two major and consistent criteria supporting NCGS and ruling out CD have been negative CD disease serology (including IgA endomysial antibodies, IgA tissue transglutaminase antibodies and IgG deamidated gliadin peptide antibodies) and the absence of villous atrophy on duodenal biopsies[7-9]. Nonetheless, it is accepted that NGCS patients do not have villous atrophy but might have an increased number of intraepithelial duodenal lymphocytes (>25 intraepithelial lymphocytes/100EC), i.e, lymphocytic enteritis (LE), which represent Marsh 1 lesions in the Marsh-Oberhuber histological classification for CD[7-9]. LE is a non-specific histological lesion which may be associated not only to CD, but also to *Helicobacter pylori* infection, small bowel bacterial overgrowth or use of anti-inflammatory drugs. However, the most frequent cause of LE in patients with positive HLA-DQ2/DQ8 after exhaustive diagnostic work-up has been CD, ranging from 16% to 43%[25-28]. Furthermore, seronegative CD is more common in patients without villous atrophy, but Marsh 1 patients may have similar clinical manifestations than those with villous atrophy[29,30] and may show similar clinical-histological remission and reversal of haematological or biochemical disturbances on a GFD[31,32].

As such, it would be important to make a clear distinction between CD and NCGS in patients with gluten-dependent symptoms, especially upon the absence of autoantibodies and/or villous atrophy. In this regard, consensus guidelines from the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) state that a high count of $\gamma\delta$ cells (or $\gamma\delta$/CD3 ratio) in immunohistochemical assessment of biopsies or the presence of IgA anti-TG2 intestinal deposits might be specific for CD in patients with LE[10]. Similarly, Catassi and Fasano nicely published simplified rules for

diagnostic criteria of CD, accepting that celiac enteropathy in the small intestine biopsy could be LE associated with IgA subepithelial deposits, whereas response to a GFD supporting a diagnosis of CD could be assessed histologically in patients with seronegativity[11].

In an upcoming review on adequate exclusion of CD in NCGS patients[33], our group has found significant methodological flaws in available literature regarding thorough diagnostic efforts to rule out CD before giving a diagnosis of NCGS, in agreement with the aforementioned Australian survey[17]. Among 1561 NCGS evaluated patients, HLA haplotypes could not be linked to histology (normal or LE) in 1123 patients. Furthermore, 20% of patients were reclassified as CD in three studies evaluating advanced diagnostic techniques in 189 NCGS patients combining LE and HLADQ2/DQ8 haplotypes.

Overall, evolving evidence is suggesting that a subset of patients with NCGS may actually belong to the spectrum of CD, specifically some patients with negative antibodies and without villous atrophy, which some authors have so-called "celiac lite" disease[34]. There are two studies which might be prime example for this train of thought. In the first one, conducted in Germany, the authors thoroughly evaluated 102 patients with diarrhea-type IBS in whom CD had been precluded through negative serology and absence of villous atrophy[35]. Thirty five percent of patients were HLADQ2 positive, 23% had LE and notably, 30% had CD-associated antibodies in duodenal aspirate. Those HLADQ2 and intestinal antibody-positive IBS patients significantly improved on a GFD and were likely celiac patients. The second study, from Italy, showed 70 adult NCGS patients who were identified through a double-blind randomized placebo-controlled wheat trial[20]. All patients were seronegative and had no villous atrophy, but 94% NCGS patients had LE, 75% CD haplotypes and 30% positive anti-endomysium antibodies in the supernatant of biopsy culture[36]. The authors further admitted that these latter 30% of NCGS patients could actually suffer from CD[37]. Therefore, the inclusion of patients with positive HLA-DQ2/DQ8 and LE as having NCGS, in the absence of adequate efforts to exclude CD, will always cast doubt on potential misdiagnosis of *"celiac lite"* disease. In this

respect, the importance of misdiagnosing NCGS in CD patients relies not only on the possibility of a CD patient following a non strict GFD, but also on overestimating response to a GFD in NCGS patients.

5. Pathogenesis

The pathophysiology of NCGS is not fully understood yet. Several pioneers studies suggested an important role of the intestinal innate immune system in NCGS, unlike CD, which is triggered by an adaptive immune response[38,39]. However, more recent studies have posed the possibility of NCGS being a mixed disease, with an activation of both innate and adaptative immunity[40,41].

