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Non-Celiac Gluten Sensitivity among Patients Perceiving Gluten-Related Symptoms

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Key Words
Non-celiac gluten sensitivity · Gluten · Celiac disease · Wheat allergy · Gluten-related disorders · Gluten-free diet

Abstract
Background: Non-celiac gluten sensitivity (NCGS) is a recently recognized disorder, characterized by the occurrence of symptoms following gluten ingestion. It is often self-diagnosed by the patient, but should be confirmed by the response to a gluten-free diet, followed by a gluten challenge. Celiac disease (CD) and wheat allergy (WA) must first be ruled out. ***Aims:*** (1) to determine the frequency of visits performed for symptoms self-perceived as gluten-related; (2) to assess in this cohort, the proportion of patients satisfying the diagnostic criteria for NCGS. ***Methods:*** A two-year prospective study including all consecutive patients complaining of gluten-related symptoms. NCGS was diagnosed on the basis of the disappearance of the symptoms within 6 months of a gluten-free diet, followed by their reappearance with the reintroduction of gluten in the diet for 1 month. ***Results:*** Three hundred and ninety two patients complaining of gluten-related symptoms were enrolled; 26 of these (6.63%) were affected by CD, 2 (0.51%) by WA and 27 were diagnosed with NCGS (6.88%). The remaining 337 patients (85.96%) did not experience any change of symptoms with a gluten-free diet. The PPV of the gluten-related symptom was found to be 7%. ***Conclusion:*** Eighty six percent of patients reporting gluten-related symptoms have neither NCGS, nor CD, nor WA. Self-perceived gluten-related symptoms are rarely indicative of the presence of NCGS.

Introduction

The gluten-free diet (GFD) for presumed health benefits is a worldwide phenomenon with ever-increasing number of followers. They decide to avoid gluten not on the basis of medical advice but because they feel better without eating it, or they believe it to be hard to digest and that GFD is synonymous with healthy eating [1–3].

Gluten is the commonly used term for the complex of water-insoluble proteins contained in wheat, rye and barley. Wheat is one of the most important food sources in the world contributing most of the dietary calories in industrialized and developing countries. Global consumption of wheat has increased faster than for any other cereal [4].

Gluten ingestion may trigger abnormal immune reactions, causing celiac disease (CD) via the Th1 pathway in genetically predisposed people (HLA DQ2 or DQ8 haplotype), or wheat allergy (WA) via the Th2 pathway.

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Non-celiac gluten sensitivity (NCGS) is a more recently recognized disorder related to gluten ingestion in which both autoimmune and allergic mechanisms have been ruled out. The condition implies that symptoms occur on the ingestion of gluten and are alleviated on GFD despite the absence of CD or WA. Currently, there are no objective diagnostic criteria for NCGS, its diagnosis remaining one of exclusion [4, 5]. Thus, after the exclusion of CD and WA, diagnosis for NCGS relies on the disappearance of the symptoms with a GFD, followed by the relapse of the symptoms when gluten is reintroduced [2, 6]. Ideally the gluten challenge should occur blindly, a procedure that is rarely feasible in clinical practice. NCGS has become a commonly and increasingly diagnosed phenomenon, with more and more people undergoing medical visits complaining of symptoms they attribute to gluten. The growth of the gluten-free food market can contribute [7–10].

The aim of this study was to assess the following in the setting of our out-patient gastroenterology clinic:

(1) The frequency of medical visits taking place for symptoms self-perceived as gluten-related

(2) The proportion of patients in this cohort satisfying the diagnostic conditions for NCGS.

Methods

Study Design

The study consisted of a single-centre, prospective, clinical trial performed to evaluate the meaning of self-reported gluten-related disorders.

Patients were recruited evaluating all the out-patients of the Gastroenterology Unit of the University of L'Aquila during the period between August 2012 and August 2014.

Eligibility Criteria

To be part of this study, patients had to be over 16 years old with symptoms self-perceived as gluten related. All of them underwent diagnostic work-up to diagnose CD and WA. Following that, patients not having CD and WA underwent diagnostic work-up to diagnose NCGS.

