www.neurogastrolatamreviews.com PERMANYER NeuroGastroLatam Rev. 2017;1:180-186

NeuroGastroLatam Reviews REVIEW ARTICLE

Gluten sensitivity and irritable bowel syndrome

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RESUMEN

La sensibilidad al gluten (GS) es una entidad clínica que conduce a síntomas gastrointestinales y/o extra-gastrointestinales que comparten muchas características comunes con el síndrome del intestino irritable (SII). El SII y la GS todavía son condiciones poco conocidas, su patogénesis está lejos de ser aclarada y las evidencias contradictorias consideran que la GS es un subgrupo de SII o, por el contrario, una entidad separada del SII. Ambas condiciones pueden afectar en gran medida a la calidad de vida de las personas que las padecen, pero un diagnóstico circunstancial y la exclusión del gluten beneficiarán a los pacientes con GS. SII y GS carecen de un marcador de diagnóstico y su expresión clínica similar requiere someter a los pacientes a un complejo algoritmo diagnóstico. (NeuroGastroLatam Rev. 2017;1:180-186)

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Palabras clave: Sensibilidad al gluten. Patogénesis. Diagnosis. Síndrome de intestino irritable.

ABSTRACT

Gluten sensitivity (GS) is a clinical entity leading to gastrointestinal and/or extra-gastrointestinal symptoms that share many common features with irritable bowel syndrome (IBS). IBS and GS are still poorly understood conditions, their pathogenesis is far from being clarified, and conflicting evidence consider GS either a subgroup of IBS or, on the contrary, a separate entity from IBS. Both conditions may greatly affect the quality of life, but a circumstantial diagnosis and gluten exclusion will benefit GS patients. IBS and GS lack a diagnostic marker, and their similar clinical expression requires to submit patients to a complex diagnostic algorithm.

Key words: Gluten sensitivity. Pathogenesis. Diagnosis. Irritable bowel syndrome.

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Received in original form: 02-02-2017
Accepted in final form: 10-11-2017
DOI: 10.24875/NGL.M17000005

INTRODUCTION

Abdominal pain or discomfort related with bowel alterations are typical symptoms of Irritable Bowel Syndrome (IBS), but many other diseases have similar clinical expression. Thus a circumstantial diagnosis of IBS can be made in the absence of any evidence of organic abnormalities, primarily celiac disease (CD), and other more subtle alterations that present with IBS-like symptoms, such as lactase deficiency, small intestine bacterial overgrowth (SIBO), bile salt malabsorption and, more recently, non-celiac gluten sensitivity (NCGS), or GS. These conditions can be viewed as straddling the flimsy and uncertain boundary between the intestinal organic diseases and functional disorders and scientific evidence have been reported to consider each of them either a subgroup of IBS or, on the contrary, a separate entity from IBS.

DEFINITION OF GS

GS is a clinical entity leading to gastrointestinal and/or extra-gastrointestinal symptoms that resolve once the gluten-containing foodstuff is eliminated from the diet, and when CD and wheat allergy have been ruled out[1-3].

PATHOGENESIS

Symptoms of CD, lactase deficiency, SIBO, and GS usually follow, or are exacerbated by, food ingestion, but the underlying mechanisms are different. Whereas lactase deficiency and SIBO are considered food intolerance due to excessive fermentation of non-digested food by intestinal microbiota[4] expressing clinically with gastrointestinal symptomatology, CD, and food sensitivities, such as GS, are considered immune-mediated reactions with gastrointestinal and extra-gastrointestinal clinical expression.

Gluten-containing grains such as wheat, barley, and rye, are fundamental foods worldwide, yet their ingestion is not without adverse effects in a large proportion of the human population, the best known being CD, wheat allergy, and GS. The oligosaccharide contents of grains can also cause disturbances such as abdominal pain, bloating, and bowel alterations, in IBS patients due to a hypersensitive gut reaction triggered by gas and water distension of the bowel secondary to microbiota fermentation of carbohydrates[5]. It is thus possible that GS cannot be distinguished from IBS, as evidenced by two studies in which the reduction of carbohydrate, rather than gluten, containing foods improved the symptoms attributed to GS[6,7].