Over the last 3 years, we have witnessed a progressive weakening of an unquestioned dogma, such as gluten-related proteins being the cause for NCGS. As a matter of fact, wheat has multiple constituents, so discussion of NCGS cannot be divorced from considering the role of other components in wheat as potential responsible for NCGS[42]. The two major components of wheat, quantitatively speaking, are carbohydrates (71 g/100 mg) and proteins (12.6 g/100 g). Dietary carbohydrates can be classified into sugars, oligosaccharides and polysaccharides based on their degree of polymerisation. A discrete group of carbohydrates are described as 'fermentable' owing to their availability for fermentation in the colon, which is either due to the absence, or reduced concentration, of suitable hydrolase enzymes for digestion (for example, lactase deficiency), or in the case of monosaccharides because of incomplete absorption in the small intestine. These short-chain fermentable carbohydrates (termed FODMAPs *"Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols"*) are known to induce gastrointestinal symptoms (abdominal pain, flatulence and diarrhoea) through their effects on luminal water handling and colonic gas production[43]. Indeed, emerging evidence is highlighting the efficacy of the low-FODMAP diet for irritable bowel-syndrome symptoms[43]. Regarding improvement of NCGS on a GFD, the withdrawal of gluten may inadvertently be reducing the ingestion of

fructans, the main carbohydrate in wheat, that could actually be the offending agent.

Apart from carbohydrates, other potential culprits in wheat grain for GI symptoms have been postulated, such as non-gluten proteins (α-amylase/trypsin inhibitors), which have recently been suggested to induce intestinal inflammation, polyphenols or wheat germ agglutinin[42].

Several studies have addressed different hypothesis to explain symptom production after wheat ingestion in NCGS patients[44-50], which are summarized in Table 3.

Table 3. Putative pathogenic mechanisms to explain symptoms in NCGS patients after wheat ingestion.

Effects of gliadin in intestinal mucosa
• Increase of epithelial permeability with alteration in protein expression of components of the tight junction (zonulin)[44] • Activation of the innate immune response determined as IL-15 production (in vitro studies) and increased number of intraepithelial lymphocytes[45] • Induction of apoptosis, increase of oxidative stress and inhibition of epithelial cells growth (in vitro studies)[46] • Enhance of cytokine production by peripheral blood mononuclear cells, independent of DQ-status and induction of basophil activation (in vitro studies)[44] • Stimulation of cholinergic nervous system secondary to acetylcholine release by the myenteric plexus (animal studies)[47]
Fructans and undigested gluten proteins
• Carbohydrates present in wheat, such as fructans, are poorly absorbed and may produce gastrointestinal symptoms[48] • Fermentation of undigested gluten protein by sulphate-reducing bacteria can produce hydrogen sulphide and ammonia. Such gases might have a local effect of luminal distension and systemic effects (tiredness)[49] • Other gluten proteins, including alpha-amylase/trypsin inhibitors, and even yeast, could also play a role as triggers of the innate immune response[50]

6. Gluten-free Diet for NCGS: is it Gluten or Carbohydrate Restriction the Key?

So far today, four placebo-controlled dietary interventions in patients with presumptive NCGS have been published[20,51-53]. Carroccio *et al* reported that NCGS patients could be selected on the basis of a double-blind placebo-controlled gluten challenge[20]. In this regard, 276 out of 920 (30%) IBS patients symptom-free on a GFD were considered as NCGS. Compared to placebo, wheat induced significantly more symptoms in patients categorized as NCGS. Nevertheless, it is important to emphasize, as aforementioned, that 30% of NCGS patients in this trial had HLA haplotypes, LE and EmA positive in culture medium of biopsy, so most likely 1 out of 3 NCGS patients included in this trial had actually CD, as admitted by the own authors[37]. The other three trials have been performed by the same Australian group with conflicting results[51-53]. On a first gluten *vs.* placebo rechallenge trial, patients who received gluten challenge had more abdominal symptoms than those on placebo[51]; however, in a second trial with a crossover design, there were no differences between, high-gluten, low-gluten or placebo challenge[52]. In the run-in period of this latter study, patients received a diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) while maintaining the GFD. Noteworthy, patients whom had been included in the study due to symptom improvement on a GFD, showed a further significant clinical improvement on this run-in period[51]. Furthermore, high-gluten challenge did not worsen abdominal symptoms in a third trial, but NCGS patients showed high depression scores when compared to placebo, but interestingly not to high-whey[53]. In these three trials, CD was excluded on the basis of a HLA-DQ2 and DQ8 negative genetic study or a normal duodenal histology (Marsh 0) on patients HLA-DQ2/8 positive.

