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REVIEW ARTICLE

Non-celiac gluten sensitivity in pediatric patients: a literature review

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Glutens,
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Abstract

Objective: This study aims to review the relevant bibliography about non-celiac gluten sensitivity in children and to summarize the main data of pathogenesis, symptomatology and diagnostic methods currently established, useful for clarifying the pediatric physician regarding this pathology. **Methods:** The databases selected were: PubMed (The National Center for Biotechnology Information), LILACS (Latin American and Caribbean Health Sciences Literature) and SciELO (Scientific Electronic Library Online). Publications that contributed to the present review in the 2016-2021 interval, in English, Portuguese or Spanish, were chosen using the terms child, pediatrics, non-celiac gluten sensitivity and gluten sensitivity. **Results:** Non-celiac gluten sensitivity occurs in patients in whom celiac disease and wheat allergy have been ruled out. Intestinal and extra-intestinal manifestations occur after eating gluten-containing foods and disappear after they are removed from the diet. The pathophysiological basis of non-celiac gluten sensitivity is related to the bodys innate immune response triggered by gluten peptides. The placebo-controlled double blind challenge test is considered the gold standard for diagnostic investigation, despite limitations. New methods are being tested in order to correctly affirm the diagnosis of non-celiac gluten sensitivity. **Conclusion:** The diagnostic determination of non-celiac gluten sensitivity is essential in order that the pediatric patient don't be subjected, unnecessarily, to gluten-free diets that can have a negative impact on their nutrition and development.

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INTRODUCTION

Non-celiac gluten sensitivity (NCGS) was first challenged in 1978 with the case report of a 43-year-old female patient whose gastrointestinal symptoms, mainly characterized by referred abdominal pain in the periumbilical region and abdominal distension, entered in remission after the institution of a gluten-free diet[1]. A similar clinical history was discussed again in 1980, with a group of patients, in whom the clinical picture consisted of chronic diarrhea and abdominal pain, with mild abnormalities in intestinal biopsies and absence of steatorrhea and biochemical deficiencies, present in celiac disease[2]. The withdrawal of gluten-containing foods from these individuals promoted a significant improvement in symptoms[2].

Since then, the inclusion of non-celiac gluten sensitivity as a diagnostic possibility has made it possible to classify patients who until then did not meet the criteria for either celiac disease or wheat allergy. Although there are similar gastrointestinal symptoms, it is necessary to investigate and exclude the latter two. For this, in celiac disease, the correlation with other clinical signs, for example, weight loss and iron deficiency anemia, associated with serological tests, such as positive anti-endomysium antibodies (EmA-IgA) and anti-tissue transglutaminase (anti-tTG-IgA) duodenal biopsy, in which intestinal villous atrophy ('flat' villous) is found in genetically predisposed individuals – HLA DQ2/DQ8[3-5]. Wheat allergy, in turn, presents, in addition to gastrointestinal involvement, respiratory and skin repercussions, which can be characterized as a rapidly evolving immune-mediated response. Its investigation involves the determination of wheat-specific IgE, as well as the prick test[6].

Some studies consider not only gluten as the cause of NCGS, but also proteins found in wheat, called α-amylase and trypsin inhibitors (ATI)[7]. Because of this, some authors suggest changing the designation to Non-Celiac Wheat Sensitivity[7]. FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) have also been identified as possible triggers for NCGS. However, studies have shown that adopting a gluten-free diet also reduces the intake of FODMAPs (foods containing gluten are rich in FODMAPs), so the significant clinical improvement was falsely related to the withdrawal of gluten, that is, the individual did not have NCGS, but irritable bowel syndrome[7]. For this review, we chose to use the term Non-Celiac Gluten Sensitivity, as it is the term most commonly used in consensus papers and scientific recommendations.

Added to these considerations, there are no specific serological and histopathological markers for the diagnosis of NCGS. Duodenal biopsies in patients with NCGS are shown to be incompatible with celiac disease, being classified as Marsh types 0-1[8]. The absence of markers corroborates the existence of difficulties in establishing an assertive diagnosis, since the placebo-controlled double-blind challenge test - gold standard for diagnostic investigation, still has limitations[9]. Thus, the importance of clinical knowledge about the pathology, since the removal of gluten from the diet of children without medical evidence can have consequences, such as increased risk of dyslipidemia and even the permanence of preexisting symptoms, if this is not the true cause[10].

