Diseases caused by gluten

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Abstract
Introduction Gluten is the protein fraction of wheat flour, composed of prolams and glutenins. Prolamins vary according to the cereals: gliadin in wheat, hordein in barley and secalin in rye, all capable of producing different immune diseases. The peptides of these toxic gluten fractions trigger the following conditions: gluten allergy, non-celiac gluten sensitivity and celiac disease, which present different fundamental characteristics. Non-celiac gluten sensitivity is a disease described in recent years that has caught the attention of the medical community.

Objective Update the most recent criteria on the conditions that can be triggered by gluten, their mechanisms, clinical symptoms and diagnostic elements.

Methods A search related to gluten allergy, non-celiac gluten sensitivity and celiac disease was carried out in publications in PubMed, sCielo and Latindex databases from 2011 to 2017.

Development The fundamental characteristics of gluten allergy, non-celiac gluten sensitivity and celiac disease were reviewed. Their mechanisms, clinical manifestations and diagnostic criteria are updated in the light of the most recent knowledge.

Conclusions The participation of gluten as agent responsible for different conditions and its impact on health is evidenced. The different criteria discussed on the pathogenesis, clinical manifestations and the diagnosis of these conditions are analyzed. Attention is drawn to the importance of non-celiac gluten sensitivity as a recently described condition.

Keywords: gluten, gluten allergy, non-celiac gluten sensitivity, celiac disease.

INTRODUCTION
In the light of recent knowledge, the spectrum of diseases caused by gluten has been extended with the appearance of a new condition, non-celiac gluten sensitivity or gluten intolerance, which has allowed delimiting three diseases triggered by gluten: gluten allergy, celiac disease (CD) and non-celiac gluten sensitivity (NCGS), which have different forms of presentation, causative mechanisms, clinical manifestations, and diagnosis; thus knowing their particularities and differences is decisive for the doctor and the benefit of the patient.(1–3)

Gluten is the protein portion of a well-known cereal, wheat, which contains a variety of indigestible peptides that can stimulate the immune system and is not soluble in water. It represents 90% of wheat flour, while the remaining 10% of these proteins is soluble in water. Gluten is constituted by gliadin, soluble in alcohol, and glutenin, insoluble in alcohol. Gluten is capable of causing the aforementioned conditions of gluten allergy, CD and NCGS.(3)

The objective of this article is to review the mechanisms and effects of gluten that cause these three different diseases.

DEVELOPMENT

GLUTEN ALLERGY
Gluten allergy (GA) is an uncommon condition, with differential diagnosis from celiac disease and NCGS, all caused by different mechanisms. GA is an IgE-mediated condition with immediate response to gluten. The onset of symptoms is rapid, with predominance of urticaria, skin edema and respiratory symptoms, characterized by respiratory distress.(1)

Depending on the route of exposure to the allergen and the underlying immune mechanisms, wheat allergy is classified as a classic food allergy, which affects the skin and the gastrointestinal and respiratory tracts, causing; wheat induced anaphylaxis; occupational type asthma (baker's asthma), rhinitis and contact urticaria.(4)

Wheat is one of the eight main food allergens that affects 0.4% to 1% of the population. Gluten allergy is included among food allergies, since it is an adverse reaction with abnormal clinical response due to the ingestion of food or its derivatives with an additive contained in it. These reactions are mainly present in individuals with this allergic condition, depending on the dose received. A feature of food...
In recent years, there is the suspicion that the high markers have yet been established for NCGS.\(^{(11)}\) Symptoms caused by these mediators, although no biological nervous system is activated, determining the presence of the celiac patients and controls. Consequently the cholinergic gliadin to induce production of interleukin-15 (IL-15), in classification) together with the immunological capacity of lamina propria (according to Marsh stage I histological classification) established for celiac disease, and activation of the cholinergic nervous system, also described in CD, although biological markers have not yet been established for the NCGS.\(^{(14)}\) Recent studies have shown that gluten is the main trigger of NCGS, but not the only one.

