Non-Celiac Gluten Sensitivity: A Systematic Review

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ABSTRACT

Non-celiac gluten sensitivity (NCGS) is a wheat associated disorder diagnosed by exclusion diagnosis. This review was conducted to collect current information about NCGS, clinical and pathologic manifestations, and problems faced by health professionals. It also highlights the obstacles faced when adopting a gluten-free diet. A search of international literature was conducted through PubMed and Google Scholar till September 2017. The heterogeneous groups of patients affected by NCGS are composed of a number of subgroups, and each demonstrates different clinical and pathological manifestations. The presence of certain underlying factors can be utilised to identify susceptible individuals, namely, incidence of food allergies in infancy, anti-gliadin IgG-antibodies, activation test for flow cytometric basophils, atopy, and increased intraepithelial duodenal eosinophil presence. There is urgent need for reliable biomarkers to decisively diagnose and differentiate NCGS from related disorders. Patients willing to adopt gluten-free products have to choose from products which have high fat and sugar content.

Key Words: *Gluten, Gluten sensitivity, Celiac disease, Irritable bowel syndrome, Non-celiac gluten intolerance.*

INTRODUCTION

Non-celiac gluten sensitivity (NCGS) or gluten intolerance is a recently recognised syndrome characterised by an inherent intolerance to gluten. In literature, various names have been suggested and used to describe this relatively new disorder, such as gluten hypersensitivity, gluten sensitivity and non-celiac gluten intolerance.[1-5] In 2011, the first Expert Meeting members proposed a name for the syndrome, gluten sensitivity (GS).[1] The Oslo definition was later on announced by 16 experts of celiac disease, suggesting that non-celiac gluten sensitivity is a more appropriate name instead of GS.[4] In Munich in 2012, a second meeting was held which decided to change the name from GS to NCGS in an effort to make the disorder distinguishable from celiac disease.[5] Classification of gluten associated disorders is given in Figure 1.

The disease state is defined as an onset of a spectrum of clinical manifestations in response to the ingestion of wheat, rye, and barley in the absence of celiac disease and wheat allergy.[4] Originally, gluten sensitivity first received recognition during the 1980s, but it was not until 2010 that enough research commenced which recognised the full magnitude of this novel syndrome that has been affecting people since the last five decades. Gluten intolerance is a disease state characterised by sensitivity to gluten proteins found in wheat, barley, and rye, in subjects which test negative for celiac disease and wheat allergy, respectively. The symptoms of NCGS are enumerated in Table I.[6] Table II enumerates some of the important characteristics of gluten-related disorders. This review aims to critically review the current available evidence on diagnostic exclusion criteria, pathologic manifestations of disease, obstacles faced by patients when going on a gluten-free diet; and lastly, the problems faced by healthcare professionals in dealing with NCGS patients.

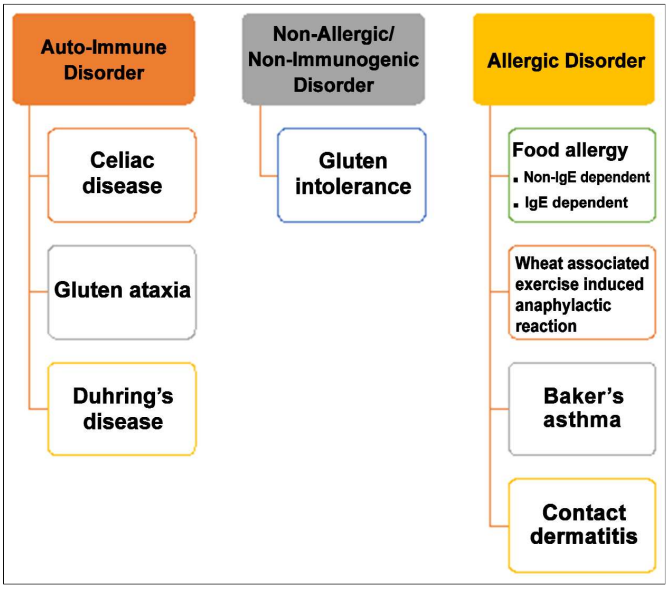

Figure 1: Classification of gluten associated disorders.