METHODOLOGY

We ran a literature review regarding NCGS in children and selected the following databases: Pubmed (National Center for Biotechnology Information), Lilacs (Latin American and Caribbean Literature on Health Sciences) and Scielo (Scientific Electronic Library Online). To search for articles, we used the following controlled keywords: child and pediatrics and the keywords: non-celiac gluten sensitivity and gluten sensitivity in their combinations in Portuguese, English and Spanish, together with the Boolean operators AND and OR.

In addition, articles that included the SGNC published in the last 5 years (2016-2021) in English, Portuguese and Spanish were also used.

The combinations performed showed more than 150 results. Initially, articles that only addressed celiac disease or that emphasized themes secondary to NCGS, such as other disorders associated with it, and those that focused on gluten-free diets were excluded. Duplicate articles were also discarded. This first filtering totaled 31 articles.

With these papers, we ran another screening. Due to the scarce literature addressing the profile of NCGS in pediatric patients, articles covering the adult population with NCGS were also selected, in order to elucidate the pathophysiological bases of the disease, as well as to point out the differences found between age groups. In this sense, preference was given to review articles, as well as articles with unpublished points, mainly in the scope of diagnosis and differential diagnoses. Thus, through a critical reading, we decided to select 18 papers for this present review.

As an exception to the inclusion criteria, it is worth noting: addition of the article that describes the current gold standard method in the diagnostic investigation of the disease, published in 2015[3]. We also decided to add, by way of relevance and history of SGNC, the first two papers published about the SGNC, in the mid-1980s, since they boosted the progress in the study on this theme[1,2]. In conclusion, 21 articles were used and cited.

The authors of the cited articles were correctly referenced, aiming to respect the ethical recommendations and their copyrights.

DISCUSSION

Definition

Non-celiac gluten sensitivity can be defined as a combination of intestinal and extra-intestinal symptoms that occur from hours to days after eating foods that contain gluten and disappear after they are removed from the diet of individuals in whom celiac disease and wheat allergies were ruled out[11].

Epidemiology

Among the world population, about 4-13% of individuals report symptoms after ingestion of gluten or wheat[12]. The German Society of Allergy and Immunology emphasizes that many publications related to NCGS are devoid of validated diagnostic criteria and appropriate biomarkers, being based on in self-reported diagnoses and unconfirmed etiologies of reported symptoms, and therefore, studies on the prevalence of NCGS are not clearly established[10].

Some data show that NCGS affects about 6% of the adult population, which may vary according to the region evaluated, affecting mainly women[6,13]. Unlike adults, NCGS in children has been more frequently diagnosed in men than in women[12]. In New Zealand, about 5% of children and adolescents consume gluten-free foods[14].

According to a double-blind placebo-controlled study carried out in a population of 1,114 children referred due to gastrointestinal symptoms of a functional nature, a prevalence of NCGS ranging from 0.36% to 0.98% was calculated; however, the same authors clarify that this estimate can be underestimated, as there are patients who are unable to establish a positive correlation between gluten consumption and symptoms[14]. Another study carried out in a tertiary care center specializing in gluten-related disorders evaluated 500 pediatric patients, aged between 7 months and 18 years old, showed that 26 of them, between 2 years and 18 years old, were diagnosed with NCGS, based on the London consensus criteria, that is, 5.2% of the group[13]. However, as it is a center specialized in gluten-related pathologies, this prevalence is higher than expected in the clinical routine of pediatricians and pediatric gastroenterology centers[13].

In a group of 555 high school students in southern Sicily, Italy, with a mean age of 17 years, the prevalence of non-celiac self-diagnosed wheat-sensitive individuals was 12.2%[15]. Adolescents who, according to a questionnaire applied, reported symptoms after ingesting wheat at least once a week and who showed clinical improvement with the institution of a wheat-free bed were considered to be sensitive to wheat for non-celiac patients[15]. As this is data exclusively reported by patients, there is a limitation recognized by the study and, therefore, this prevalence should be analyzed with caution[15].

It is worth mentioning that the overlap of symptoms between irritable bowel syndrome and non-celiac gluten sensitivity, in addition to the incomplete pathophysiological understanding of both diseases, can also generate conflicts in the establishment of epidemiological data[4,16].

