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REVIEW ARTICLES

Non-celiac gluten sensitivity

Sensibilidade ao glúten não-celíaca

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ABSTRACT

Introduction: Recurrent abdominal pain accounts for up to 5% of consultations in pediatric primary care. An organic cause is found in only 5–10% of children. Non-celiac gluten sensitivity is a condition characterized by intestinal symptoms (including abdominal pain) and extra-intestinal symptoms related to the ingestion of gluten-containing foods in subjects who are not affected by celiac disease or wheat allergy. Treatment is based on a gluten-free diet.

Objectives: The aim of this work was to review relevant studies in Pediatrics on the subject published in recent years, with the purpose of increasing knowledge among pediatric specialists and contributing to raising awareness and maintaining a high index of clinical suspicion of the condition and improving the diagnosis and management of the condition while reducing the use of gluten-free diet without medical advice.

Development: A review was carried out on PubMed and Cochrane databases using terms related to non-celiac gluten sensitivity, and the evidence about gluten, non-celiac gluten sensitivity, biomarkers, epidemiology, and Salerno Criteria (used in the diagnosis of the disease) was assembled and reported.

Conclusion: Establishing the diagnosis of non-celiac gluten sensitivity and other gluten-related disorders is crucial to design measures to facilitate access to gluten-free diets for patients who really need them. More standardized clinical trials in Pediatrics are needed to draw specific conclusions about the disease.

Keywords: gluten-free diet; gluten-related disorder; non-celiac gluten sensitivity

RESUMO

Introdução: A dor abdominal recorrente é responsável por até 5% das consultas de cuidados pediátricos primários, sendo que apenas 5–10% dos casos têm uma causa orgânica. A sensibilidade ao glúten não celíaca é uma doença caracterizada por sintomas intestinais (entre os quais dor abdominal) e extraintestinais relacionados com a ingestão de alimentos contendo glúten em indivíduos que não são afetados por doença celíaca ou alergia ao trigo. O tratamento é baseado na dieta isenta de glúten.

Objectivos: O objetivo deste estudo foi rever a evidência sobre o tema na população pediátrica publicada nos últimos anos, com o propósito

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de contribuir para aumentar o conhecimento dos especialistas de Pediatria, alertar para a necessidade de manter um elevado índice de suspeição para a condição e contribuir para otimizar o diagnóstico da doença e reduzir a utilização da dieta isenta de glúten sem orientação médica.

Desenvolvimento: Foi realizada uma revisão da literatura nas bases de dados PubMed e Cochrane utilizando termos relacionados com sensibilidade ao glúten não celíaca e reunida a evidência encontrada relativa ao glúten, sensibilidade ao glúten não celíaca, biomarcadores, epidemiologia, e Critérios de Salerno (metodologia indicada para o diagnóstico da doença).

Conclusão: O estabelecimento do diagnóstico de sensibilidade ao glúten não celíaca e outras doenças relacionadas com glúten é fundamental para que seja possível projetar medidas que facilitem o acesso a dietas sem glúten aos doentes que realmente delas necessitam. São necessários mais ensaios clínicos padronizados em Pediatria para tirar conclusões mais específicas sobre a doença.

Palavras-chave: desordem relacionada com glúten; dieta sem glúten; sensibilidade ao glúten não celíaca

INTRODUCTION

Abdominal pain is a very frequent complaint in routine pediatric consultations, with recurrent abdominal pain accounting for up to 5% of cases.[1] An organic cause is found in only 5–10% of cases.[2] When there are no anatomical, metabolic, infectious, inflammatory or neoplastic disorders, it is defined as functional abdominal pain. The global prevalence of functional abdominal pain in children is 13.5%. The diagnosis is based on clinical observation according to the Rome Criteria, a standardized system that helps in the diagnosis and treatment of gastrointestinal functional disorders in childhood (GIFD).[2] These criteria divide functional abdominal pain into functional dyspepsia, irritable bowel syndrome (IBS), functional abdominal pain not otherwise sourced, and abdominal migraine. Functional abdominal pain not otherwise sourced is the most frequent classification (53.8%), followed by IBS (38.5%) and functional dyspepsia (7.7%).[2] It should be noted that these data predate the Rome IV Criteria, where abdominal migraine was part of the undifferentiated functional abdominal pain group.