Non-Celiac Gluten Insensitivity: What Is It? NCGS is a heterogeneous entity which characteristically possesses distinct patient subgroups.[7] A negative criterion is used to define NCGS, because of the fact that the diagnosis is based on a negative serology for celiac disease. In addition to negative serology, duodenal histological tests are also negative, and immunological

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Table I: Symptoms of NCGS.[1,6]

Intestinal	General	Behavioural	Hematological
Pain in abdominal region after ingestion of gluten associated products	Headache, joint pains	Lack of attention	Anemia because gluten causes damage to areas of intestine from where iron, folate and vitamin B12 is absorbed
Diarrhea and loss of body mass	Involuntary muscular contractions	Depression	
Flatulence, bloating	Hands and feet going numb	Ataxia	
Nausea	Chronic fatigue	Hyperactivity	

Table II: Characteristics of gluten associated disorders.[6]

Characteristics	NCGS	Celiac disease	Wheat allergy
Morbidity	Not know	1%	1%
Genetic background	HLA-DQ2 & HLA-DQ8 positive in 50% cases	HLA-DQ2 & HLA-DQ8 positive in 95% cases	Atopy in 100% of cases
Pathogenesis	Not known, possibly a disturbance in underlying primary immune response initiated to gluten ingestion	Acquired gluten dependent immune response disturbance in combination with HLA-DQ2 or HLA-DQ8	sIgE mediated immune response, high Th2 response upon wheat ingestion
Serum antibodies	In 50% of cases; Anti gliadin antibodies of IgG class	Endomysium antibodies, tissue transglutaminase, deaminatedgliadin peptide, and anti gliadin antibodies of IgA class with lesser frequency of IgG class	sIgE antibodies against wheat and gliadin
Duodenal mucosa histological features	Marsh 0 and 1	Marsh I to IV with predominantly higher frequency of Marsh III i IV	Marsh 0, I and II
Duodenal villi atrophy	Absent	Present	Might or might not be present
Symptoms	Extra intestinal and intestinal	Extra intestinal and intestinal	Extra intestinal and intestinal
Mortality	Not known	Raised	Raised
Required gluten-free diet time period	Not known	Lifelong	A duration of 6 years on average with lifelong abstinence to avoid anaphylaxis

Table II mentions the diagnostic criteria for wheat associated disorders.

IgE assays are also negative. The only aspect positive in diagnosing the disease is the presence of troublesome symptoms like those in wheat allergy and celiac disease upon the ingestion of gluten containing products.[4,8,9]

In a consensus meeting, an international panel of experts gathered in 2011, from 14 participating countries, in an effort to put forward a definition of gluten intolerance. In accordance with the definition, the disease was labelled as a non-autoimmune and non-allergic response to consumption of gluten containing products with the observance of symptoms like those observed in celiac disease and wheat allergy.[8] A retrospective review published in the year 2012, conducted on 920 patients, illustrated NCGS as a separate entity. The patients selected for the study fulfilled the criteria for both Rome II irritable bowel syndrome like symptoms together with symptoms associated with gluten sensitivity. The study involved a double blind, placebo controlled challenge for wheat consumption which was followed by a specified duration of at least one month of wheat elimination time period. The study revealed that 30% of the study sample, *i.e.* (n=276) subjects presented with classic symptoms of gluten intolerance, were diagnosed with wheat sensitivity. The serologic inflammatory indices presented no change of values before and after dietary challenge in wheat sensitive patients. After the first week of wheat reintroduction in such patient diagnosed with wheat sensitivity, they presented symptoms such as abdominal pain, stool consistency changes and bloating ($p < 0.001$); and the intensity of such self-reported symptoms increased during the second week of wheat reintroduction ($p < 0.001$).[7]

