REVISTA CHILENA DE PEDIATRÍA
Sociedad Chilena de Pediatría
www.scielo.cl

Rev Chil Pediatr. 2017;88(3):417-423
DOI: 10.4067/S0370-41062017000300017

REVIEW ARTICLE

Celiac disease, non celiac gluten sensitivity and wheat allergy: comparison of 3 different diseases triggered by the same food

Enfermedad celíaca, sensibilidad no celíaca al gluten y alergia al trigo: comparación de patologías diferentes gatilladas por un mismo alimento

Catalina Ortiz[a], Romina Valenzuela[b], Yalda Lucero A.[b,c]

[a]Medical Student, Eastern Campus, Faculty of Medicine, University of Chile
[b]Research Unit, Department of Pediatrics and Pediatric Surgery, Faculty of Medicine, University of Chile
[c]Gastroenterology Unit, Departament of Pediatrics, Clínica Alemana de Santiago, Faculty of Medicine-UDD

Received: 16-6-2016; Accepted: 17-12- 2016

Abstract

Gluten and other related proteins of the wheat, rye and barley, have antigenic properties that may trigger adverse reactions in susceptible individuals. Celiac disease was the first pathology with clear causal association related to the intake of these proteins. Recently, wheat allergy and non celiac gluten sensitivity have been described. Although, clinical presentation and its relation with protein ingestion may be similar and elicit confusion, their pathogenic mechanism, diagnosis and treatment are quite different. Since the prevalence of these diseases is relatively high as a whole, it is essential that these become familiar to primary care doctors and general pediatricians, thus they will know how to differentiate and face them. The aim of this review is to compare the main aspects of epidemiology, pathofisiology, diagnosis and treatment of these 3 conditions.

Keywords:
Celiac disease;
wheat allergy;
non celiac gluten sensitivity;
food adverse reaction.

Introduction

Celiac disease (CD) has been known for more than 2,000 years and it was already in the middle of the 20th century that its relationship with gluten intake was established.

Until recently this was the main condition that needed to be treated with gluten-free diet. However, in recent years a gluten/wheat-free feed stream has emerged, in addition to identifying other pathologies triggered by the intake of these foods, which has created some confusion regarding the conditions that actually need to be treated with said diet. Thus wheat allergy (WA) and non-celiac gluten sensitivity (NCGS) have been described as independent entities[1,2]. These 3 conditions are the only ones that have so far proven to respond to the gluten/wheat exclusion diet.

Their prevalence as a whole is relatively high (up to 10% of the population), so it is necessary for primary care phy-

Correspondence:
Yalda Lucero Alvarez
ylucero@gmail.com

sicians and pediatricians to become familiar with these pathologies[1,2]. On the other hand, although their forms of clinical presentation and their relation with gluten/wheat ingestion may be similar, their pathogenic mechanisms, form of diagnosis and treatment differ. The objective of this article is to compare the main aspects of epidemiology, pathophysiology, diagnosis, and treatment of these pathologies (see summary in table 1). For a more comprehensive review of CD and NCGS we suggest the reader refer to recently published specific articles[3-5].

Is it the same to talk about gluten than about wheat proteins?

No, it is not the same. Gluten and related prolamins are proteins found in wheat, rye and barley. Humans do not have the enzymes to achieve their complete digestion, and intestinal peptidases only achieve their hydrolysis to peptides of 30-40 amino acids that maintain potentially antigenic properties. In genetically susceptible individuals, these peptides can cross the epithelial barrier reaching the intestinal wall where they can be presented and recognized by cells of the immune system that eventually trigger an allergic (WA) or autoimmune (CD)[1] adverse reaction.

On the other hand, wheat contains not only gluten, but also other proteins that potentially activate the immune system, among which alpha amylase/trypsin inhibitors (ATI) are prominent. These proteins have been identified as potent activators of the innate immune response, triggering the release of proinflammatory cytokines in monocytes, macrophages and dendritic cells. They have also been identified as Specific allergens in hypersensitivity plaques[6].