Some theories have been put forward to explain the pathophysiology of IBS, including increased pain sensitivity or visceral hypersensitivity, abnormal intestinal motility, small bowel bacterial growth, low-grade intestinal inflammation, psychosocial factors, and dysregulated intestinal-brain axis.[3] Furthermore, diet and nutrition are believed to be important factors in this condition, since nutrients can interfere with motility, sensitivity, barrier function, and intestinal microbiota, leading to an atypical modulatory mechanism in the intestine.[3] Several disorders with gluten-related intestinal manifestations are reported, including celiac disease (CD), non-celiac gluten sensitivity (NCGS), and wheat allergy (WA).[4] In a double-blind placebo-controlled (DBPC) study in adults with IBS, the prevalence of NCGS was up to 28%.[5]

NCGS was first described in 1980, but its pathophysiological mechanisms, diagnostic criteria, and therapeutics remain undetermined to date.[6] Therefore, some authors consider that the current knowledge of CD is the same as 40 years ago.[7] NCGS has a reported prevalence of 0.6–6% and is characterized by intestinal and extraintestinal symptoms related to the ingestion of gluten-containing foods in individuals who are not affected by CD or WA. Treatment comprises the adoption of a gluten-free diet (GFD). There are no specific and objective markers of the disease. Indirect findings suggest that NCGS is more common than CD, which affects approximately 1% of the general population.[7] Gluten-related diseases (GRD) are emerging as a relevant clinical entity, together with the growing popularity of GFD.[5] Several publications in the adult population argue in favor of the effectiveness of eliminating gluten from the diet in these disorders. In recent years, several studies have described a correlation between the ingestion of gluten-containing foods and the onset of neurological and psychiatric disorders/symptoms, such as ataxia, peripheral neuropathy, schizophrenia, autism, depression, anxiety, and hallucinations.[7] The evidence on NCGS in children is scarce, and due to this, there are no guidelines regarding the management of the condition in the pediatric population.[5]

OBJECTIVES

The aim of this study was to assemble evidence published in the literature about NCGS in Pediatrics in recent years and contribute to increasing and disseminating knowledge of the condition among pediatric specialists, namely regarding clinical suspicion and diagnosis, and to reducing the use and associated risks of GFD among the general population without medical advice.

MATERIAL AND METHODS

A search was conducted on PubMed and Cochrane databases.[9,10] For the PubMed search, the following filters were applied: Species: “human”; date range: “2011 to 2021”; Age: “between zero

and 18 years old"; Studies of type: "Clinical Trial, Meta-analysis, Randomized Controlled Study, and Systematic Review". The following search terms were used: "gluten-related disorder" OR "Non-coeliac gluten sensitivity" OR "Non-celiac gluten sensitivity" OR "wheat hypersensitivity" OR "wheat allergy" OR "Gluten sensitivity" OR "Wheat sensitivity" OR "Gluten intolerance" OR "Wheat intolerance", with filter: "Title/Abstract". Exclusion criteria: Language other than English. A total of 42 articles were identified. Of these, eight were excluded for not being available for reading (n=1) or for being written in languages other than English (German, Greek, Hungarian, Russian, French, and Japanese), leaving 34 articles. Of these, 19 articles were excluded for addressing other gluten-related disorders (WA, CD, dermatitis herpetiformis) or the prevalence of gluten-related disorders in Asia, leaving 15 articles. Of these, five articles focusing the adult population and two articles about gluten-related psychiatric disorders in adults and children were also excluded, making a final sample of eight pediatric articles, seven of which were review articles and one was a DBPC randomized clinical trial.