Wheat sensitive patients were then subjected to second wheat elimination dietary challenge which was followed by a double blinded placebo-controlled challenge conducted with cow's milk. This led to the categorisation of patients into two groups, namely, subjects with wheat sensitivity (n = 70) and secondly, those having wheat sensitivity coupled with hypersensitivity to multiple foods (n = 206). The patients with wheat sensitivity presented with symptoms of anemia and experienced loss of weight. These symptoms were demonstrated to have a frequency which was intermediate between that of celiac disease and irritable bowel syndrome controls. On the contrary, a higher frequency than both celiac disease and irritable bowel syndrome controls were observed in relation to comorbid atopic states, self-reported intolerance to wheat, and history of infantile allergy to

multiple foods.[7] An either positive HLA-DQ2 or negative DQ8 haplotype were observed in all 100 patients with celiac disease. This observation was demonstrated to a significantly lesser extent in wheat sensitive patients and those with irritable bowel syndrome, 53%, and 28%, respectively. Furthermore, the medium of duodenal biopsy culture of all celiac disease patients presented a positive test for anti endomysial antibody; whereas, those with wheat sensitivity and irritable bowel syndrome presented positive tests to (40%/55%) considerably lesser extent at 8% and 0%, respectively. The serum from wheat sensitive patients presented a positive test for AGA IgA/IgG to a lesser frequency than in patients with celiac disease (72%/78%, p=0.001/ p=0.01) (10, 20). However, AGA IgA/IgG was observed to a greater frequency in wheat sensitivity subjects compared with irritable bowel syndrome controls (10%/14%, p=0.0001 in both).[7]

Differential Diagnosis: The diagnosis of NCGS relies on exclusion of celiac and wheat allergy due to the absence of reliable diagnostic biomarkers.[9-11] The disease is most often self-reported, who consult the physician upon experiencing celiac disease like symptoms upon wheat ingestion. One of the pivotal points observed in such patients is the role of emotion.[12]

For a patient to be diagnosed with gluten intolerance, it is essential to eliminate both CD and WA through extensive laboratory and histological tests. The clinical consensus rests on a criterion for diagnosis which includes the presence of self-reported symptoms of intolerance coupled with an absence of celiac disease serology. NCGS patients may have a duodenal intraepithelial lymphocytosis, which is presented in the form of A-grade lesions. Such lesions are a characteristic appearance in histological testing for celiac disease; and in some instances, might also be presented in patients with gluten intolerance.[9-11] The results of a study conducted on participants, revealed the performance of Salerno Experts' Diagnostic criteria for NCGS and identified NCGS patients from a pool of gluten-free diet responsive patients.[13] Table III enumerates the diagnostic criteria for wheat associated disorders

Pathogenesis and Clinical Manifestations: In terms of etiology, NCGS remains a disorder whose pathogenesis still requires elucidation.[5] The causative grain ingredients for gluten intolerance have yet to be identified. The incubation of gliadin with the duodenal mucosa of patients demonstrating gluten intolerance does not show an increased expression of inflammatory markers, a typical feature of celiac disease. In addition, the basophils in such patients are also not activated in response to gliadin proteins.[14] Another study reveals that a major triggering role might be played by wheat amylase trypsin inhibitors in initiating a response of innate immune system leading to the development of symptoms of NCGS.[15] It is believed by Eswaran *et al*. that the role might also be undertaken by FODMAPs, *i.e.* fermentable oligosaccharides, disaccharides, monosaccharides, and polyols, which are those carbohydrates that have been poorly absorbed from the intestinal tract.[6,14] Upon reduced intake of FODMAPs, an improvement in symptoms is observed in all patients of NCGS. The process of fermentation is responsible for the generation of short chain fatty acids and gases. The gastrointestinal symptoms are in part caused by a change in intestinal microbiota.[14]

Role in NCGS: On the contrary, the pathogenesis and clinical manifestations associated with NCGS is not well understood. The foremost issue with defining the disease mechanism is not being able to find the cause of symptoms. The evidence does not describe the

Table III: Diagnostic criteria for wheat associated disorders.[6,57]