Pathogenesis

The pathophysiology of non-celiac gluten sensitivity focuses primarily on an innate immune response of the organism, being characterized by the participation of toll-like receptors (TLR-1, TLR-2) and also by the alteration of other components of this immunity, such as interleukin -10 derived from whole peripheral blood mononuclear cells (PBMC), granulocyte colony stimulating factor (GCSF), transforming growth factor alpha (TGF-α) and the chemokine CXCL-10[8,17].

The most discussed trigger of this pathology is gluten. The protein fraction of gluten that is soluble in alcohol is called prolamin, in wheat it is called gliadin and the insoluble fraction is called glutenin. Peptides derived from gliadin seem to induce the innate immune response in celiac disease and it is believed that they may also be involved in the pathogenesis of NCGS, which may be related to the presence of antigliadin antibodies in 50% of patients with NCGS[4,16].

Some studies also include α-amylase and trypsin (ATI) inhibitors, wheat proteins, as possible triggers for SGNC, acting on the toll-like receptor 4 (TLR-4) stimulation pathway[6].

As well as α-amylase and trypsin inhibitors, FODMAPs are also investigated about their possible participation in the genesis of NCGS. However, non-celiac gluten-sensitive children submitted to gluten-free diets containing FODMAPs responded with complete remission of symptoms, an aspect that was even highlighted by the study, in order to warn that the simultaneous interruption of gluten and FODMAPs intake in these patients should be contraindicated[18]. In contrast, other data suggest that a low FODMAP diet is beneficial for the non-celiac gluten sensitive patient[4]. Future clinical studies should be performed to elucidate and determine precisely which foods and nutrients play a key role in this non-celiac gluten sensitivity[6].

Undigested peptides, generated by insufficient degradation of gluten and, possibly, other wheat proteins through intestinal proteases, manage to cross the intestinal epithelial barrier, whose permeability is increased[3,4]. Then, they reach the submucosa and activate dendritic cells and resident macrophages[16]. This activation occurs by the effect of gliadin via TLR-4, through the primary differentiation response of myeloid factor 88 (MYD88), which increases the expression of pro-inflammatory cytokines, responsible for the systemic effects[8]. Also as a result of this cascade of events, it is possible to explain the mild chronic inflammation of the duodenum, characterized by Marsh-type 1 enteritis, identified in some of the results of intestinal biopsies of these patients[18]. It is worth noting that, for the most part, intestinal biopsies of these patients do not present alterations, being classified as Marsh 0[18].

Evidence shows that in non-celiac gluten-sensitive patients there is a decrease in epithelial electrical resistance, which justifies an increase in permeability, associated with a reduction in IL-10 secretion in duodenal biopsies exposed to gliadin[18]. The increase in IL-10 production IL-15, as well as increased enterocyte apoptosis and abnormalities in smooth muscle contractility, seen in rats during studies, appear to be consequences of exposure to digested gluten products[14].

Other studies also point out that patients with NCGS have a different microbiota from the general population, with a lower proportion of Lactobacillus and Bifidobacterium and a high presence of Bacteroides and Escherichia coli[12]. These patients, especially those who do not respond to a gluten-free

diet, may present a bacterial overgrowth in the small intestine in about 9 to 55% of cases[12]. It is speculated that such dysbiosis can cause an immune dysfunction of the intestine[17].

Clinical manifestations

The clinical picture present in NCGS can be varied, and there may be isolated gastrointestinal symptoms or combined with extraintestinal manifestations[11]. The latency between gluten ingestion and the onset of manifestations can occur from hours to days, a fact that helps to distinguish from other gluten-related disorders, since in wheat allergy this latency ranges from minutes to hours, and in celiac disease it ranges from weeks to months[11].

The main symptoms reported by patients in NCGS are abdominal pain and distension, as well as diarrhea, epigastric pain, nausea and constipation[3]. Such gastrointestinal changes do not accompany weight loss[12]. Extraintestinal manifestations, in turn, include associated symptoms, such as headaches, in addition to musculoskeletal and skin manifestations, chronic fatigue and difficulty concentrating[6]. In a multicenter study in children, fatigue was reported as a prominent symptom (85%), followed by abdominal pain (78%), headache (71%) and muscle/joint pain (57%)[14]. In another cohort study, 15 pediatric patients with NCGS were evaluated and the most common gastrointestinal symptoms included abdominal pain (80%), chronic diarrhea (73%), bloating (26%), %) and constipation (20%).

