Coeliac Disease and Noncoeliac Gluten Sensitivity

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ABSTRACT

The spectrum of gluten-related disorders was restricted to coeliac disease and wheat allergy, but the new contemporary entity referred to as noncoeliac gluten sensitivity has gained recognition mainly in adults but also in children. Noncoeliac gluten sensitivity is defined as the presence of a variety of symptoms related to gluten ingestion in patients in whom coeliac disease and wheat allergy have been excluded. The pathophysiology and biomarkers of coeliac disease and wheat allergy are well known, but this is not the case for noncoeliac gluten sensitivity. It is also not clear whether noncoeliac gluten sensitivity is caused by consumption of gluten or by consumption of fermentable oligosaccharides, disaccharides, monosaccharides, and polyols. Randomized trials on noncoeliac gluten sensitivity in children are lacking and are hardly needed to evaluate its role in paediatric patients with gastroenterology to avoid the use of unnecessary restrictive diets in children and interference with proper diagnosis of coeliac disease.

Key Words: gluten, gluten intolerance, gluten-related disorders, noncoeliac gluten sensitivity, wheat intolerance, wheat sensitivity

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Gluten is the term used to identify a mixture of proteins (prolamines) that occurs in the endosperm of wheat (gliadins) and other cereals such as barley (hordeins) and rye (secalins). Up to recently, the most common gluten-related disorders in children included only coeliac disease (CD) and wheat allergy (WA). To these, the entity known as noncoeliac gluten sensitivity (NCGS) has been added. The common feature among these gluten-associated disorders is their treatment: a gluten-free diet. The aim of the present review is to present a summary and up-to-date overview of the similarities and differences of these gluten-related disorders, especially when they concern children.

We reviewed the literature through PubMed and Medline from January 2008 to May 2014, using the search terms *gluten (hyper) sensitivity, NCGS, gluten intolerance, gluten-related disorders, gluten-related disease, gluten avoidance, wheat intolerance*, and *wheat sensitivity*.

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What Is Known

- The pathophysiology of noncoeliac gluten sensitivity is unknown and without specific biological markers.
- Gastrointestinal manifestations of gluten-related disorders can be indistinguishable from each other.
- The diagnosis of noncoeliac gluten sensitivity should not be established before coeliac disease and gluten allergy have been ruled out.

What Is New

- Unlike coeliac disease and wheat allergy, noncoeliac gluten sensitivity is an unclear and controversial entity.
- It is not clear whether noncoeliac gluten sensitivity is triggered by gluten consumption or by ingestion of fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.
- High-quality randomized clinical trials in children are needed to evaluate the role of gluten in noncoeliac gluten sensitivity in the paediatric population.

CD

CD is an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals that is characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies, human leucocyte antigen (HLA)-DQ2 or HLA-DQ8 haplotypes, and enteropathy (1). CD is a common disorder, with a prevalence in the general Western population of 1% to 3% (2). Furthermore, first-degree family members of patients with CD have an increased risk for the disease, already at a young age, ranging from 5% to 30%, depending on their sex and HLA makeup (1,3). Patients with other autoimmune diseases, including type 1 diabetes mellitus and autoimmune thyroid disease, or patients with selective immunoglobulin A deficiency, and those with certain syndromes such as Down syndrome, Turner syndrome, and Williams syndrome, have an increased risk of CD (1). More than 95% of patients with CD carry the HLA-DQ2 or -DQ8 heterodimers, and the rest express HLA-DQ that contain ''half'' of the CD-associated molecules. In CD, gluten peptides, after crossing the small intestinal epithelium into the lamina propria, are deaminated by the enzyme tissue-transglutaminase and presented by HLA-DQ2–positive or HLA-DQ8–positive antigen-presenting cells to activated T cells. Once activated, the T cells produce interferon-γ and other cytokines, leading to a higher expression of the HLA-DQ molecules and thereby to increased gluten peptide presentation. This inflammatory process mediated by T cells leads to mucosal damage of the small bowel.

The incidence of CD is increasing worldwide, and many patients remain undiagnosed, probably because of the heterogeneity of the clinical picture, because CD can affect any organ, and not just

the gastrointestinal tract (1,4–6). The development of CD and the onset of symptoms may occur at any age. The classical clinical picture of overt malabsorption with diarrhoea, abdominal distension, and weight loss is observed, but only in a minority of children. Nonspecific signs and symptoms such as iron deficiency anaemia, osteoporosis, or fatigue are now common and could be the only sign of CD (1). In addition, CD may be asymptomatic.