A recent study published in abstract form evaluating the efficacy of a GFD and afterwards a low FODMAP diet in patients given a diagnosis of NCGS[54], disclosed that the proportion of NCGS patients responsive to carbohydrate restriction outnumbered that of patients responding to a GFD. Overall, evolving evidence suggests there might be different patients lumped together

under the NCGS term: "celiac lite" patients, NCGS patients (an entity mediated through activation of the innate immunity) and patients intolerant to FODMAPs (carbohydrate intolerance).

7. Conclusions

NCGS is an emerging novel entity overlapping with CD and irritable bowel syndrome, lacking diagnostic criteria or biomarkers. This novel concept has been adopted by public far more readily than the medical scientific community (the ratio for the number of Google vs. PubMed citations for the terminology non-celiac gluten sensitivity was 4,598:1)[55]. In fact, epidemiology, diagnosis and the efficacy of a GFD are largely surrounded by controversy. Concerns about labelling minor forms of CD disease as NCGS have lately arisen, since both diseases have radically different levels of dietary restriction and prognosis if untreated. We currently now that gluten withdrawal may definitely provide clinical benefit to a subset of non-celiac patients, but possibly fermentable carbohydrate (FODMAP) restriction during a GFD may play a major role in symptom improvement. Now, more than ever, we need to separate the wheat from the chaff regarding NCGS and upcoming research will probably shed more light on all of these questions[56].

8. Epidemiology

- The overall prevalence of NCGS in the general population is still unknown, mainly due to lack of diagnostic markers, besides many patients are currently self-diagnosed and start a gluten-free diet (GFD) without medical advice or consultation.
- The growing market for gluten-free foods, which rocketed three-fold during the last 5 years, makes it even harder to decipher whether NCGS is a medical insight or a fad.

9. Natural History

- Unlike CD, no familiar aggregation, coexisting conditions (malabsorption and nutrition deficiencies, auto-immune disorders) and long-term complications have been described for NCGS.
- A diagnosis of NCGS in patients with gluten-dependent symptoms and familiar history of CD, malabsorption signs/symptoms or auto-immune diseases will always cast doubt on the possibility of these patients actually belonging to the spectrum of CD ("celiac-lite" disease).
- The importance of misdiagnosing NCGS in CD patients relies not only on the possibility of a CD patient following a non strict GFD, but also on overestimating response to a GFD in NCGS.

10. Diagnosis

- Gastrointestinal and extraintestinal symptoms in NCGS are indistinguishable from those present in CD.
- NCGS lacks diagnostic biomarkers, so it still remains a diagnosis of exclusion of CD
- Emerging evidence is pointing out inadequate exclusion of CD in a remarkable proportion of NCGS patients.
- Seronegativity and/or absence of villous atrophy may not positively rule out CD in patients with gluten-dependent symptoms

11. Pathogenesis

- Unlike CD, NCGS is mainly driven by activation of innate immunity
- Currently, gluten is not believed to be the only culprit component in wheat for NCGS
- Other wheat components, specially fructans as fermentable carbohydrates, have been postulated as a potential explanation for

symptoms after wheat consumption. These pathogenic pathways do not activate innate immunity but have to do with carbohydrate colonic fermentation.

12. Therapy

- Currently, no solid evidence support a GFD for NCGS patients.
- Compared to a GFD, recent randomized double-blind trials have shown a higher efficacy of a low FODMAP diet for NCGS patients.
- On account of variable responses to different dietary intervention, emerging evidence is posing the possibility of different patients lumped together under the NCGS term: "celiac lite" patients, NCGS patients (an entity mediated through activation of the innate immunity) and patients intolerant to FODMAPs (carbohydrate intolerance).

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