Table 1. Comparison of epidemiological, pathogenic and diagnostic features between celiac disease, non celiac gluten sensitivity and wheat allergy

	Celiac disease	Non celiac gluten sensitivity	Wheat allergy
Prevalence	0,5-1% of population; it has been duplicated in the last 20 years	There are no population studies. 20-40% of patients with irritable bowel syndrome	0,5-9% in children
Pathogenia	Autoimmune. Acquired immunity. Gastrointestinal and systemic inflammatory reaction.	Innate immune response	Type I and IV hypersensitivity (type I reactions are better characterized)
Most frequent gastrointestinal symptoms	Abdominal pain Constipation or chronic diarrhea. Abdominal distension Vomits	Abdominal pain Chronic diarrhea Abdominal distension	Vomits, diarrhea immediately after wheat ingestion
Extra-digestive symptoms	Ferropenic anemia refractory to supplementation Tiredness Herpetiform dermatitis Weight lost Aftoid ulcers Short stature Delayed puberty Infertility Repetitive spontaneous abortion Increased transaminases Headaches Cerebelar ataxia Idiopathic Epilepsia Periferic neuropathy Depresion, anxiety	Tiredness Eczema Headaches Blurred vision Depression Anemia Paresthesias Arthralgias	Exercise induced anaphylaxis. Atopic dermatitis. Urticaria. Chronic asthma and rinitis.
Serological markers	anti-tTG IgA anti- Endomisium IgA IgG anti-DGP	anti-gliadin IgA/IgG (AGA)	Wheat specific IgE or prick test
Duodenal biopsy	Necessary for confirmation* Villous atrophy can be observed	Necessary for CD exclusion	It is not necessary

*ESPGHAN suggest that duodenal biopsies are not necessary for CD confirmation in symptomatic patients, with anti-tTG IgA > 10 times the upper normal limit, positive EMA and DQ2/DQ8 HLA.

Which demonstrated conditions are related to gluten ingestion?

Celiac disease and non-celiac gluten sensitivity. Following we will briefly summarize its main features. Table 1 and 2 compare their clinical characteristics, diagnosis and treatment.

Celiac disease

Definition: It is a systemic autoimmune disease triggered by the ingestion of gluten and related prolamins in genetically susceptible individuals and characterized by a variable combination of clinical manifestations, specific antibodies, HLA DQ2 and DQ8 haplotypes and enteropathy[7].

Epidemiology

Its prevalence worldwide fluctuates around 0.5-1% of the population[2,8,9]. An increase in frequency has been reported in the last years, doubling its prevalence in the last 20 years[10,11]. Environmental factors have been proposed to explain this phenomenon, such as increased wheat consumption and infections at the beginning of life[10,12], although the evidence is not yet conclusive. According to the 2010 national health survey, a prevalence of between 0.6 and 0.8% is estimated in Chile[13].

Pathogenesis

CD develops in genetically susceptible individuals, exposed to certain environmental factors. The genetic factor best characterized so far is the presence of HLA DQ2 or DQ8 haplotypes of the MHC class II locus; This represents about 40% of the genetic risk of developing CD[8,14]. These variants are present in 30-35% of the general population and 95% of individuals with CD, suggesting that it is a necessary but not sufficient condition to produce the disease[8,14].

Other predisposing factors are dietary patterns (age of introduction, method of preparation, amount of gluten intake), infections at the beginning of life and intestinal microbiota[12,15]. A key point in the pathogenesis of CD is the alteration in the integrity of the tight junctions of the intestinal epithelium, allowing the passage of macromolecules such as gluten to the submucosa[8,16]. Gluten is only partially digested, to peptides rich in glutamine and proline residues, called gliadin[17]. Gliadin peptides cross the epithelial barrier, by increasing permeability, by contacting the transglutaminase (tTG) enzyme that deamines them by converting the glutamine residues to glutamic acid, increasing the negative charges and generating highly related peptides to interact with MHC molecules Type II HLA-DQ2 or HLA-DQ8 expressed on the surface of antigen presenting cells (APC) in the intestinal lamina propria[16]. APCs present these peptides to CD4 T lymphocytes, triggering a cellular and humoral gliadin-specific immune response. The result of this process is an inflammatory state in the intestinal mucosa that can lead to flattening of the villi and eventually malabsorption[8]. This inflammatory process can spread to other organs such as skin and joints, generating extradigestive manifestations.