CD is diagnosed by a combination of clinical suspicion, detection of specific autoantibodies to tissue-transglutaminase, endomysium, and deamidated forms of gliadin peptides, and histology of small bowel biopsies performed when the patient is on a gluten-containing diet (1). The characteristic histological alterations of the small bowel mucosa of patients with CD who consume gluten are partial to total villous atrophy with crypt hyperplasia and intraepithelial lymphocytic infiltration, rated according to the Marsh classification III and IV. At present, the only treatment of CD is lifelong adherence to a gluten-free diet that reduces the risk of complications and the increased mortality.

WHEAT ALLERGY

In contrast to CD, WA is an immunoglobulin E–mediated reaction to the insoluble gliadins, particularly ω-5 gliadin, the major allergen of wheat-dependent, exercise-induced anaphylaxis (''baker's asthma'') (7). Usually, patients with WA are not allergic to other prolamines containing grains, such as rye or barley, and their wheat-free diet is less restrictive than the strict gluten-free diet for patients with CD. The symptoms of WA develop within minutes to hours after gluten ingestion and are typical for an immunoglobulin E–mediated allergy, including itching and swelling in the mouth, nose, eyes, and throat; rash and wheezing; and life-threatening anaphylaxis. The gastrointestinal manifestations of WA may be similar to those of CD, but WA does not cause (permanent) gastrointestinal damage.

A recent systematic review and meta-analysis aimed to provide up-to-date estimates of the prevalence of food allergy in Europe has reported an overall pooled estimate for all of the age groups of self-reported lifetime prevalence of allergy to wheat (95% confidence interval) of 3.6% (3.0–4.2), lower only to cow's-milk allergy of 6.0% (5.7–6.4). The prevalence of food-challenge–defined allergy to cow's milk and wheat was 0.6% (0.5–0.8) and 0.1% (0.01–0.2), respectively (8). WA usually develops during early infancy or the toddler years and is less common in adolescents and adults. Most children with WA also have other food allergies.

NCGS

NCGS is a clinical condition in which intestinal and extraintestinal symptoms are triggered by gluten ingestion, in the absence of CD and WA. The symptoms usually occur soon after gluten ingestion, improving or disappearing within hours or a few days after gluten withdrawal and relapsing following its reintroduction (9). The prevalence of NCGS in the general population is unknown, but it has been estimated to be anywhere between 0.5% and 6% in different countries. No data on prevalence are available for the paediatric population, and the scarce data on children refer to gluten avoidance and not to NCGS per se (10,11). The disorder seems to be more common in girls and in young/middle-aged adults (10,12).

Although the first reports on NCGS date back more than 30 years ago, the disorder was not frequently diagnosed (13–16). The entity was brought to the attention of the gastroenterologists by 2 well-conducted double-blind, randomized, placebo-controlled trials in adults, suggesting the existence of NCGS as a distinctive disorder in a selected group of patients with symptoms of irritable bowel syndrome. The first study was performed in Australia and the second one by the Mayo Clinic group (17,18). The existence of the gluten-dependent character of the disease, however, was again put in doubt after a later double-blind, randomized, placebo-controlled trial performed by the same group of Australian investigators, suggesting that fermentable oligosaccharides, disaccharides, monosaccharides, and polyols, instead of gluten or other wheat proteins, were the cause of the symptoms (19,20). It is also possible that other grain proteins, different from gluten, may be responsible for the symptoms in NCGS. This has been suggested for the α-amylase/trypsin inhibitors, which are a group of low-molecular-weight proteins found in wheat and related cereals and are strong activators of the innate immune responses in vitro and in vivo (21). There are no randomized controlled trials examining NCGS in children.

During the past several years, many additional publications, most of them reviews of previous reports, have described the epidemiology, possible pathogenesis, clinical characteristics, histological alterations, and diagnostic approach to NCGS. Important drawbacks of many of these studies, however, are the varied definition of NCGS and inclusion criteria, the small number of patients included, the inclusion of some patients with potential CD and not with NCGS, the nondistinction between gluten and wheat, and the lack of double-blind, (placebo) controlled randomized studies. Table 1 shows the most relevant publications on NCGS for the studied period.