For the Cochrane Library search, the only filter used was: Date range: "2011 to 2021", and search terms included "gluten-related disorder" OR "Non-coeliac gluten sensitivity" OR "Non-celiac gluten sensitivity" with the filter: "Title/Abstract". Five trials were identified, but only one referred to the pediatric population, which represented a duplicate of the article by Francavilla *et al*. previously identified in PubMed. In a second moment, the references of the studies included were also assessed to retrieve additional relevant publications on the subject.

RESULTS

Gluten and wheat

Gluten and other wheat proteins have been consumed by humans since before the practice of agriculture, more than 10,000 years ago. Wheat cultivation is simple, adapts well to different climates, and has a high yield and low cost in relation to its nutritional value. In addition, it adds flavor and versatility and can have several cooking applications. For this reason, it is used in most processed foods.[11] Today, almost half of the calories consumed by the human population worldwide come from cereals, with wheat being the most popular grain in Europe and the Americas. Flour and bran are used in the production of bread, breakfast cereals, pasta, couscous, and sweets. Wheat is added as a binder in cold cuts, desserts, ice creams, and creams. Starch is used to coat tablets, bonbons, and roasted coffee beans, as well as in the cosmetic, paper, and even toy industries (like Play-Doh).[12,13] The prevalence and frequency of adverse food reactions have increased, with these being often attributed to allergy. Up to a third of parents report one or more food reactions in their children.[14] Gluten is a protein derived from wheat, barley, and rye.[13] The ingestion of gluten and other related proteins can produce well-established adverse reactions in susceptible individuals.[11] Traditionally, GFD has been indicated in the treatment of celiac disease and wheat allergy.[13] However, in recent years, GFD has become widespread, with an estimated 20% of the U.S. population opting for this diet, mostly without medical advice. Due to this increased demand, a rapidly growing industry with a growing diversity of gluten-free products has emerged. Most of the time, this gluten avoidance is motivated by the subjective notion of well-being with GFD and not by medical diagnosis of a gluten-related disorder.[15] The correct diagnosis of these patients is important for proper management and for avoiding useless and expensive diets and the risk of nutritional deficits.[16] GFD without the supervision of a healthcare provider carries risks of vitamin (especially B and folic acid) and micronutrient (especially iron and zinc) deficiencies, as well as lower fiber intake. On the other hand, GFD patients tend to consume more simple carbohydrates and fats than grain-containing/rich foods.[11]

Non-celiac gluten sensitivity

Studies indicate that NCGS is not restricted to adults and can also occur in children and adolescents. The first report of NCGS in children dates back to 2014.[15] NCGS has been interpreted as a multifactorial condition involving both genetic and environmental factors (including ingested grain proteins).[11] The study to exclude celiac disease and wheat allergy is mandatory before considering the diagnosis of NCGS.[14] In 2011, an international group of experts defined this expanding variant as a "non-allergic, non-autoimmune disease in which gluten consumption can lead to symptoms similar to those seen in celiac disease."[13] Even today, there are no specific tests to detect or diagnose gluten sensitivity.[14] Skodje *et al.* reported in 2017 that NCGS may correspond to a set of clinical entities, with some patients reacting to gluten and others reacting to FODMAP. FODMAP stands for fermentable oligosaccharides, disaccharides, monosaccharides and polyols and are a set of foods that contain certain components that are being implicated in the pathophysiology of GIFD,[8] including foods with excess glucose fructose (pears and apples), oligosaccharides including fructans (wheat and onions), gallate-oligosaccharides (found in some vegetables), sugar polyols such as sorbitol and mannitol (fruit stone and artificial sweeteners), and lactose.[3]