Diagnostic criteria	Celiac disease	Wheat allergy	Gluten intolerance
Clinical presentation	Upon wheat ingestion, gastrointestinal symptoms are experienced which resolve upon exclusion of gluten from diet	Upon wheat ingestion, gastrointestinal symptoms are experienced which resolve upon exclusion of gluten from diet	Upon wheat ingestion, gastrointestinal symptoms are experienced which resolve upon exclusion of gluten from diet
Antibodies against Tissue transaminase	+	-	-
Antibodies against gliadins	+	-	In half of the cases it comes out +
Antibodies against endomysium	+	-	-
Antibodies against deaminated peptide from gliadins	+	-	-
Duodenal histological tests (Classification of Marsh Oberhuber)	+ (1-3)	+	(0-1)
DQ2-DQ8 HLA Haplotypes	+	-	-/+
IgE antibodies	-	+	-

+ = Positive result; - = Negative result.

causative factor responsible for inducing disease symptoms. The field of research is faced with the dilemma of whether gliadin proteins are responsible or peptides of gliadin proteins, or other constituents of wheat including amylase trypsin inhibitor or contaminants of gluten are causing associated pathogenic mechanism. In accordance with evidence provided by broader research, the experimental models of both celiac and non-celiac disease demonstrate the way epithelial cell damage and abnormalities are induced as a result of gluten ingestion. A number of non-immune mechanisms and pathways also play a role in the said damage and abnormality initiation.[16-21] Furthermore, mucosal homeostasis is altered by toxic effect mediated by gliadin resulting in a reduction of F-actin composition of the mucosal epithelial layer of the small intestine. In addition, gliadin proteins also create an oxidative stress state leading to the generation of damaging free radicals, induce apoptosis in the mucosal cells, and produce an inhibition of the normal growth process of epithelia. Lastly, the proteins cause an inhibition of the synthesis of RNA and DNA in the already damaged mucosal epithelial cells.[16,22-25] Noteworthy evidence is provided by mice experimental models (DQ8-restricted), which reveal the gluten, induced an increased release of acetylcholine from the myenteric plexus. Consequently, an increase in cholinergic activation is observed which inevitably might be responsible in part for the neuromuscular abnormalities of the gastrointestinal tract. The events, initiated in response to increased cholinergic activation, include a rise in the luminal water content, and increased contractility of the smooth muscles. Such effects are caused due to a prosecretory state of the epithelia which is, in turn, a neuro-mediated effect. However, it is also true that other antigens present in wheat might also produce a similar response and trigger a similar cascade of events. The enteric nervous system might also be responsible for triggering the symptoms, through indirect stimulation of the mast cells, to release neurotransmitter or directly through, the enhanced supply of neuroactive molecules. The ingestion of gluten and other proteins in wheat-based cereals leads to the generation of neural active peptides which upon gaining access to the nerve endings in the enteric nervous system, might play a role in disease generation. However, they have limited permeability in NCGS patients' gastrointestinal tract so their exact role is not known as yet.[16,26-28] The abnormalities in gastrointestinal motor activity are demonstrated in 30-60% of the patients of celiac disease with varying degree of abnormalities in different parts of the gastrointestinal tract.[29] The development of bacterial overgrowth in the small intestine contributes to the presentation and maintenance of celiac disease symptomatology. A predisposing factor, the development of bacterial overgrowth is motility disorders.[29-34] The colonic transit time is increased up to almost 46% in patients suffering from irritable bowel syndrome, providing evidence for the motility disorders occurring in digestive disorders. Positivity in the values of HLA-DQ2/DQ8 and improvement in gastrointestinal motility is observed with gluten withdrawal. Thus, the possibility of gluten and gliadin mediating a motility disorder of the gastrointestinal tract in the patients of NCGS is significant.[35] Recent studies have raised the possibility that low fermentable and carbohydrates with short chains might also be responsible for generation of NCGS symptoms. Additionally, wheat amylase trypsin inhibitors may also contribute to symptom production in such patients.[36]