Clinical picture

Initial descriptions of CD focused on digestive symptoms, especially diarrhea. At present, a broad clinical spectrum has been evidenced, including asymptomatic pictures, digestive and extradigestive symptoms[8,18,19].

Within the digestive symptoms, with 90%, abdominal pain is the most frequent symptom in children[20]. Other common symptoms are: chronic or intermittent diarrhea, chronic constipation, vomiting, weight loss, bloating and malnutrition; The latter in case of late diagnosis[7,8].

Regarding extradigestive manifestations, the most

Table 2. Comparison of treatment of celiac disease, non celiac gluten sensitivity and wheat allergy

	Celiac Disease	Non celiac gluten sensitivity	Wheat allergy
Treatment	Gluten free diet (wheat, barley and rye)	Gluten free diet (wheat, barley and rye)	To avoid all contact only with wheat
Level of adherence required for remission	Strict exclusion diet	Transgressions are permited according to symptoms presentation	Strict avoidance to wheat contact through digestive, respiratory and cutaneous pathway
Duration of treatment	For life	It is still not completely elucidated. Se Yearly challenge is rocommended	In children a wheat challenge under medical supervision is recommended after 6-12 months of exclusion In adults, exclusion is recommended for life
Complications without treatment	Autoimmunity, nutritional deficit, intestinal malignancies	Not described	Anaphylactic reaction

frequent presentation is iron deficiency anemia, especially when it is refractory to oral iron supplementation[7]. Fatigue, dental enamel hypoplasia, aftoid ulcers, dermatitis herpetiformis, osteopenia/osteoporosis, hypertransaminasemia, low stature, pubertal delay, infertility and repeated abortions can also be observed. They may present neurological symptoms including headache, cerebellar ataxia, epilepsy, peripheral neuropathy[7]. Other manifestations include psychiatric symptoms, especially in adolescents, such as depressive symptoms, hallucinations, anxiety and panic attacks[21].

CD is related to other autoimmune conditions, which can occur in up to 20% of cases[8,22], including diabetes mellitus type 1, autoimmune thyroiditis, inflammatory bowel disease, autoimmune hepatitis and Addison's disease.

On the other hand, it has been found an association between EC and selective IgA deficiency, and some chromosomopathies such as Down, Turner and Williams syndrome[7].

Diagnosis

Diagnostic suspicion is initiated by the presence of a suggestive clinical picture or by belonging to a risk group, either familiar of first degree of patient with CD or carrier of some autoimmune condition or associated chromosomopathy. In suspect cases, serology should be sought for anti-tTG and anti-endomysial antibodies (EMA)[23]. These antibodies are usually of the IgA type and since the IgA deficiency is more frequent in celiac than in the general population, they must be determined in conjunction with total IgA to validate the result. In case of IgA deficiency, the same autoantibodies should be determined but in their IgG version. Recently the measurement of deaminated gliadin peptide antibodies (DGPs), a marker that has shown greater sensitivity in children younger than 4 years old, in whom the other antibodies have a lower yield[23,24].

For confirmation and evaluation of the degree of intestinal damage, duodenal biopsies should be obtained by endoscopy. It is recommended to analyze at least 4 biopsies of the second/third portion of the duodenum and at least one of the duodenal bulb because the lesions may be in a patch[23,25]. Patients who have some degree of villous atrophy are considered to have active CD and should initiate treatment. Those who do not have villous atrophy, are considered to have a potential CD and have no indication of starting treatment, but to maintain serial follow-up by gastroenterologist.