De Geeter *et al.* reported that patients with NCGS can also react to a number of proteins found in wheat, grouped under the name amylase-trypsin inhibitors (ATI), or to wheat with non-immunoglobulin E (IgE)-mediated mechanisms, or that they may simply respond to the placebo/nocebo effect.[14] De Geeter suggested that, since gluten accounts for, at best, a small fraction of these patients, the term NCGS is a misnomer and should be abandoned for the least compromising "non-celiac wheat sensitivity".[14] According to Llanos *et al.*, patients with NCGS have an intestinal microbiota with lower proportion of

fecal Lactobacillus and Bifidobacterium and increased duodenal presence of Bacteroides and Escherichia coli compared to the general population.[17] Around 9–55% of these patients may present bacterial overgrowth in the small intestine, especially patients unresponsive to GFD or with symptom recurrence after an initial response to GFD.[17] NCGS has been reported to be more common in male children. A New Zealand study reported that 5% of children without a diagnosis of CD avoided gluten-containing foods to prevent gastrointestinal symptoms and unspecified behavioral changes.[17] Unlike CD and WA, NCGS is relatively unknown to pediatric specialists.[18]

Epidemiology

In 2017, a study carried out in Italy with higher education students with an average of 17 years reported that 12.2% self-reported gluten intolerance, with symptoms very similar to IBS.[15] In a New Zealand cohort study of asthma and allergy, 5.2% of children with a mean age of 10.6 years were found to avoid gluten-containing foods.[15,16]

Pathophysiology

Wheat is composed of four types of proteins: albumin, globulin, gliadin, and glutenin. The first two have enzymatic functions, such as alpha and beta amylase and their inhibitors. Gliadins and glutenins are part of the structure of gluten - a prolamine - and are the storage proteins of wheat grain.[18] It has been proposed that the innate immune response is involved in the pathogenesis of NCGS, but its components are still unknown.[11] Some studies have identified other prolamines and ATI as triggers of disease symptoms.[11] These proteins can thus cause immunological abnormalities in the intestine even in patients without celiac disease, namely in those with IBS symptoms.[11]

In studies performed in mice with NCGS and without CD, increased smooth muscle contractility, abnormal immune reaction (associated with IBS), stimulation of the innate pathway by ATI and wheat lecithin agglutinin, and release of acetylcholine in the myenteric plexus were observed.[17] The existence of synergism between the causal mechanisms of the disease by ATI and gluten or even the coexistence of these two mechanisms in NCGS has been proposed.[17] The increase in intestinal motility in this experiment occurred following T cell response against the human leukocyte antigen (HLA) in DQ8-positive transgenic mice and was also observed in a study with a subgroup of adult patients positive for HLA-DQ2/DQ8.[17,18] No mucosal reaction or atrophy were observed in mice sensitized with gluten-free protein.[17]

Patients without CD and positive for a HLA-DQ2 genetic haplotype have been shown to have two to three times greater release of interleukin 8 (IL-8) than patients negative for HLA-DQ2.[17] This led to the hypothesis that the innate immune system contributes to the pathogenesis of NCGS, which also showed increased expression of the toll-like receptor 2 (TLR2) in the intestinal mucosa compared to celiac patients, and reduced expression of FOXP3 regulatory T cells.[17,18] Other findings included the expression of proinflammatory cytokines and costimulatory molecules in monocytes and dendritic cells, and increased production of IL-15 and apoptosis in enterocytes in patients after gliadin exposure.[17] However, to date it was not possible to directly and reproducibly correlate gluten peptides with NCGS symptom triggering. It should be noted that wheat contains many other components that may be responsible for patients' symptoms, such as ATI, lipopolysaccharides, wheat germ agglutinins (WGA), and FODMAP.[15]

Biomarkers

Although there are no specific biomarkers for NCGS to date, some studies report anti-gliadin antibodies (AGA) IgG and IgA positivity in 50% and 8% of patients with suspected NCGS compared to 80% and 75% of patients with CD. Patients with NCGS tend to have negative AGA IgG after undergoing GFD.[11,15,18] However, AGA is positive in many patients with increased intestinal permeability without a specifically related diagnosis and also often in the general population, highlighting the need to be careful with this result. Vrizinga *et al.* reported that half of patients with NCGS have positive HLA-DQ2- or HLA-DQ8, a prevalence only slightly higher than in the general population (40%).[15,18]