Challenges in Adopting Gluten-Free Diet: The unwillingness to officially register the production of gluten-free products by food manufacturing companies coupled with an inappropriate labelling of food in national databases are two major obstacles that limit the range of processed food products available for consumption by individuals diagnosed with gluten intolerance. An adherence to gluten-free diet on a lifelong basis is the only proven effective treatment for gluten intolerance and other wheat associated disorders because only minute amount of it can cause considerable problems.[25,37-39]

Consequences of Lack of Quality Evaluation: The tremendous rise in both the popularity and consumption of gluten-free diet does not commensurate with the rigidity of the evaluation procedures followed for standardisation of gluten-free products. There is a lack of evaluation of nutritional profile of such processed foods as well as a comparison in terms of food value with products that are not gluten-free. The assessment of these products is tremendously important for a number of reasons.[40] The consumption of a gluten-free diet produces nutritional deficiencies which are the foremost reason why such products need rigorous assessment in terms of nutritional value. The results of several studies have revealed that nutritional deficiencies are produced due to the consumption of gluten-free diets in terms of calories, vitamins, minerals, dietary fiber, and protein.[41-47] Since, the only treatment available at present for patients with NCGS, celiac disease is gluten abstinence. Thus, the implications of a gluten-free diet pertinent to nutritional deficiencies are quite alarming.[48-50] The most deficient minerals in a gluten-free diet are reported in several studies to have been iron, calcium, and magnesium.[50] Numerous authors claim that gluten-free diets are unable to fulfill adequate amounts of folate and B complex vitamins.[45,51] Currently available gluten-free products demonstrate a poor balance of nutritional elements, with some products even containing higher than healthy levels of sugars together with sugars. The high content of sugar and lipids is kept in an effort to improve the taste of such products. Such unhealthy levels might precisely be the

major reason for increased incidence of obesity in patients of wheat associated disorders.[52] These are some of the reasons why assessment and nutritional evaluation of gluten-free products are necessary.

METHODOLOGY

A search of international literature was conducted through PubMed and Google Scholar with no time restriction until September 2017. All full-text articles were utilised and those pertinent to exclusively celiac disease, irritable bowel syndrome were excluded as well as those in languages other than English. An exhaustive list of articles, since the inception, were utilised that provided information related to gluten sensitivity. Duplicate articles were removed.

Literature Search Strategy: The data search was conducted by using Boolean terms in PubMed and Google Scholar. The terms used were "non-celiac* gluten sensitivity*" or "wheat allergy", "gluten intolerance* or NCGS*", "wheat sensitivity* and wheat hypersensitivity* and non-celiac gluten sensitivity*", "gluten intolerance* not celiac disease*". Figure 2 illustrates PRISMA flow chart for this review.

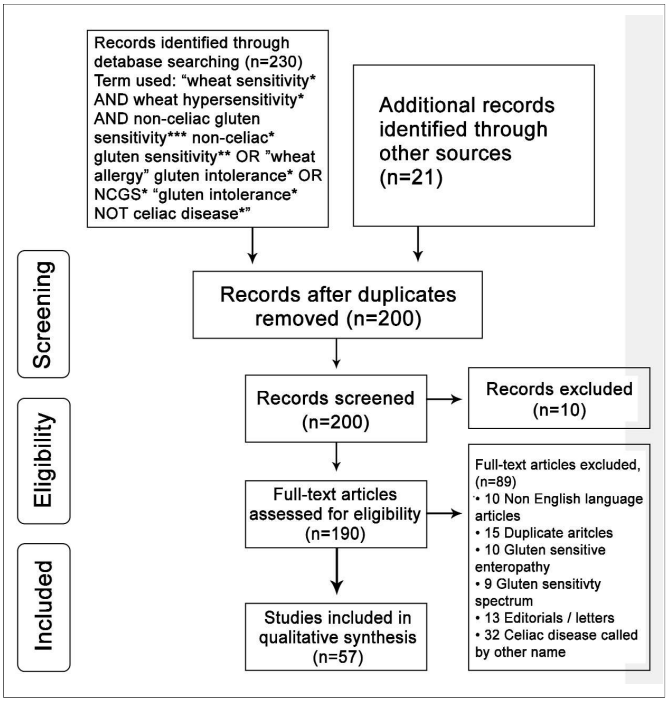

Figure 2: PRISMA flow chart of literature search conducted for this review.