Among the most recognized interpretations, other possible pathogenic mechanisms found are the immunological activation of gliadin due to its ability to induce the production of interleukin-15 (IL-15), found in celiac patients and controls. Such activation may be related to an exclusively innate immune response against the aggressive agent with markers of innate immunity, presence of modifications of the duodenum-jejunum mucosa by expression of macrophages in the lamina propria, changes in accordance with Marsh stage 1 histological classification established for celiac disease, and activation of the cholinergic nervous system, \(^{(10–13)}\) Besides wheat, fructans are found in garlic and onion, in some vegetables (chicory, beet and watercress); in fruits (watermelon, cherry, mango and pear), milk and honey.\(^{(4)}\)

Foods that contain gluten are generally introduced after six months of age, and sometimes even later, but occasionally they are administered after three months of age. Gluten allergy is an uncommon disease. The elimination of foods containing gluten is decisive for the diagnosis and treatment of gluten allergy.\(^{(9)}\)

**NON-CELIAC GLUTEN SENSITIVITY (NCGS)**

This is a disease established in recent years, it is a new condition, 6 to 10 times more frequent than celiac disease (13% of the population). There is no allergy or permanent sensitivity to gluten due to celiac disease.\(^{(9)}\) There are no specific diagnostic tests. Serological antibody tests and changes in the duodenum-jejunum mucosa, fundamental for celiac disease diagnosis, are negative.\(^{(10)}\)

**Pathogeny**

The mechanism by which gluten or wheat components can trigger clinical signs of NCGS is unknown.\(^{(10)}\) The most accepted interpretation is the activation of the adaptive immune response as the only response against the aggressive agent. This is unlike CD where adaptive and innate responses arise, determining a mild inflammatory response of the intestinal mucosa by expression of the macrophages in the lamina propria (according to Marsh stage I histological classification) together with the immunological capacity of gliadin to induce production of interleukin-15 (IL-15), in celiac patients and controls. Consequently the cholinergic nervous system is activated, determining the presence of the symptoms caused by these mediators, although no biological markers have yet been established for NCGS.\(^{(11)}\)

In recent years, there is the suspicion that the high carbohydrate content of fructan, a wheat component that has the ability to ferment FODMAPs, poorly absorbed short chain oligosaccharides: disaccharides, monosaccharides and polyalcohols (polyols) causes the symptoms described in NCGS and in the irritable bowel syndrome (IBS). They generate short-chain fatty acids, lactate and gas, in relation to the release of ammonium fatty acids, and hydrogen sulfide, associated with the local and extra-digestive symptomatology described.\(^{(10–13)}\)

**Clinical manifestations**

Diagnosis can result complicated. There is no predominance of specific symptoms. Preference is reported in the adult, regarding childhood, with predominance in the female sex. The symptoms can appear from a few hours after gluten intake to several days. The natural history of the disease is not established. The symptoms related to the ingestion of gluten can be digestive or extra-digestive. Clinically, it can present a digestive response of pain and/or abdominal distension, diarrhea on occasions, flatulence, and accumulation of gasses; in other cases there is absence of digestive symptoms, and the manifestations are limited to fatigue, tiredness and sudden changes in behavior. Symptoms can be temporary or permanent. Due to the characteristics of the clinical picture, NCGS is considered by some experts as a syndrome (Table 1. See after references).\(^{(4,15)}\)

Gluten intolerance triggers the symptoms produced by its ingestion and improvement is achieved by suppression of the foods that contain it. Diagnosis, unlike gluten allergy, is not based on the exclusion of gluten.\(^{(10)}\)

**Diagnosis**

The European Group meeting in Salerno, Italy, in 2015 under the sponsorship of the Dr. Schär Institute (international information platform on celiac disease, gluten sensitivity and gluten-free diet integrated by international experts from different latitudes) established the methodology for the study of gluten sensitivity. A Scale of Gastrointestinal
Disorder Classification is used to guide diagnosis when there is response to a diet without harmful cereals (gluten). By using it, the effects of reducing (by ≥ 30%) a gluten-free diet are determined, based upon the fact that NCGS diagnosis does not rely on the sole criterion of gluten exclusion. (16, 17)

The established diagnostic strategy is to administer a preparation with 8 g of gluten for seven days, rest for seven days and determine the cross effect. (16)

Indication of the serologic markers of celiac disease is necessary to rule out celiac disease, and even a biopsy of the duodenum-jejunum may be indicated. Sometimes (50%), the antigliadin antibody can be positive. In intestinal biopsies, there may be an increase in intraepithelial lymphocytes (Marsh I) and the presence of markers associated with innate immunity. (18, 19)

The suppression of gluten from the diet and even the reduction of fructans are necessary for treatment.