Patients who were on GFD at the time of examination were placed on gluten-containing diet for at least 8 weeks before the evaluation.

Diagnostic Criteria

Celiac Disease

The diagnosis was made in the presence of anti-tissue transglutaminase (anti-tTG) antibodies and/or anti-endomysial antibodies (EmA) of both the IgA and IgG class, associated with specific duodenal alterations at biopsy, according to the modified Marsh-Oberhuber classification [11].

In patients with discordant results between serology and histology, genetic testing for HLA DQ2 and/or DQ8 haplotypes presence was employed: if the results were negative, celiac disease was ruled out.

Wheat Allergy

The diagnosis was made in the presence of serum specific IgE antibodies to wheat and/or skin prick tests [4]. Prick testing was performed after the discontinuation of antihistamine medication and read after 15 minutes.

Non-Celiac Gluten Sensitivity

This entity was considered in the presence of a rapid resolution of symptoms on gluten-free diet for 6 months and upswing of previous symptoms with the reintroduction of gluten in the diet for 1 month [6].

Diagnostic Work-Up

All enrolled patients underwent clinical, laboratory, endoscopic and histological examination. They then completed a questionnaire investigating symptoms' features related to gluten ingestion.

The questionnaire included the following items: age and sex, gastrointestinal and extraintestinal symptoms and their features (frequency, onset time after gluten ingestion, duration), who it was that initially suspected the diagnosis (the patients themselves, friends, physician, gastroenterologist, pharmacist, homeopath or other professionals), associated diseases, family history for CD, WA and NCGS, known allergies.

Laboratory examination included: anti-tTG, anti-EmA and anti-deamidated gliadin peptide antibodies (for all, both IgA and IgG), genetic testing for CD (HLA-DQ2 and HLA-DQ8 haplotypes), IgE antibodies to wheat, skin prick test. Complete blood cell count, acute phase reactants, iron, ferritin and immunoglobulins were also tested.

Upper endoscopy was completed by gastric and duodenal biopsies. All biopsies were fixed in formalin and stained in haematoxylin and eosin. Duodenal biopsy samples were orientated on filter paper and also evaluated by immunohistochemstry.

Diet

A 6 months GFD was advised to patients with neither CD nor WA, with a subsequent challenge with gluten for 1 month to those who experienced benefit without gluten. Education to gluten-free diet and compliance with it were assessed on a monthly basis by a trained nutritionist throughout a direct interview.

Statistical Measures

The following parameters were assessed:

Frequency of visits due to symptoms related to gluten was defined as the actual number of patients complaining of gluten-related symptoms relative to all those visiting the GI unit (excluding hepatological and proctological problems).

Frequency of NCGS was defined as the actual number of patients with NCGS relative to all those visiting for gluten-related symptoms.

Specificity of the gluten-related symptom was defined as the number of subjects without NCGS who do not have gluten-related symptoms/number of subjects without NCGS regardless of the presence of gluten-related symptoms.

Positive predictive value (PPV) of the gluten-related symptom was defined as the probability that someone with the symptom related to gluten really has NCGS. It is defined as the number of patients with gluten-related symptoms affected by NCGS/all the subjects referring gluten-related symptoms.

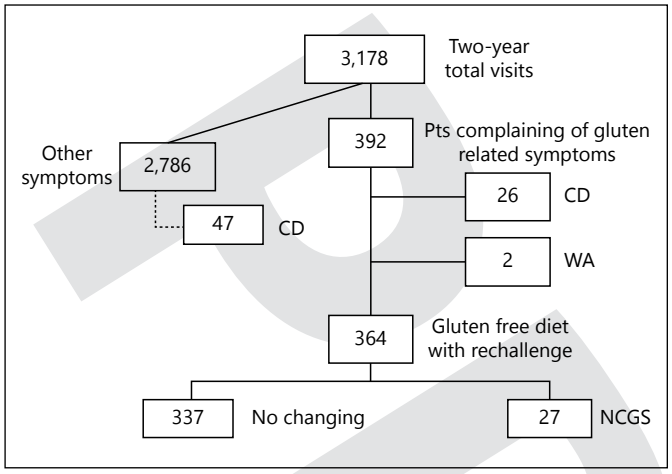

Fig. 1. Flowchart illustrating the progress of patients through the study.