Intestinal and extraintestinal symptoms

According to Erlickman *et al.*, NCGS is most often self-diagnosed in patients with symptoms such as abdominal distension, diarrhea, and abdominal pain that disappear when gluten is removed from the diet, and return when gluten is reintroduced.[13] According to Cruchet *et al.*, the most frequent NCGS symptoms are abdominal pain (80%), chronic diarrhea (73%), fatigue (33%), and bloating (26%), which commonly overlap with those of IBS.[11] The Salerno expert criteria list bloating and abdominal pain as the most common gastrointestinal symptoms, followed by diarrhea, epigastric pain, nausea, and alternating bowel habits or constipation. Some patients also report oral aphthous ulcerations or reflux symptoms that evoke gastroesophageal disease.[15] NCGS also manifests by extraintestinal symptoms, like headaches, mental confusion, chronic fatigue, joint pain, muscle aches, numbness, eczema, anemia, depression, and attention deficit disorder.[13] Migraine, blurred vision, depression, and paresthesia of the members have also been reported in some patients.[11] Ruemmele *et al.* reported symptoms as malaise, tiredness, anxiety, and muscle pain.[15] Other even less specific symptoms, such as sleep disturbances or hallucinations, have been reported after gluten ingestion.[15] Almost all NCGS bowel symptoms

overlap with those of classic CD, and even more with those of forms of IBS, whether with diarrhea or constipation. A small pediatric study in 15 children with gluten sensitivity reported that bowel symptoms were clearly predominant − with abdominal pain as the main symptom (80%), followed by diarrhea (73%) −, while extraintestinal symptoms were markedly less frequent.[15,17] Due to the variability of NCGS clinical signs, it is mandatory to demonstrate the causal relationship between gluten-containing foods and symptoms.[15] NCGS tends to have a greater incidence of extraintestinal symptoms than IBS.[17] Some studies suggest an association between NCGS and neuropsychiatric disorders, such as schizophrenia and autism spectrum disorders.[18]

Studies and evidence in Pediatrics

In 2018, a consensus on NCGS in adults was published, called the Salerno Criteria.[16] This consensus defined the DBPC challenge as the gold standard for the diagnosis of NCGS. However, the magnitude of the effects of NCGS in pediatric patients is still to be defined, particularly since GFD is becoming popular in this age group.[16] Despite several studies in the adult population, this entity has not been properly studied in children.

Francavilla *et al.* conducted a multicenter study aiming to assess the prevalence of NCGS in children with chronic functional gastrointestinal symptoms associated with gluten ingestion using a double-blind, randomized placebo-controlled crossover gluten challenge.[16] This study initially enrolled 1114 patients with intestinal symptoms, but only 36 reported symptom worsening with gluten ingestion. Of these, five improved spontaneously and three showed no improvement with gluten removal from the diet. A DBPC study was conducted with the remaining 28 patients without celiac disease who had IBS symptoms. These patients were divided into two groups (cases and controls) and submitted to gluten challenge (double-blind diets with and without gluten). The study showed that 68% of the group that received gluten (cases) reported symptom worsening in one week versus only 40% of the placebo group. All patients had symptom improvement after removal of FODMAP from the diet and all had symptom worsening with the introduction of gluten or whey. No differences were found in the prevalence of symptoms, appearance of expelled stools, or analysis results between the two groups. Noteworthy, some symptoms, such as fatigue, abdominal pain, headaches, and joint/muscle pain were correlated with gluten intake, and patients with NCGS experienced fatigue worsening during gluten consumption. No differences were found in diet composition or in the amount of FODMAP consumption during the various clinical trial phases.