Celiac Disease

Celiac disease is a systemic autoimmune condition, described in London in 1888 by Samuel Gee, but it was not until the end of World War II that it was determined to be a permanent intolerance produced by sensitivity to the ingestion of prolamin, present in wheat flour, in barley and rye; so called, because of their content in glutenins and prolines, which are potent toxic substances in individuals with genetic susceptibility. (10) These substances are gliadin in wheat, hordein in barley and secalin in rye. In the introduction to this article, it was mentioned that gliadins are found in gluten, the protein fraction of wheat. CD is considered a hypersensitivity of autoimmune origin that occurs in individuals with genetic predisposition. (21–23)

The prevalence of celiac disease (CD) is high worldwide, corresponding to 1 – 2% of the population in Europe and North America, however, there are countries of the Latin American region in which it is still scarcely diagnosed, so the magnitude of the disease cannot be determined. (24 – 28)

Pathogenicity

Wheat flour is a complex mixture consisting of starch, fats, cellulose, ash and protein. The latter make up 70% of said flour. In these proteins (gluten) four protein groups with different physical-chemical characteristics and which represent four heterogeneous groups are found: 1) gliadins (soluble in alcohol), 2) glutenins (soluble in weak acids and alkalis), 3) albumin and 4) globulins. Gliadins are soluble in aqueous solution of 70% ethanol; glutenins, in saline solutions and the albumins, in water. By electrophoresis, four gliadin components have been established: alpha, beta, gamma and omega. The largest fraction in certain varieties of wheat is alpha-gliadin, of greater toxicity regarding the beta, gamma and omega fractions. (20, 21)

The gluten content in the diet is a decisive factor. There is no appearance of CD without the ingestion of gliadin and other prolamins. To exert its harmful effects, gliadin must cross the intestinal mucosa. The release of zonulin, a protein in the tight junctions of enterocytes, increases intestinal permeability and enables the passage of molecules into the submucosa. (2, 26)

In the pathophysiology of celiac disease there are three converging mechanisms: 1) environmental factors, 2) immunological factors and 3) genetic factors. Environmental factors are represented by wheat, rye and barley prolamins. Immunological ones are represented by activation of the immune response, both innate and adaptive, by exposure to the so-called toxic cereals. And the genetic factors are HLA class II genes, haplotypes DQ2 and DQ8. (2, 29)

Clinical manifestations

The clinical symptoms of gluten intolerance are very diverse: typical, atypical and silent forms. Although the symptomatology is very variable with possibility of different systemic manifestations, the most frequent correspond to the digestive system. Specific antibodies have been identified such as anti-tissue transglutaminase (tTGA), anti-endomysial (EmA) and deamidated gliadin (DGP-AGA) antibodies and there is presence of damage of the duodenum-jejunum mucosa, depending on the degree of flattening of the intestinal mucosa; hyperplasia of the crypts and inflammatory infiltrate of the lamina propria. (21 – 23)

In recent years, the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) has established new criteria for CD diagnosis, in which the intestinal biopsy is omitted in patients with symptoms of the disease, and serological tests with high tTGA (values 10 times above the normal upper limit) and also positive EmA antibodies and positive HLA-DQ2 and/or DQ8 genetic markers. (30)

CD is associated with autoimmune conditions such as diabetes mellitus type 1, dermatitis herpetiformis, autoimmune thyroiditis, autoimmune arthritis, selective IgA deficiency, autoimmune hepatitis, Sjögren’s syndrome, ulcerative colitis and sclerosing cholangitis, among others. (20, 21)

CD requires a gluten-free diet for life. Transgressions can produce severe complications, such as celiac crisis and malignant diseases such as intestinal lymphoma. (26)

CONCLUSIONS

The diseases caused by gluten are reviewed: gluten allergy, non-celiac gluten sensitivity and celiac disease. Their
pathogenic mechanisms, prominent features for the specific diagnoses and the differences between them are presented. That SGNC is a disease described in recent years is emphasized. It is six times more frequent than celiac disease, an ancient disease recognized since 1888, reported in 1 to 2% of the world population. The involvement of the immune system is different in gluten allergy and celiac disease. The antibody produced in gluten allergy is IgE, while in celiac disease the specific antibodies determined by serological tests are of other types: antigliadin, endomysial, tissue anti-transglutaminase and deamidated gliadin antibodies. In addition, in celiac disease changes occur in the duodenum-jejunum mucosa. In the SGNC, clinical guidance is complex and biological markers have not been established up to now. Its pathogenesis together with the involvement of gliadin, factors such as fermentation of gluten carbohydrates and polyols are suspected.

Enfermedades provocadas por el gluten

Resumen

Introducción El gluten es la fracción proteica de la harina de trigo, formada por prolaminas y glutelinas. Las prolaminas y glutelinas de producir distintas enfermedades inmunas varían según el cereal: gliadina en el trigo, ordeina en el centeno y secalina en la cebada. Los péptidos de dichas fracciones tóxicas del gluten desencadenan las siguientes afecciones: alergia al gluten, sensibilidad al gluten no celiaca y enfermedad celiaca, exponiendo sus aspectos fundamentales. La sensibilidad al gluten no celiaca es una enfermedad descrita en años recientes que ha llamado la atención de la comunidad médica.