CD occurs when Gliadin, a protein constituent of gluten gets in contact with the intestinal epithelium in genetically human leukocyte antigen (HLA) genotypes DQ2 and DQ8 predisposed people in the presence of a still unidentified, most likely immunological or environmental, factor. In these conditions, gliadin activates T-cells with the production of antibodies against tissue transglutaminase-2 (TG2), and an auto-immune cascade leading to epithelial inflammation, and loss of epithelial barrier function. In wheat allergy gluten and non-gluten contained proteins trigger immune cells to release immunoglobulin E, histamine and other allergy-inducing mediators[8].

In GS, differently, from CD, there is no mucosa inflammation and histologic alterations of the epithelium with the exception of the possible finding of scattered intraepithelial lymphocytes that matches a Marshall I definition[9]. In GS there is evidence that gliadin peptides, releasing zonulin, can increase gut permeability and thus activate an innate immune response[10,11] and the clinical features of NCGS. A possible factor that contributes to NCGS may be amylase-trypsin inhibitors (AT), plant-derived proteins that inhibit enzymes of common parasites, and are present in the same grains that contain gliadin[12]. Some studies indicate that these proteins can induce innate immune responses activating the TLR4 complex[13]. It has been hypothesized that ATIs could be the inducers of innate immunity in patients with GS[13]. Following this consideration, the NCGS has been re-named non-celiac wheat sensitivity, despite ATIs are present also in rye and barley.

THE OVERLAPPING PATHOGENESIS AND COMORBIDITIES IN GS AND IBS

IBS and GS are difficult to differentiate one from the other as they share many common clinical and pathophysiologic features. Both conditions affect mainly young-middle aged women. Furthermore, two epidemiological studies report a 28–30% prevalence of GS in IBS patients[14,15]. Many reports emphasize the presence of extra-gastrointestinal symptoms to differentiate GS from IBS. But also IBS patients have many comorbidities, gastrointestinal, and extra-gastrointestinal, with a variety of symptoms referred to many different districts of the body with a high request of different medical specialist visits[16]. The presence of psychological and mood alterations have been reported in both IBS and GS. Several studies have reported some degree of abnormalities regarded as low-grade inflammation and/or abnormal immune function, with main emphasis on an increased innate immunity response, and increased intestinal permeability[17,18], conditions that have been also related to GS. Although genetic, environmental and psychosocial factors predispose to develop IBS, not differently from GS, gluten-containing food is a relevant and frequent factor for triggering the onset or exacerbating IBS-like symptoms[19]. Furthermore, a symptomatic improvement after exclusion of gluten from the diet is not guaranteed of GS diagnosis since gluten is contained in highly fermentable foods that also trigger symptoms of IBS. As said, two studies have reported clinical improvement after a low-fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) diet in patients clinically diagnosed as having GS[6,7]. A double-blind controlled clinical trial has shown that a diet with low contents of FODMAPs performs better than a combined low-FODMAP and gluten-free diet to obtain clinical improvement in IBS patients[20].

DIAGNOSIS

The diagnosis of GS should be considered in patients not affected by CD and wheat allergy and reporting worsening of intestinal, mainly IBS-like, and/or extra-intestinal, complaints after eating gluten-rich food. In the diagnostic work out, however, we should be aware that gluten and saccharides are present in the same food, and any exclusion of gluten from diet decreases the quantity of FODMAP ingestion.

At medical history, GS patients refer gastrointestinal abdominal symptoms (Table 1) at all similar to functional intestinal disorders, often identical to IBS. These gastrointestinal symptoms can be accompanied by several other extra-gastrointestinal symptoms (Table 1) that, when present, largely contribute to enhance the severity of illness. Many patients had already experienced symptom resolution by avoiding gluten-containing foods and ever since have maintained a gluten-free diet (GFD) without having being tested for CD. In these cases, the proper diagnostic investigation would require that patients resume a gluten-containing diet to be then properly investigated with an assessment of antibodies against tissue TG. Alternatively, the genetic analysis of HLA can only offer the possibility to exclude with high probability CD only in DQ2 and DQ8 negative patients. In the patients who are still on gluten-containing diet, it is usually sufficient to assess the antibodies against tissue TG to diagnose or exclude CD.