Finally, in doubtful cases and in those in whom there is a disagreement between the results of antibodies and duodenal biopsies, the HLA DQ2-DQ8 determination may be useful (especially for its negative predictive value), as these haplotypes are present in about 95% of Caucasian individuals with CD. Its value in Amerindian population has not yet been fully established.

Non-celiac gluten sensitivity (NCGS)

Definition

It is a pathology recently described and still controversial, characterized by the appearance of a series of digestive and extra-digestive manifestations related to the ingestion of gluten and other wheat proteins in patients in whom CD and WA have been ruled out[25,27,28]. In recent years, its name has been questioned, since the main trigger is not gluten (see below) and it has been proposed to call it Wheat Intolerance Syndrome[29]. However, for the purposes of this review we will continue with its most widely used name today.

Epidemiology

There is still no certainty about its prevalence. In a general population evaluated at a research center for CD in the USA, a prevalence of 6% was found among the 5,896 patients evaluated, superior to CD[2].

In patients older than 16 years with irritable bowel, a frequency between 15 and 40% of NCGS has been described[30,31].

Pathogenesis

Not yet fully elucidated. Unlike CD, patients with NCGS do not present alterations in intestinal permeability[32] and instead of predominating the activation of acquired immunity, the evidence suggests that mechanisms of innate immunity would be activated[32,33]. Gluten would not be the only triggering wheat antigen in the NCGS. Other proteins including alpha-amylase/trypsin inhibitors, some carbohydrates (FODMAPs) and even yeast may contribute to the onset of NCGS symptoms[34].

Clinical picture

The clinical picture may be quite similar to CD. The symptoms most frequently described are abdominal pain (80%), chronic diarrhea (73%), fatigue (33%), abdominal distension (26%), eczema, headache, blurred vision, depression, anemia, paresthesias in the legs, Arms and hands and joint pain[25,35]. As for CD in children with NCGS, extraintestinal manifestations are less frequent than in adults[36,37].

Although the symptoms of malabsorption, family history of CD and family and personal history of other autoimmune diseases are more frequent in patients with CD, they can also be seen in individuals with NCGS[38].

Diagnosis

Clinically it is not possible to distinguish the CD from the NCGS, since the symptomatology can be very similar, unlike the WA, whose clinical picture is in most cases sufficient to differentiate it[39].

The diagnosis is made in the presence of symptomatology in relation to gluten/wheat intake with negative CD serology, negative immune-allergy tests (prick test, specific IgE and patch test for wheat), normal duodenal biopsy, and resolution of Symptoms when adhering to a gluten/wheat free diet for at least 3 weeks[27,38]. The confirmation is made based on the reappearance of symptoms when doing a counter-test with foods with gluten. In a study carried out in Italy, 15 children with a diagnosis of NCGS showed the presence of anti-gliadin IgG antibodies (AGA) in 66% of patients. There were no differences in nutritional, biochemical and inflammatory markers among children with NCGS and controls[35].

Treatment

Gluten free diet (GFD) guided according to the symptomatology. It does not require strict adherence unlike CD, because no long-term complications have been described so far.

Prognosis

Good prognosis according to adherence to GFD. No long-term complications have been reported.

Which demonstrated conditions are related to the ingestion of wheat protein?

In addition to CD and NCGS, there is wheat allergy (WA). Briefly summarizes its main features, which are compared with the other conditions in tables 1 and 2.

Definition

Hypersensitivity reaction to wheat proteins (not only gluten) in which IgE and release of chemical mediators such as histamine play a fundamental role. It is characterized by the presence of digestive, respiratory and/or cutaneous symptoms, triggered by exposure to wheat through mucous (digestive or respiratory) or skin[2].

Epidemiology

Studies in Europe describe prevalences of anti-protein IgE of wheat of 0.5-9% in children. According to a study carried out in Stockholm with a cohort of 2,336 children, its prevalence decreases with age[40-42].