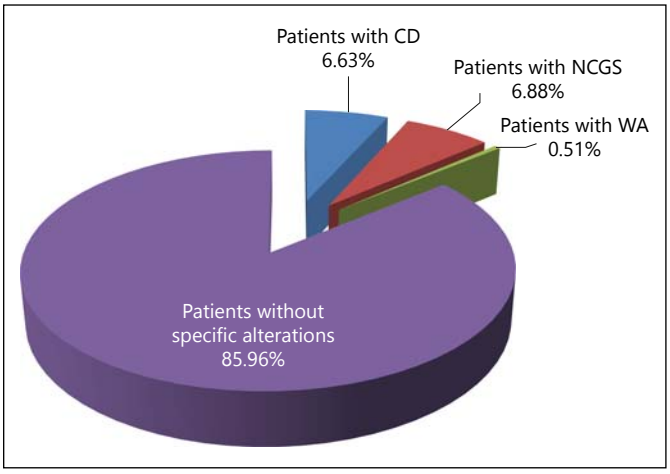

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Fig. 2. Proportion of CD, WA and NCGS in the population.

Table 1. Demographic characteristics of patients

Patients	n (%)	Median age, years	Women, n (%)	Men, n (%)
Total patients	392 (100)	43.58	307 (78.31)	85 (21.68)
CD patients	26 (6.63)	37.7	23 (88.46)	3 (11.53)
NCGS patients	27 (6.88)	43.3	23 (85.18)	4 (14.81)
WA patients	2 (0.51)	37.5	1 (50)	1 (50)
Patients without specific alterations	337 (85.96)	44.23	251 (74.48)	86 (25.51)

CD = Celiac disease; WA = wheat allergy; NCGS = non-celiac gluten sensitivity.

Results

Over the 2-year period, 3,178 patients were screened. Of these, 392 complained of gluten-related symptoms and were enrolled (12.3% of the screened population). These consisted of 307 females and 85 males with a mean age of 43.5 (range 17–85 years).

Figure 1 shows the flowchart illustrating the progress of patients through the study. At the end of the diagnostic work-up, 26 patients (6.6%) were found affected by CD, and 2 patients (0.5%) by WA. Out of the 364 remaining patients, 27 patients were diagnosed as having NCGS (6.8% of the entire eligible population; 7.4% of the patients not having CD nor WA). The remaining 337 patients (85.9% of the entire eligible population; 92.5% of the patients not having CD nor WA) did not experience any change with GFD. Figure 2 shows the proportion of the groups. Table 1 shows demographic characteristics of the studied population.

Statistical weight of the presence of a gluten-related symptom was assessed: specificity was 88.4% and PPV was 6.8%.

NCGS Clinical Features

Out of the 27 patients with NCGS, 23 were females (85.1%) with F/M ratio of 5.7 to 1. The mean age was 43.3 (range 17–78 years). A majority of them referred to more than two gastrointestinal or extra-intestinal symptoms related to gluten consumption.

Referred gastrointestinal symptoms were abdominal bloating in 20 patients (74%), abdominal pain/discomfort in 19 (70.3%), diarrhea in 9 (33.3%), constipation in 2 (7.4%), alternating bowel function in 3 (11.1%), epigastric pain in 3 (11.1%).