The diagnostic algorithm of GS in patients (Fig. 1) on gluten-containing diet differs from those on gluten-free diet as agreed in the Salerno consensus[21]. In the former group, a full diagnostic evaluation includes the following two steps: (1) assessing the clinical response to the GFD, (2) measuring the effect of reintroducing gluten after a period of treatment with a GFD. During step (1), to establish the baseline symptoms, patients on their habitual gluten-containing diet, will report on a standardized self-administered gastrointestinal symptom rating scale (GSRS) questionnaire[22], revised with the addition of extra-intestinal symptoms of GS, for 3 consecutive weeks. The report of at least three GS symptoms with the severity of 3 out of 10 in the GSRS is considered to be clinically relevant to be compared with the following 6 weeks during which the patients will take a GFD.

Responders should have >30% reduction of one to three main symptoms or at least one symptom with no worsening of others for at least 50% of the observation time (usually at least 3 of 6 weekly evaluations). The diagnosis of GS is excluded in subjects failing to show symptomatic improvement after 6 weeks of GFD. Patients not responding to a GFD should be investigated for other possible causes of IBS-like symptoms, e.g., intolerance to FODMAPs or SIBO.

On the other hand, a definitive diagnosis of GS cannot be made in responders to step (1) since the exclusion of gluten-containing food from the diet implies a sensible reduction of those fermentable foods that contain gluten, thus, a symptomatic improvement in IBS patients.

Step 2, based on a double-blind crossover controlled challenge with gluten and placebo, is regarded as the best evidence to diagnose GS in responders to GFD in Step 1 and those patients already on a GFD not willing to reintroduce gluten for a Step 1 assessment. The challenge includes a 1-week gluten or placebo ingestion followed by a 1-week washout of strict GFD and by the crossover to the second 1-week alternative substance. The modified GSRS questionnaire is self-administered and filled in at baseline, and daily during the first 7-day challenge (or less if symptoms prevent completion of 7 days), the washout period, and the second 7-day challenge (or less if symptoms prevent completion of 7 days). During the

Table 1. The clinical manifestations of NCGS

Frequency	Intestinal	Extra-intestinal
Very common	Bloating Abdominal pain	Lack of well-being Tiredness
Common	Diarrhea Epigastric pain Nausea Aerophagia GER Aphthous stomatitis Alternating bowel habits Constipation	Headache Anxiety Foggy mind Numbness Joint/muscle pain Skin rash dermatitis
Undetermined	Hematochezia Anal fissures	Weight loss Anemia Loss of balance Depression Rhinitis/asthma Weight increase Interstitial cystitis Ingrown hairs Oligo or polymenorrhea Sensory symptoms Disturbed sleep pattern Hallucinations Mood swings Autism Schizophrenia

NCGS: non-celiac gluten sensibility.