Objetivo Actualizar los criterios más recientes de las afecciones que puede desencadenar el gluten, sus mecanismos de producción, sintomatología clínica y elementos para el diagnóstico.

Métodos Se realiza búsqueda en publicaciones relacionadas con la alergia al gluten, sensibilidad al gluten no celiaca y enfermedad celiaca en bases de datos de PubMed, sCielo y Latindex del año 2011 al año 2017.

Desarrollo Las características fundamentales de la alergia al gluten, la sensibilidad al gluten no celiaca y la enfermedad celiaca son revisadas. Se actualizan sus mecanismos de producción, manifestaciones clínicas y criterios diagnósticos a la luz de los conocimientos más recientes.

Conclusiones Se evidencia la participación del gluten como agente responsable de distintas afecciones y su repercusión para la salud. Se analizan los distintos criterios argumentados en la patogenia, manifestaciones clínicas y el diagnóstico de dichas afecciones. Se llama la atención sobre la importancia de la sensibilidad al gluten no celiaca como afección descrita en los últimos años.

Palabras claves: Gluten, alergia al gluten, sensibilidad al gluten no celiaca, enfermedad celiaca.

Conflict of interests: The author declares no conflict of interest.

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9,000 people died from it in 2016. 

It is perhaps the most contagious mild childhood illness. It is perhaps the most contagious disease known, it can also be lethal. Worldwide, nearly 20,000. Thirty-five people died.

5,273 cases; in 2017, the number surged 400% to more than 20,000. Italy, a developed country, in 2017, had 5,006 cases, an incidence of 0.04 per 100,000 people. Thus, in 2017, on a per capita basis, Italy had more than 200 times as many measles cases as the U.S.

Though tragic, this is understandable in developing countries, which often lack vaccines and other basic necessities of healthcare. But it is an outrage that measles occurs anywhere in the developed world. 5,000 Measles Cases in Italy

Italy, a developed country, in 2017, had 5,006 cases, for an incidence of about 8 measles cases per 100,000 people. Compare to the U.S., which had 118 cases for an incidence of roughly 0.04 per 100,000 people. Thus, in 2017, on a per capita basis, Italy had more than 200 times as many measles cases as the U.S.

Worsening matters is the fact that the anti-vaccine movement is being enabled by populist politicians. Some Italian politicians are fighting back. According to Politico Europe, there is an effort to expand the number of vaccines that are required for children to enter school. The U.S. State of Oregon is taking matters a step further. Starting on February 21, children who are not fully vaccinated will be kicked out of school and day care facilities. Desperate times call for desperate measures.

Source: https://www.acsh.org/news/2018/02/20/measles-europe-italy-has-200-times-many-cases-us-12596

Measles in Europe: Italy Has 200 Times as Many Cases as U.S.

The anti-vaccine movement is not limited just to the United States. Anti-vaxers are influential in Europe, and the results have been entirely predictable: Europe is in the grip of a measles outbreak.

The year 2016 saw a record low for measles on the continent, according to the BBC. That year, there were 5,273 cases; in 2017, the number surged 400% to more than 20,000. Thirty-five people died.

One of the persistent myths about measles is that it is a mild childhood illness. It is perhaps the most contagious disease known, it can also be lethal. Worldwide, nearly 90,000 people died from it in 2016.

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### Table 1: Clinical symptoms of non-celiac gluten sensitivity

<table>
<thead>
<tr>
<th>Digestive</th>
<th>Extra-Digestive</th>
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<tbody>
<tr>
<td>Abdominal pain</td>
<td>Headaches</td>
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<tr>
<td>Diarrhea</td>
<td>Increased asthenia</td>
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<tr>
<td>Constipation</td>
<td>Fibromyalgia</td>
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<tr>
<td>Fluctuating abdominal distention</td>
<td>Generalized muscle-skeletal pain</td>
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<tr>
<td>Flatulence</td>
<td>Atopy</td>
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<tr>
<td>Gastro-esophageal reflux</td>
<td>Anemia, ferropenia and folic acid deficit</td>
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<tr>
<td>Lactose intolerance</td>
<td>Allergy, rhinitis, asthma</td>
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<td>Food intolerance</td>
<td>Anxiety, depression</td>
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<tr>
<td>Aphtous stomatitis</td>
<td>Psychiatric disorders: autism, schizophrenia</td>
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<td></td>
<td>Attention deficit-hyperactivity</td>
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<td>Ataxia</td>
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