The clinical picture of NCGS is a combination of irritable bowel syndrome–like symptoms and systemic manifestations such as headache, joint/muscle pain, tiredness, body mass loss, anaemia, dermatitis, and behaviour disturbances (9,12,17). In children, NCGS tends to manifest with gastrointestinal symptoms, such as abdominal pain and chronic diarrhoea, whereas the systemic manifestations seem to be less frequent, the most common systemic symptom being tiredness (26). Unlike patients with CD, patients with NCGS do not appear to be at a higher risk for long-term complications such as nutrient deficiencies secondary to malabsorption. Patients with NCGS do not seem to have autoimmune comorbidities, as observed in CD, but allergy is more frequently seen in patients with NCGS (10,12).

An association between NCGS and neuropsychiatric disorders, such as schizophrenia and autism spectrum disorders, has been suggested (27,28). The conclusion of a Cochrane review including 2 small randomized controlled trials, however, is that there is no evidence for efficacy of gluten exclusion in these disorders (12,29). The major effect of gluten in patients with NCGS is in the perception of their general well-being (30).

The diagnosis of NCGS is based on exclusion of other gluten-related disorders, especially CD and WA. Unfortunately, there are no biological markers specific to NCGS. The only antibodies observed in a retrospective study of adults with NCGS are immunoglobulin G and immunoglobulin A anti-gliadin antibodies (AGAs), which occur in, respectively, 56% and 8% of the patients compared with 80% and 75% in the population with CD (31). It, however, has to be taken into account that AGAs are also frequently present in the general population. The vast majority of patients with NCGS showed immunoglobulin G AGA disappearance after gluten withdrawal. Half of the patients with NCGS were HLA-DQ2 or -DQ8 positive, a prevalence only slightly higher than in the general population (30%–40%) (9,12). A double-blind, placebo-controlled challenge has been suggested to confirm NCGS diagnosis. This is a complicated procedure to be performed in practice, given the difficulty in preparing the intervention products, the need for highly trained personnel, and high costs (32). An alternative is the open food challenge, but this is less reliable because of the important placebo effect. It is necessary to confirm the diagnosis of NCGS on a gluten-containing diet to avoid missing the diagnosis of true CD

TABLE 1. Overview of most relevant publications on noncoeliac gluten sensitivity (January 2008 to May 2014)*

Author (reference)	Design	No. patients	Intervention	Results/conclusions
Campanella et al (22)	Retrospective	61 adults with non-CD with gastrointestinal symptoms similar to CD improved after GFD	Gluten reintroduction median duration of 5 mo from a daily slice of bread until normal Italian gluten intake	Clinical exacerbation in 54.2%
Sapone et al (34)	Observational, comparative	Adults on a gluten-containing diet: 13 with active CD, 11 with NCGS, and 7 controls	Immunohistochemistry, duodenal biopsies	Mucosal expression of IL-17† not increased in NCGS compared with that in controls
Biesiekierski et al (17)	Prospective, randomized, double-blind, placebo-controlled	34 adult patients with improvement in IBS symptoms (Rome III) after a GFD	Food intervention with gluten (16 g/day) (n = 19) or placebo (n = 15) for 6 wk	Clinical exacerbation after gluten and not after placebo
Sapone et al (35)	Observational, comparative	Adults: 26 with NCGS, 42 with active CD, and 39 controls	Intestinal permeability and study of expression of genes involved in barrier function and immunity in mucosal biopsy specimens	In contrast to CD in NCGS, no increased permeability or IL-6 and IL-21‡ but increased TLR2 and reduced FOXP3§
Carroccio et al (23)	Retrospective	Adults: 276 with NCGS, 100 with CD, and 50 with IBS	Elimination diet: wheat, cow's milk, eggs, tomato, and chocolate for 4 wk. Reintroduction of a single food at a time.	Two distinct populations of NCGS: isolated NCGS (70) and NCGS + multiple food hypersensitivity (206)
Brottveit et al (24)	Observational, comparative	Adults: 17 with CD and 31 with NCGS (HLA-DQ2+) on GFD	Gluten challenge, 4 slices of gluten-containing white bread daily for 3 days	Patients with NCGS reported significantly more symptoms after gluten challenge
Volta et al (31)	Retrospective	Adults: 78 with NCGS and 80 with CD	Serum determinations of IgG/IgA AGA, IgG DGP, IgA TGA, and IgA EMA	Patients with NCGS: 56% IgG AGA, 7.7% IgA AGA but no EMA, TGA, or DGP
Bucci et al (25)	Observational, comparative	Adults: 34 with CD on GFD, 35 with untreated CD, 16 with NCGS, 34 controls	In vitro gliadin peptide challenges in duodenal mucosal samples	Patients with NCGS do not express markers of inflammation
Brottveit et al (36)	Observational, comparative	Adults on a GFD: 30 with HLA-DQ2–positive NCGS and 15 with CD	Duodenal biopsies before and after gluten challenge with 4 slices of gluten-containing bread daily for 3 days	Innate and adaptive immune response of patients with CD to gluten challenge. Patients with NCGS had increased intrae pithelial T cells before challenge compared with controls and increased IFN-γ mRNA after challenge.
Vazquez-Roque et al (18)	Single-centre, randomized controlled 4-wk trial	45 adults with IBS-D (Rome II) including 22 HLA-DQ2/DQ8+	22 patients receiving GCD (11 HLA-DQ2/DQ8+), 23 patients receiving GFD (11 HL-DQ2/DQ8+)	Improvement in symptoms after GFD. Increased permeability after gluten in HLA-DQ2/8+ patients.
Biesiekierski et al (19)	Double-blind, placebo-controlled, randomized cross-over rechallenge	37 adults with IBS (Rome III)	Reduced FODMAP diet for 2 wk, and then placed on high-gluten (16 g/day), low-gluten (2 g/day), and whey protein (14 g/day) or control (16 g/day whey protein) diets followed by a washout period of at least 2 wk	FODMAPs and not gluten cause symptoms in NCGS