Other recent data report that there are personal and family histories of atopy in patients with NCGS[13]. As well as the various studies related to celiac disease, some authors also consider the existence of possible neurological and psychiatric manifestations in NCGS, such as ataxia, peripheral neuropathy, depression, anxiety and even autism, which could possibly be related to ingestion of gluten[3]. However, this association is still far from being fully clarified, since the possible latency time between the ingestion of gluten and the appearance of these first signs is not known[3].

It should be noted that FODMAPs, possible triggers of NCGS, do not promote the appearance of extraintestinal manifestations, common in NCGS, hence the doubt about their true involvement in this pathogenesis[16].

Diagnosis

As already pointed out, the diagnostic criteria for non-celiac gluten sensitivity are more difficult to establish, since there is no specific marker[7]. Although anti-gliadin IgG antibodies (AGA) are present in about 50% of patients with NCGS and normalize in almost all patients about 6 months after the introduction of a gluten-free diet, it is still unclear whether monitoring these values adds to the diagnostic value[3]. It is worth mentioning that AGA is present in other conditions, such as autoimmune diseases, connective tissue diseases and even in healthy patients[12]. Another nonspecific finding is the positivity of HLA DQ2-DQ8 haplotypes in around 50% of patients with NCGS, present in almost all celiac patients[4]. Furthermore, recent data reveal a high prevalence of autoimmune markers, such as antinuclear antibodies (ANA) and autoimmune disorders, such as Hashimoto's thyroiditis, among non-celiac gluten-sensitive patients[17].

In general, duodenal biopsies from patients with NCGS, even on a non-gluten-free diet, are normal, but around 40% of them may have an increase in intraepithelial lymphocytes[12]. In an evaluation of intestinal biopsies from 11 patients sensitive to gluten, 10 had their biopsies classified as Marsh 0, without mucosal changes, and only one was classified as Marsh 1, characterized by intestinal mucosa with lymphocytic infiltration[18].

During the investigation of clinical manifestations, in addition to excluding the possibilities of celiac disease and wheat allergy and identifying the main differential diagnoses of NCGS for better diagnostic certainty, a controlled process of gluten withdrawal and reintroduction should be carried out, together with simultaneous evaluation of the patient[19,20].

The gluten challenge test, performed through a double-blind placebo-controlled study, considered the gold standard for the diagnostic certainty of NCGS, became known through the criteria of the Salerno specialists[3]. Through this test, the individual response of the organism in the face of gluten withdrawal, as well as during the reintroduction of gluten after a period of restriction[3]. The description of the symptoms manifested by the patient is performed using the Gastrointestinal Symptom Assessment Scale (GSAS) Questionnaire and they are quantified by the Numerical Pain Scale, where 1 is mild pain and 10 is severe[3].

For this systematization, initially, it must be defined which patients may be responsive to gluten, that is, those who report the appearance of symptoms after gluten ingestion, in the absence of celiac disease and wheat allergy[3]. The selected patients, who will undergo the gluten challenge test, must have been on a gluten-containing diet for at least 6 weeks in order to report their current clinical status[3]. Then such patients are placed on a gluten-free diet for 6 weeks and, even if there is a report of improvement in the first weeks, the restriction must be maintained[3]. The evaluation methods must be completed by patients and those who present a clinical response - characterized by the relief of at least 30% of the main initial symptoms or of at least one symptom without exacerbation of the others - should continue in the challenge; however, individuals whose symptoms have not improved should be reassigned to another diagnostic investigation.

To conclude the NCGS hypothesis, reintroduction of gluten must be performed, which can be single-blind or double-blind, often lasting 3 weeks[3]. In the first and third weeks, patients receive gluten (about 8g of gluten and at least 0.3g of ATI) or placebo (gluten-free), not necessarily in that order.[3] The second week works as a comparison interval between what was and what will be administered[3]. In this way, the evaluation of symptoms, also using the GSAS questionnaire and numerical pain scale, confirms the NCGS if there was a

variation of at least 30% in symptoms between the experiment with gluten and placebo[3].