Pathogenesis

Like any food allergy, its pathogenesis is based on the loss of immune tolerance to diet antigens. Such tolerance is understood as the antigen-specific suppression of cellular or humoral immune responses. It has been proposed that an increase in the permeability of the intestinal mucosal barrier/epidermis, given by an alteration or lack of maturation of the epithelial architecture would be the cause of allergic sensitization. Once it crosses the mucosa, the antigen is introduced by dendritic cells that trigger a Th2 response characterized by the production of IL-4, IL-5, and IL-13 from CD4 + T cells. This Th2 response leads to IgE production from B lymphocytes, which binds to their receptors on the surface of skin mast cells, GI, respiratory and cardiovascular systems, prepares them to react to a re-exposure to the allergen.

The classic clinical picture occurs minutes after antigenic exposure, when mast cells and basophils bound to IgE recognize the antigen and are activated, releasing powerful vasoactive compounds such as histamine, which account for the symptomatology characteristic of type 1 hypersensitivity responses[43].

Clinical picture

Depending on the form of exposure to the antigen we find:

Respiratory Allergy: Baker's Asthma and Rhinitis. They are allergic responses secondary to inhalation of wheat and cereal flours[39]. Baker's Asthma is one of the most prevalent occupational allergies in many countries.

Gastrointestinal Allergy: Wheat-Dependent Exercise Anaphylaxis: Syndrome caused by W5-gliadins proteins. Patients develop a broad spectrum of clinical manifestations, from generalized urticaria to severe allergic reactions such as anaphylaxis[39].

Other reactions triggered by wheat intake: Atopic dermatitis, urticaria, anaphylaxis.

Diagnosis

The diagnostic suspicion begins with the temporal relationship between the intake of some food with wheat and the appearance of symptoms.

As confirmation, Prick test or determination of specific IgE anti-wheat flour, barley, and rye can be used, as well as anti-

Alpha amylase in serum[2,39]. However, the positive predictive value for these tests is less than 75%, particularly in adults given cross-reactivity with grass pollen, but also because many commercial prick test reagents have low sensitivity since they are mixtures of water and protein of Salt-soluble wheat lacking the allergens of the insoluble fraction of gliadin[2].

Treatment

Avoid strict exposure to wheat-related proteins by the cutaneous, gastrointestinal and respiratory routes.

Prognosis

In children, WT may be transient, while in adults it usually persists. Since the susceptibility threshold is very low, potentially fatal anaphylactic reactions can be triggered with minimal amounts of this protein[43].

Conflicts of Interest

Authors state that any conflict of interest exists regards the present study.