DISCUSSION

A double-blinded placebo controlled Australian study was the first to report the presence of a clinical response in NCGS patients upon reintroduction of gluten. Studies reveal that NCGS individuals with HLA-DQ2+ have a low prevalence of celiac disease.[8,9,53] An American study demonstrated the presence of a higher density of CD3+ intraepithelial T cells, also known as intraepithelial lymphocytes IELs, in patients of NCGS compared to control groups. In addition, mucosal Toll-like receptor 2 undergoes an increased expression in NCGS individuals, which together with the presence of a higher density of IELs is an indication of immune activation.[53-55] A possible sign of lack of activation of T regulatory cells is demonstrated by NCGS individuals through a decreased level of mucosal mRNA for FOXP3.[55] The expression of IFN-gamma increases in NCGS individuals upon ingestion of gluten.[55]

Studies show that NCGS is also associated with certain characteristically nonspecific gastrointestinal symptoms, such as abdominal pain, diarrhea, bloating, and flatulence. Additionally, certain extra intestinal symptoms are also associated with gluten intolerance, including, ataxia, attention deficit or hyperactivity disorder, lethargy, headache, and recurrent oral ulceration.[35,56] However, the exact mechanisms by which such symptoms are precipitated has not yet been precisely delineated. Thus, no diagnostic criteria and no serological testing are available for detection and diagnosis of NCGS. A suggestion has been proposed by multiple studies that the presence of increased production of anti-gliadin IgG antibodies in patients can be utilised as a diagnostic tool.[8,56] The presence of an undefined etiology coupled with a lack of a definitive diagnostic test heightens the fear of undiagnosed cases being left out undetected. The diagnostic procedure involves an exclusion of celiac disease and wheat allergy through performing serological tests for both diseases and, if they come out negative, it leads to the patient being diagnosed with gluten intolerance. If the person presents classic symptoms of celiac disease and wheat allergy and the serological tests come out negative, the patient is conclusively given a definitive diagnosis of gluten intolerance.[9-11] The pathogenesis of NCGS is complex and has not been completely delineated. The disease has symptoms that demonstrate an overlap with celiac disease, wheat allergy and irritable bowel disease. A controversial evidence exists in support of benefits gained from either a gluten-free diet or a diet that is based on low FODMAPS. However, option for these diets shows promising results for patients with wheat-related disorders as they help in the management of functional gastrointestinal symptoms. NCGS has overlapping features with IBS and celiac disease so more research needs to be done in order to delineate the exact mechanism by which NCGS mediates its symptoms. Health professionals face the dilemma when putting patients on a gluten-free diet because gluten-free products available on the market are expensive and not extensively subjected to quality evaluation and; hence, are high in caloric content. Similarly, patients wanting to adopt a gluten-free diet face issues of high calorie content and increased price.

CONCLUSION

The rising number of cases surfacing is partly due to increased awareness about the disadvantages associated with gluten and partly due to more toxic gluten present in industrialised varieties of wheat. The disease has no current diagnostic criteria or reliable biomarkers and is diagnosed on the basis of exclusion of celiac disease, wheat allergy, and irritable bowel syndrome. The heterogeneous group of individuals suffering from NCGS has individualised pathogenesis and present varying sets of symptoms together with different clinical histories. Health professionals face a dilemma when dealing with such patients because the only available treatment is gluten abstinence which becomes difficult because of high caloric gluten-free products available. Such products do provide relief from gluten intolerance associated symptoms but they may be a leading cause of obesity because of unbalanced nutritional values. There is a need to regulate the processing and production of gluten-free products in the market.

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