Referred extra-intestinal manifestations were malaise in 16 (59.2%), chronic fatigue in 11 (40.7%), headache in 9 (33.3%), anxiety in 6 (22.2%), 'confused mind' in 6 (22.2%), depression in 1 (3.7%), joint/muscle pain

Table 2. Non-celiac gluten sensitive clinical features

Gastrointestinal symptoms, %	
Bloating	74
Abdominal pain/discomfort	70.3
Diarrhea	33.3
Constipation	7.4
Alternating bowel function	11.1
Epigastric pain	11.1
Extra-intestinal manifestations, %	
Malaise	59.2
Chronic fatigue	40.7
Headache	33.3
Anxiety	22.2
Confused mind	22.2
Depression	3.7
Joint/muscle pain	22.2
Weight loss	14.8
Anemia	18.5
Dermatitis and rash	11.1
Time intervals between gluten intake and onset of symptoms, %	
Within 6 h	85.1
Between 6 and 24 h	11.1
More than 24 h	3.7
Time intervals between the onset of symptoms and the diagnosis of NCG, %	
Duration longer than 6 months	77.7
Between 1 to 6 months	14.8
Less than 1 month	7.4

resembling fibromyalgia in 6 (22.2%), weight loss in 4 (14.8%), anemia (iron deficiency) in 5 (18.5%), dermatitis and rash in 3 (11.1%). No patient reported asthma or allergic rhinitis.

The evaluation of the time intervals between gluten intake and onset of symptoms for the 27 patients showed: an interval within 6 h for 23 patients (85.1%), an interval between 6 and 24 h for 3 (11.1%), and an interval of more than 24 h in 1 (3.7%).

The assessment of the time intervals between the onset of symptoms and the diagnosis of NCGS showed a duration longer than 6 months in 21 (77.7%) patients, between 1 and 6 months in 4 (14.8%), and less than 1 month in 2 out 27 patients (7.4%) (Table 2).

Disorders associated with NCGS were irritable bowel syndrome (IBS) according to Rome III criteria [12] – found in 6 patients (22.2%), lactose intolerance – found in 6 (22.2%), autoimmune thyroiditis – found in 3 (11.1%), type 1 diabetes – found in 1 (3.7%), psoriasis – found in 1 (3.7%) and sarcoidosis – found in 1 (3.7%). Three patients (11.1%) had a family history for CD.

Discussion

The results of this study indicated that the attribution of symptoms to gluten giving rise to hospital visits turns out far more often than not to be ill-founded. Approximately 12% of gastroenterological consultations are due to symptoms self-perceived as gluten related. For most of these patients, accounting for the 85% of the whole cohort, the exclusion of gluten from diet does not result in alleviating of their symptoms. The frequency of gluten-related disorders in our population was approximately 7% for CD, 7% for NCGS and 0.5% WA. Results indicate that having a symptom self-perceived as gluten-related has little predictive value for the presence of NCGS: the PPV was, in fact, 7%.

Prevalence rates for NCGS are extremely variable in literature, ranging from 0.5 to 13%, reflecting differences in the recruited target population and the absence of objective diagnostic criteria [13].

Our data about NCGS prevalence, although referring only to the patients reporting symptoms related to gluten ingestion, are in line with literature.

Given the absence of objective diagnostic criteria for NCGS and the fact of its emergence as an increasingly commonly diagnosed phenomenon [14–16], attention must be paid to interpreting data reported in literature. The diagnostic 'gold standard' of NCGS should be a double-blind placebo-controlled (DBPC) gluten challenge, a method not easy to apply in daily practice. In literature there is only a survey using this criterion for the diagnosis of NCGS. This study included 920 IBS-like patients without CD and WA whose symptoms resolved on GFD. Of these patients, 276 (30%) were considered real NCGS as they became asymptomatic on GFD and showed recurrence of symptoms during the DBPC challenge. Although it is a retrospective study, it suggests NCGS to be a distinct clinical condition compared to IBS [17].