References

1. Gasbarrini G, Mangiola F. Wheat-related disorders: A broad spectrum of "evolving" diseases. United Eur Gastroenterol J. 2014;2(4):254-62.
2. Sapone A, Bai JC, Ciacci C, et al. Spectrum of gluten-related disorders: consensus on new nomenclature and classification. BMC Med [Internet]. 2012 [citado el 22 de noviembre de 2016];10(1). Available from: http://bmcmedicine.biomedcentral.com/articles/10.1186/1741-7015-10-13.
3. Araya M, Bascuñán K. Enfermedad celíaca. Una mirada actual. Rev Chil Pediatr. 2014;85(6): 658-65.
4. Navarro E, Araya M. Sensibilidad no celíaca al gluten: Una patología más que responde al gluten. Rev Med Chile. 2015;143(5):619-26.
5. Moscoso JF, Quera PR. Enfermedad celíaca.Revisión. Rev Med Chile. 2016;144(2):211-21.
6. Nijeboer P, Bontkes HJ, Mulder CJJ, Bouma G. Non-celiac gluten sensitivity. Is it in the gluten or the grain? J Gastrointest Liver Dis JGLD. 2013;22(4):435-40.
7. Husby S, Koletzko S, Korponay-Szabó IR, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Guidelines for the Diagnosis of Coeliac Disease. J Pediatr Gastroenterol Nutr. 2012;54(1):136-60.
8. Guandalini S, Assiri A. Celiac Disease: A Review. JAMA Pediatr. 2014;168(3):272.
9. Catassi C, Gatti S, Lionetti E. World Perspective and Celiac Disease Epidemiology. Dig Dis. 2015;33(2):141-6.
10. White LE, Merrick VM, Bannerman E, et al. The Rising Incidence of Celiac Disease in Scotland. Pediatrics. 2013;132(4):e924-31.
11. Rubio-Tapia A, Kyle RA, Kaplan EL, et al. Increased Prevalence and Mortality in Undiagnosed Celiac Disease. Gastroenterology. 2009;137(1):88-93.
12. Myléus A, Hernell O, Gothefors L, et al. Early infections are associated with increased risk for celiac disease: an incident case-referent study. BMC Pediatr [Internet]. 2012 [citado el 22 de noviembre de 2016];12(1). Available from: http://bmcpediatr.biomedcentral.com/articles/10.1186/1471-2431-12-194.
13. Minsal Chile. Encuesta Nacional de Salud Chile 2009-2010. p. 1-1064 [Internet]. 2010. Available from: http://web.minsal.cl/portal/url/item/bcb03d7bc28b64dfe040010165012d23.pdf.
14. Lebwohl B, Green P. Risk of celiac disease according to HLA haplotype and country. N Engl J Med. 2014;371(11):1073-4.
15. Kemppainen KM, Lynch KF, Liu E, et al. Factors that Increase Risk of Celiac Disease Autoimmunity Following a Gastrointestinal Infection in Early Life. Clin Gastroenterol Hepatol [Internet]. 2016 [citado el 22 de noviembre de 2016]; Available from: http://linkinghub.elsevier.com/retrieve/pii/S1542356516310436.
16. Lundin KEA, Sollid LM. Advances in coeliac disease: Curr Opin Gastroenterol. 2014;30(2):154-62.
17. Shan L, Qiao S-W, Arentz-Hansen H, et al. Identification and Analysis of Multivalent Proteolytically Resistant Peptides from Gluten: Implications for Celiac Sprue. J Proteome Res. 2005;4(5):1732-41.
18. Telega G, Bennet TR, Werlin S. Emerging New Clinical Patterns in the Presentation of Celiac Disease. Arch Pediatr Adolesc Med. 2008;162(2):164.
19. Roma E, Panayiotou J, Karantana H, et al. Changing Pattern in the Clinical Presentation of Pediatric Celiac Disease: A 30-Year Study. Digestion. 2009;80(3):185-91.
20. Garnier-Lengliné H, Cerf-Bensussan N, Ruemmele FM. Celiac disease in children. Clin Res Hepatol Gastroenterol. 2015;39(5):544-51.
21. Ludvigsson JF, Sellgren C, Runeson B, Långström N, Lichtenstein P. Increased suicide risk in coeliac disease-A Swedish nationwide cohort study. Dig Liver Dis. 2011;43(8):616-22.
22. Cooper BT, Holmes GK, Cooke WT. Coeliac disease and immunological disorders. Br Med J. 1978;1(6112):537-9.
23. Giersiepen K, Lelgemann M, Stuhldreher N, et al. Accuracy of Diagnostic Antibody Tests for Coeliac Disease in Children: Summary of an Evidence Report. J Pediatr Gastroenterol Nutr. 2012;54(2):229-41.
24. Schwertz E. Serologic Assay Based on Gliadin-Related Nonapeptides as a Highly Sensitive and Specific Diagnostic Aid in Celiac Disease. Clin Chem. 2004;50(12):2370-5.
25. Tonutti E, Bizzaro N. Diagnosis and classification of celiac disease and gluten sensitivity. Autoimmun Rev. 2014;13(4-5):472-6.
26. Zevit N, Shamir R. Diagnosis of Celiac Disease: Where Are We Heading After the ESPGHAN 2012 Guidelines? J Pediatr Gastroenterol Nutr. 2014;59:S13-5.
27. Catassi C, Elli L, Bonaz B, et al. Diagnosis of Non-Celiac Gluten Sensitivity (NCGS): The Salerno Experts' Criteria. Nutrients. 2015;7(6):4966-77.
28. Ludvigsson JF, Leffler DA, Bai JC, et al. The Oslo definitions for coeliac disease and related terms. Gut. 2013;62(1):43-52.
29. Jericho H, Assiri A, Guandalini S. Celiac Disease and Wheat Intolerance Syndrome: a Critical Update and Reappraisal. J Pediatr Gastroenterol Nutr. 2016.
30. Elli L, Tomba C, Branchi F, et al. Evidence for the Presence of Non-Celiac Gluten Sensitivity in Patients with Functional Gastrointestinal Symptoms: Results from a Multicenter Randomized Double-Blind Placebo-Controlled Gluten Challenge. Nutrients. 2016;8(2):84.
31. Shahbazkhani B, Sadeghi A, Malekzadeh R, et al. Non-Celiac Gluten Sensitivity Has Narrowed the Spectrum of Irritable Bowel Syndrome: A Double-Blind Randomized Placebo-Controlled Trial. Nutrients. 2015;7(6):4542-54.
32. Sapone A, Lammers KM, Casolaro V, et al. Divergence of gut permeability and mucosal immune gene expression in two gluten-associated conditions: celiac disease and gluten sensitivity. BMC Med [Internet]. 2011 [citado el 22 de noviembre de 2016];9(1). Available from: http://bmcmedicine.biomedcentral.com/articles/10.1186/1741-7015-9-23.
33. Sapone A, Lammers KM, Mazzarella G, et al. Differential Mucosal IL-17 Expression in Two Gliadin-Induced Disorders: Gluten Sensitivity and the Autoimmune Enteropathy Celiac Disease. Int Arch Allergy Immunol. 2010;152(1):75-80.
34. Junker Y, Zeissig S, Kim S-J, et al. Wheat amylase trypsin inhibitors drive intestinal inflammation via activation of toll-like receptor 4. J Exp Med. 2012;209(13):2395-408.
35. Francavilla R, Cristofori F, Castellaneta S,