The prevalence of NCGS in Francavilla study varied according to the criteria employed. It was 39.2% according to the Salerno Criteria (95% confidence interval [CI] 23.6-53.6%), but only 14.3% according to Di Sabatino criteria (95% CI 5.7–31.5%).[7,20] Considering the overall population of 1114 children referred for gastrointestinal symptoms, the prevalence of NCGS was estimated to range between 0.36% (95% CI 0.14–0.92%) and 0.98% (95% CI 0.5-1.8%). This number could be underestimated, as patients were unable to objectively associate gastrointestinal symptoms with gluten consumption, and thus it could not be clearly ascertained that gluten was responsible for those symptoms.

Although a gluten-free diet may improve gastrointestinal symptoms in patients reporting NCGS, further research is needed to determine the relationship between NCGS, a gluten-free diet, and extraintestinal symptoms in children. For this reason, some authors advise working closely with a pediatric gastroenterologist and a pediatric nutritionist when dealing with families reporting NCGS as the cause of the child's symptoms.[13]

According to Francavilla, the suspicion of a deleterious action caused by gluten needs to be balanced with the widespread perception of the nocebo effect, which, according to recent data, can reach 40%.[16] Therefore, the voluntary adoption of FGD should be strongly discouraged for a number of clinical and social reasons, such as the impossibility of an adequate CD diagnosis, risks associated with an exclusion diet, and unjustified economic burden. Gluten DBPC crossover challenge studies in adult patients with suspected NCGS are multiplying, and show conflicting results due to the heterogeneity of populations studied, diets used, gluten characteristics, and assessment methods, among others.[5,20, 21]

Although the studies carried so far show methodological flaws, namely due to the heterogeneity of study populations and outcome measures (type of protein, gluten dose, delivery mode, and duration of the elimination period), all clearly show that the vast majority of patients with symptoms self-attributed to gluten are not, in fact, affected by NCGS.[16] Francavilla extrapolated these findings to the pediatric population, since more than 60% of patients suspected of NCGS in his study were classified as not having the disease by a gluten challenge. Thus, until a reliable NCGS marker is available, gluten challenge should be mandatory for disease diagnosis.[16] Francavilla concluded that IBS symptoms can be present when individuals are exposed to gluten, even without NCGS diagnosis. Functional abdominal pain and IBS can be triggered, not only by gluten, but also by other wheat components, such as ATIs, wheat, lectin, agglutinin, and fructans.[16]

The epidemiology of gluten-related GIFD in children, and the genetic predisposition specifically based on HLA haplotypes is unclear. Based on the above definition, NCGS and IBS were suggested to be two different entities with overlapping features. In some studies, these two clinical entities were considered synonymous, leading to great confusion in data and result interpretation.[17] A diet excluding FODMAP may resolve symptoms in a subgroup of patients with IBS, and have no effect on patients with true NCGS, as FODMAP do not induce an immune response and the elimination of gluten-containing foods only minimally reduces the total FODMAP intake. Other gluten-containing cereal proteins have been shown to trigger

immune responses, resulting in the alternative designation of 'wheat sensitivity' or 'non-celiac wheat sensitivity' (NCGS).[17]

Diagnosis - Salerno Criteria

As previously mentioned, a DBPC food challenge was proposed to confirm the diagnosis of NCGS.[20] This approach is very difficult to replicate in daily clinical practice due to difficulties in preparing the intervention products, the need for highly trained people, and high costs. The open food challenge was alternatively proposed, but it can generate false-positive results. In general, NCGS, like celiac disease and wheat allergy, is usually treated with GFD. Vriezinga *et al.* suggested that, in the impossibility of carrying out a diagnostic assessment through a DBPC intervention, the periodic reintroduction of gluten in the diet should be advised.[18]

In 2014, the Salerno Criteria were published to improve the diagnostic criteria and characterization of NCGS. According to these criteria, NCGS is defined as a syndrome of intestinal and extra-intestinal symptoms related to the ingestion of gluten-containing foods,[7,15] and the DBPC gluten challenge with crossover is the gold standard and so far the only diagnostic test that allows confirming true gluten sensitivity causing intestinal and/or extraintestinal symptoms after gluten ingestion.[16]