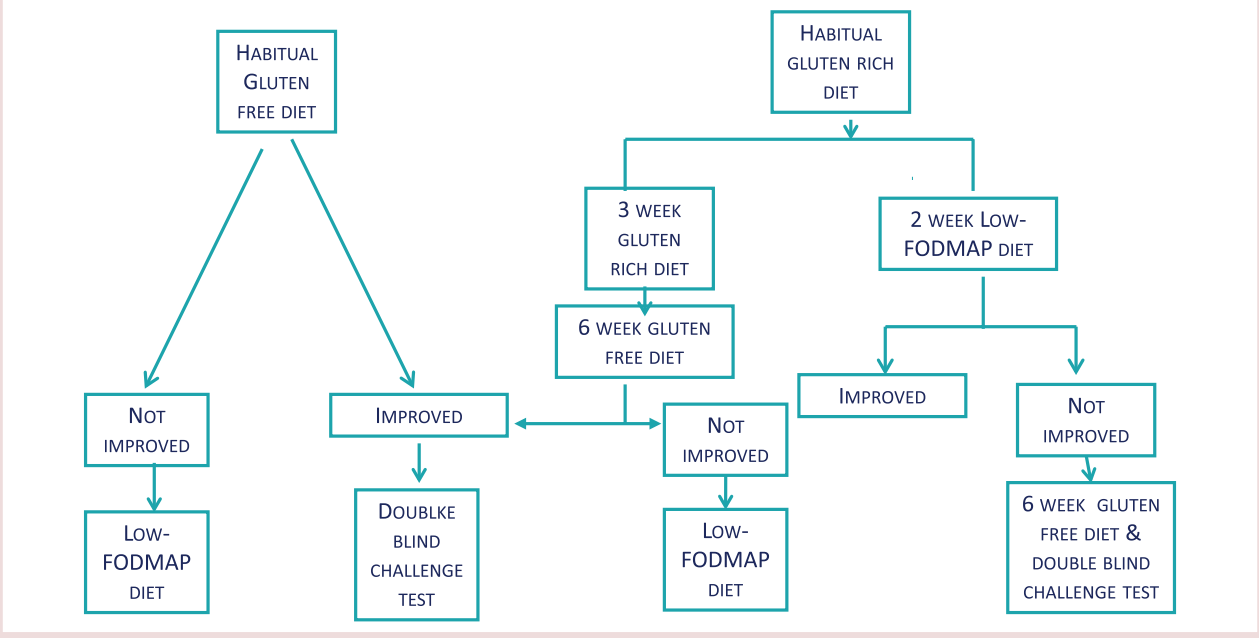

Figure 1. Diagnostic algorithm of gluten sensitivity in patients on gluten-free and gluten-rich habitual diets.

challenge, the patient will identify and report one to three main symptoms. At least a variation of 30% between the gluten and the placebo challenge should be detected to discriminate a positive from a negative result. In those with negative results, a trial of low FODMAP diet for a 2-week time period can be helpful to identify the patients who benefit of a low fermentable food regimen without the need of total gluten exclusion from the diet.

A less cumbersome diagnostic algorithm than the one proposed by the Salerno Consensus experts can be based on the assessment of FODMAP role in triggering the IBS-like symptoms (Fig. 1). A dietary diary filled in for 1–2 weeks by patients on gluten-containing diet and by those patients not benefiting of a GFD would verify whether the symptoms are triggered by FODMAP containing foods. In this case, a clear-cut symptom improvement during a trial with a low-FODMAP diet for a 2-week time period will confidently identify the IBS patients who benefit of a low fermentable food regimen without the need of total gluten exclusion from the diet. For those patients not having benefit with the low-FODMAP diet, the double-blind cross-over controlled challenge with gluten and placebo is then indicated.

About 50% of GS patients have IgG antibodies against native gliadin and this marker, although not diagnostic, may support the diagnostic suspicion and can be monitored to verify its reduction during GFD[22,23].

CONCLUSIONS

IBS and GS are still poorly understood conditions that share many common features. Their pathogenesis is far from being clarified. Both conditions lack a diagnostic marker, and their similar clinical expression requires to submit patients to a complex diagnostic algorithm. IBS and GS may markedly impair the quality of life, but a circumstantial diagnosis and gluten exclusion will benefit GS patients.