The first double-blind randomized crossover study has placebo-rolled test for the diagnosis of non-celiac gluten sensitivity performed in children showed the importance of using the gluten challenge test to evaluate pediatric patients with gastrointestinal symptoms correlated to gluten ingestion[14]. This method proved the existence of NCGS in children, although less common than in adults, but also ruled out this diagnosis in about 60% of children who restricted gluten without medical indication[14]. Thus, it is clear that the gluten challenge test is a valuable tool to be used in children, in whom the diagnosis remains uncertain.

In a meta-analysis of 11 studies on reintroduction of gluten after a gluten-free period, the main findings were that, after reintroduction of gluten, 36% of subjects had recurrence of symptoms, compared to 31% of those who ingested the placebo[19]. Such information, despite having limitations, such as differences in the amount of gluten used and duration of the evaluated studies, highlights the emotional factor and the "Nocebo" effect[19].

Although the gluten challenge test is recognized as the best option for diagnostic investigation, some authors point it out as a long and complex process, difficult to be applied in clinical practice, since it depends on the total commitment of the patient so that there is no result transgression[8,16,21]. In addition, many patients refuse to reintroduce gluten into their diets, associating it with the immediate reappearance of symptoms[16]. Thus, ALCAT 5 emerges as a future alternative for the diagnosis of NCGS, because it is an easy way to perform with quick results[9]. This is an *in vitro* test that evaluates the toxic effect of gluten on the patient's neutrophils from their exposure to gluten. Test positivity occurs in the presence of changes in the volume and shape of neutrophils compared to the original shape, prior to exposure to gluten[9].

The results from the ALCAT and the gluten challenge test, according to the Salerno criteria, had a 64% agreement[9]. Although the comparison did not include a control group of healthy patients to perform both tests, the ALCAT 5 can be used, in the future, as a support tool for when there is a suspicion of NCGS, indicating the patients most likely to undergo the gluten challenge test[9].

Other markers, arising from immune activation and intestinal cell damage, such as lipopolysaccharide binding protein, antigliadin antibodies, fatty acid binding protein 2, when combined, show promising results, as they allow the differentiation between NCGS, celiac disease and control group[17].

Treatment

The recommendations bring the gluten-free diet as the main therapeutic management, capable of solving intestinal and extra intestinal symptoms, and can be as strict as that indicated for celiac patients or not, since some patients with NCGS can tolerate foods contaminated by gluten without any clinical manifestation[8,11].

Other authors, considering other possible triggers for NCGS, such as α-amylase and trypsin (ATI) and FODMAPs inhibitors, recommend the restriction, for example, of foods rich in sorbitol and fructose[4,6]. However, evidence points to that restricted diets of both wheat-containing foods and foods rich in FODMAPs can, in the long term, have harmful consequences in the nutritional sphere and directly impact the intestinal microbiota, with a significant reduction of bifidobacteria[16].

It is still discussed how long the gluten-free diet should be instituted, but the data show that after a few months of adherence, gluten can be reintroduced in small amounts with the monitoring of the individual response[6]. It is still uncertain whether NCGS is a permanent or temporary condition[11].

It is important to highlight that the absence of gluten in the diet can contribute to zinc, magnesium, iron, calcium and folate deficiency, in addition to increasing the risk of cardiovascular disease, therefore, the need for follow-up and monitoring of patients with NCGS, especially those in prepubertal stage[4,6,13].

CONCLUSION

NCGS has been acquiring increasing importance worldwide. An evaluation that combines the findings of clinical history, laboratory tests and even, eventually, histopathological data is necessary for the correct diagnosis of this entity.

Although more studies are needed to consolidate knowledge about the real pathophysiology, better diagnostic methods and adequate prognosis, it is important that pediatricians keep up-to-date and pay attention to the recommendations and diagnostic criteria, both current and to come. Knowledge of the similarities and differences between the various pathologies related to gluten helps in the decision of effective and safe conducts, in particular the orientation so that diets with gluten restriction are not prescribed unnecessarily, because, in addition to being costly and difficult to access, they can cause harm to the health of the pediatric population, both nutritionally and psychologically when considering a healthy child as sick.

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