Therefore, patients with suspicion of NCGS presenting with the intestinal and/or extraintestinal symptoms previously described should be evaluated over six weeks for CD or WA diagnosis. If these two conditions are excluded, six weeks of GFD follow, with a weekly assessment of presenting symptoms. Afterward, a double-blind challenge phase follows, in which the patient first receives either a gluten or placebo diet and then switches to the second intervention, with a one-week interval between both phases. In this interval, consisting of three weeks, a daily assessment of the patient's symptoms must be carried out using a pre-defined scale.[16]

In most cases, symptoms, especially gastrointestinal ones, become negative within a few days. However, it is necessary to adopt prolonged GFD to assess the link between gluten and other, usually more non-specific, symptoms, such as fatigue, mood changes, or headaches, which can persist for several weeks after gluten ingestion. One challenge is how to assess the decrease/resolution of symptoms in GFD and their reappearance in the gluten challenge in pediatric patients. Symptoms to be questioned are listed in the table below, proposed by the Salerno Criteria for the diagnosis of NCGS:[16]

The initial questionnaire serves as a comparative baseline for patients' weekly assessment in GFD. To obtain a quantitative value, the top three clinical symptoms are numerically rated using a Numerical Rating Scale (NRS) with a score ranging from 1 (mild) to 10 (severe). A drop of at least 30% in NRS for at least 50% of the time is considered a symptomatic response, indicating a likely link between gluten intake and experienced clinical symptoms. However, the final confirmation of NCGS diagnosis requires a DBPC crossover challenge. Gluten challenge should be based on a daily intake of at least 8 g of gluten with an amylase/trypsin inhibitor content and free of fermentable oligo, di and monosaccharides, and polyols (FODMAP) for one week (in patients with fluctuating symptoms even more), followed by one week of washout and crossover to placebo for another week or vice versa. One must be sure that the vehicle for the placebo is actually gluten-free. Ideally, patients and physicians should have no knowledge of the diet content, allowing an unbiased assessment. Patients who test negative in a blind gluten challenge should be screened for other causes of IBS-like symptoms, especially intolerance to FODMAP.[16]

Symptom Questionnaire for the Diagnosis of NCGS:
Abdominal pain or discomfort
Heartburn
Acid regurgitation
Swelling
Nausea and vomiting
Borborygmus
Abdominal distension
Eructation
Increased flats
Decrease in the frequency of evacuation
Increase in the frequency of evacuation
Fecal loss
Hardened stools
Urgency to defecate
Feeling of incomplete evacuation
Extra-intestinal symptoms
Dermatitis
Headache
Foggy mind
Fatigue
Numbness of limbs
Joint/muscle pain
Fainting
Oral and lingual injuries
Others (specify)

Impact:

To date, no long-term complications of NCGS have been reported. For this reason, it has been suggested that adherence to a GFD can be less strict than the one adopted in CD and WA and can be adjusted according to symptoms and respective control.[11]

CONCLUSIONS

NCGS is a newly defined condition, mainly related to the pediatric population. More DBPC studies should be developed in pediatric age using the same methodology, to increase the pool of studied patients and ascertain more specific conclusions.

New measures and scales should be validated to retrieve more reliable data on symptom improvement with GFD in the pediatric population. The correlation of NCGS with antibodies, HLA DQ-2/DQ-8, and trigger factors present in wheat remains to be determined. GIFD, namely IBS, is an entity closely correlated with NCGS and with FODMAP intolerance. Research on NCGS can help to better define, understand, and manage GIFD, a very frequent condition in Pediatrics.

The reproducibility of diagnostic tests based on the Salerno Criteria should be a reality, or alternatively, new routes should be determined through future studies. Establishing the diagnosis of NCGS and other gluten-related diseases is necessary to develop measures that facilitate access to GFD for patients who really need it.

AUTHORSHIP

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