REFERENCES

1. Sapone A, Bai JC, Ciacci C, et al. Spectrum of gluten-related disorders: consensus on new nomenclature and classification. BMC Med. 2012;10:13.
2. Catassi C, Bai JC, Bonaz B, et al. Non-celiac gluten sensitivity: the new frontier of gluten related disorders. Nutrients. 2013;5:3839-53.
3. Ludvigsson JF, Leffler DA, Bai JC, et al. The Oslo definitions for coeliac disease and related terms. Gut. 2013;62:43-52.
4. Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010;126:S1-S58.
5. Ong DK, Mitchell SB, Barrett JS, et al. Manipulation of dietary short chain carbohydrates alters the pattern of gas production and genesis of symptoms in irritable bowel syndrome. J Gastroenterol Hepatol. 2010;25:1366-73.
6. Biesiekierski JR, Peters SL, Newnham ED, et al. No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates. Gastroenterology. 2013;145:320-80.
7. Vanga R, Leffler DA. Gluten sensitivity: not celiac and not certain. Gastroenterology. 2013;145:276-9.
8. Ford AC, Chey WD, Talley NJ, et al. Yield of diagnostic tests for celiac disease in individuals with symptoms suggestive of irritable bowel syndrome: systematic review and meta-analysis. Arch Intern Med. 2009; 169:651-8.
9. Volta U, Caio G, Tovoli F, De Giorgio R. Non-celiac gluten sensitivity: questions still to be answered despite increasing awareness. Cell Mol Immunol. 2013;10:383-92.
10. Fasano A. Zonulin and its regulation of intestinal barrier function: the biological door to inflammation, autoimmunity, and cancer. Physiol Rev. 2011;91:151-75.
11. Lammers KM, Lu R, Brownley J, et al. Gliadin induces an increase in intestinal permeability and zonulin release by binding to the chemokine receptor CXCR3. Gastroenterology. 2008;135:194-204000.
12. Finnie C, Melchior S, Roepstorff P, Svensson B. Proteome analysis of grain filling and seed maturation in barley. Plant Physiol. 2002;129:1308-19.
13. Junker Y, Zeissig S, Kim SJ, et al. Wheat amylase trypsin inhibitors drive intestinal inflammation via activation of toll-like receptor 4. J Exp Med. 2012;209:2395-408.
14. Carroccio A, Mansueto P, Morfino G, et al. Oligo-antigenic diet in the treatment of chronic anal fissures. Evidence for a relationship between food hypersensitivity and anal fissures. Am J Gastroenterol. 2013;108:825-32.
15. Breckan RK, Asfeldt AM, Straume B, Florholmen J, Paulssen EJ. Prevalence, comorbidity, and risk factors for functional bowel symptoms: a population-based survey in Northern Norway. Scand J Gastroenterol. 2012; 47:1274-82.
16. Whitehead WE, Palsson OS, Levy RR, et al. Comorbidity in irritable bowel syndrome. Am J Gastroenterol. 2007;102:2767-76.
17. Ohman L, Simren M. Pthogenesis of IBS: role of inflammation, immunity and neuroimmune interactions. Nat Gastroenterol Hepatol. 2019;7:163-73.

18. Marshall JK, Thabane M, Garg AX, et al. Intestinal permeability in patients with irritable bowel syndrome after a waterborne outbreak of acute gastroenteritis in Walkerton, Ontario. Aliment Pharmacol Ther. 2004;20:1317-22.
19. Wahnschaffe U, Schulzke JD, Zeitz M, Ullrich R. Predictors of clinical response to gluten-free diet in patients diagnosed with diarrhea-predominant irritable bowel syndrome. Clin Gastroenterol Hepatol. 2007;5:844-50.
20. Piacentino D, Rossi S, Alvino V, et al. Effects of low-FODMAP and gluten free diets in irritable bowel syndrome patients. A double blind-randomized controlled clinical study. Gastroenterology. 2014;146:5.
21. Catassi C, Elli L, Bonaz B, et al. Diagnosis of non-celiac gluten sensitivity (NCGS): the Salerno experts' criteria. Nutrients. 2015;7:4966-77.
22. Kulich KR, Madisch A, Pacini F, et al. Reliability and validity of the gastrointestinal symptom rating scale (GSRS) and quality of life in reflux and dyspepsia (QOLRAD) questionnaire in dyspepsia: a six-country study. Health Qual Life Outcomes. 2008;6:12.
23. Caio G, Volta U, Tovoli F, De Giorgio R. Effect of gluten free diet on immune response to gliadin in patients with non-celiac gluten sensitivity. BMC Gastroenterol. 2014;14:26.