In the overwhelming majority of our patients (85%) not affected by CD or WA and who did not experience a clinical response to the GFD, other food components or concomitant disorders should be involved in the development of symptoms: lactose and oligosaccharides malabsorption and intolerance, fermentable oligo-di-monosaccharides and polyols (FODMAPs), bacterial overgrowth, IBS, microscopic colitis and systemic autoimmune diseases [18–23]. We did not assess all those conditions that should be routinely evaluated in this subgroup of patients. Furthermore, in these patients, the wrong self-reported perception that gluten may be responsible for symptoms, could be induced by the misconception pro-

moted by health-food industry that gluten is unhealthy. This belief is taking place in western countries, to the point that about a third of US adults express their willingness to exclude gluten from their diets [13].

Due to the overlap between NCGS and IBS, other studies have addressed the potential role of GFD in IBS patients.

In a randomized DBPC study, the effect of gluten was evaluated in 34 patients with IBS and without CD symptoms of which had improved on a gluten-free diet. Patients were randomized to receive gluten or placebo for 6 weeks. Symptoms reoccurred in 68% of patients receiving gluten respect to 40% of those receiving placebo ($p = 0.001$), showing that gluten is a trigger of gut symptoms [24].

A double-blind crossover trial evaluated the effect of gluten in 37 non-celiac patients with IBS who reported improvement of symptoms with a GFD. Patients were firstly assigned to a 2-week period of reduced FODMAPs diet, and then randomized to one of three treatment groups for 1 week: high gluten content, low gluten content or placebo. Symptoms improved in all participants during the 2-week period of reduced FODMAPs diet, but significantly worsened after the introduction of both gluten and placebo, showing no evidence of specific or dose-dependent effects of gluten in patients with NCGS placed diets low in FODMAPs [25].

A double-blind cross-over study investigated whether gluten acts on the mental state rather than on gastrointestinal symptoms in IBS patients without CD but symptomatically controlled on a GFD. Twenty-two patients with both IBS and NCGS were randomized to one of three treatment groups: gluten, whey or placebo for 3 days. Then, patients were crossed over to the next diet group, so that all participants undertook the three dietary challenges. Gluten ingestion was associated with significant worsening of mental state (depression) compared to placebo, without affecting gastrointestinal symptoms [26].

Taken together, data derived from the use of placebo still questions whether NCGS is a real entity, as besides gluten, other dietary components and also mood could contribute to symptoms perception.

The underlying mechanisms by which food components may be responsible for gastrointestinal and extraintestinal symptoms in NCGS are still not known. Besides gluten, FODMAPs and wheat amylase trypsin inhibitors (ATIs) (plant-derived proteins) have been considered to be involved in the development of symptoms in NCGS [25, 27].

Since no microscopic inflammation has been demonstrated in these patients, it can be hypothesized that gluten and/or other food components would act by inducing visceral hypersensitivity or through the alteration of intestinal microflora; an immune-mediated mechanism cannot be excluded, as in our study, one third of the patients with NCGS are affected by autoimmune diseases.

Despite the absence of specific histological lesions, some molecular changes have been reported.

It has been reported that intestinal mucosa of NCGS patients is characterized by an increased expression of toll-like receptor (TLR)-2, a markers of innate immune system activation [28], increased levels of IELs at baseline and an increased IFN-γ mRNA signal after gluten challenge [29]. Furthermore, an increased expression of the gene synthesizing claudine-4 has been observed, although with a normal intestinal permeability [28, 30]. On the contrary, other in vitro observations indicate that, following gliadin exposure, NCGS patients show a greater increase in intestinal permeability compared to CD patients in remission [31]. Such biological markers are aspecific, as they can be reported in many other clinical conditions. Therefore, more specific markers for NCGS are needed.

In conclusion, despite the limits of our study as the lack of blindness in the gluten-free diet challenge and the missing evaluation of possible influence by other food constituents, we confirm the high frequency of visits due to gluten-related symptoms and the low predictivity of self-reported perceptions. The existence of the entity NCGS is still debated and the benefit of a gluten-free diet must be proven [13, 27]. We still require a better understanding of the clinical presentation of NCGS, as well as its pathogenesis, epidemiology, management, and role in conditions like IBS, chronic fatigue, and autoimmunity.

Competing Interests

The authors declare that they have no competing interests.

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