et al. Clinical, Serologic, and Histologic Features of Gluten Sensitivity in Children. J Pediatr. 2014;164(3):463-7.e1.
36. The Study Group for Non-Celiac Gluten Sensitivity, Volta U, Bardella MT, Calabrò A, Troncone R, Corazza GR. An Italian prospective multicenter survey on patients suspected of having non-celiac gluten sensitivity. BMC Med [Internet]. 2014 Dec [citado el 22 de noviembre de 2016];12(1). Available from: http://bmcmedicine.biomedcentral.com/articles/10.1186/1741-7015-12-85
37. Fasano A, Sapone A, Zevallos V, Schuppan D. Nonceliac Gluten Sensitivity. Gastroenterology. 2015;148(6):1195-204.
38. Kabbani TA, Vanga RR, Leffler DA, et al. Celiac Disease or Non-Celiac Gluten Sensitivity? An Approach to Clinical Differential Diagnosis. Am J Gastroenterol. 2014;109(5):741-6.
39. Quirce S, Boyano-Martínez T, Díaz-Perales A. Clinical presentation, allergens, and management of wheat allergy. Expert Rev Clin Immunol. 2016;12(5):563-72.
40. Östblom E, Lilja G, Pershagen G, van Hage M, Wickman M. Phenotypes of food hypersensitivity and development of allergic diseases during the first 8 years of life. Clin Exp Allergy. 2008;38(8):1325-32.
41. Matricardi PM, Bockelbrink A, Beyer K, et al. Primary *versus* secondary immunoglobulin E sensitization to soy and wheat in the Multi-Centre Allergy Study cohort. Clin Exp Allergy. 2008;38(3):493-500.
42. Zuidmeer L, Goldhahn K, Rona RJ, et al. The prevalence of plant food allergies: A systematic review. J Allergy Clin Immunol. 2008;121(5):1210-8.e4.
43. Pelz BJ, Bryce PJ. Pathophysiology of Food Allergy. Pediatr Clin North Am. 2015;62(6):1363-75.