AGA = anti-gliadin antibody; CD = coeliac disease; DGP = deamidated forms of gliadin peptides; EMA = anti-endomysium; FODMAPs = fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; FOXP3 = forkhead box P3; GCD = gluten-containing diet; GFD = gluten-free diet; HLA = human leucocyte antigen; IBS = irritable bowel syndrome; IBS-D = diarrhoea-predominant IBS; IFN = interferon; IgA = immunoglobulin A; IgG = immunoglobulin G; IL = interleukin; NCGS = noncoeliac gluten sensitivity; TGA = tissue-transglutaminase; TLR2 = Toll-like receptor 2.

* Reviews excluded.

† Markers of inflammatory and autoimmune diseases.

‡ Markers of adaptive immune response.

§ Markers of innate immune response.

(33). The pathogenesis of NCGS is unknown. There is agreement among researchers that only minor histological alterations have been found in the small bowel mucosa of patients with NCGS, compatible with 0 (normal mucosa) or I (mild alterations) in Marsh classifications (10,17,34). On the contrary, there is discrepancy regarding intestinal permeability in NCGS, because some studies have reported normal permeability and others not, with increased permeability in a subgroup of HLA-DQ2/DQ8–positive patients (17,18,35). The patient selection in those contradicting studies, however, was different (Table 1).

Furthermore, gene expression analyses showed increased expression of Toll-like receptor 2 and reduced expression of the T-regulatory cell marker forkhead box P3 in patients with NCGS compared with those in patients with CD, suggesting a role of innate immunity in the pathogenesis of NCGS. Contrary to CD, however, most studies show that adaptive immunity markers are not increased in patients with NCGS (Table 1) (35,36).

In general, NCGS, and CD and WA, is treated with a gluten-free diet, but, considering the lack of knowledge about its gluten-(dose-)related character and about the permanent or transient nature of the condition, periodic reintroduction of gluten into the diet may be advised (9,37).

In summary, CD and WA are 2 well-described gluten-related diseases with clear guidelines for diagnosis and treatment. NCGS is a controversial entity with more questions than answers concerning its nature, diagnosis, and treatment. High-quality prospective, double-blind, randomized clinical trials on the role of specific diets in children with gastrointestinal symptoms are needed to evaluate the pathogenesis and treatment of NCGS. Unnecessary gluten withdrawal may have negative health effects, especially in healthy children in whom growth and well-being may be compromised by inadequate diets and in patients with CD in whom the withdrawal of gluten from the diet before excluding CD prevents a proper diagnosis.

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