ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Editorial

Advance in the Knowledge of Coeliac Disease

Carlos Castañeda Guillot[1,2]*

[1]*Emeritus Professor, Faculty of Medicine, Autonomous Regional University of Los Andes, Ambato, Ecuador*

[2]*Consulting Professor, Senior Research, Medicine Faculty Calixto García, Medical University of La Habana, Cuba*

Corresponding Author: Carlos Castañeda Guillot, Emeritus Professor, Faculty of Medicine, Autonomous Regional University of Los Andes, Ambato, Ecuador.

Received: February 08, 2023; **Published:** February 15, 2023

Abstract

Introduction: Celiac disease is an autoimmune condition with systemic repercussions with enteropathy, with a genetic predisposition due to permanent intolerance to gluten, with intestinal/extraintestinal clinical manifestations, in whose pathogenesis of autoimmunity modifications of the intestinal environment have been postulated.

Goals: To review the most current criteria on celiac disease and the participation of the intestinal microbiota in pathogenesis according to postulates in recent years.

Method: Publications in English were reviewed in PubMed, Google Scholar, ScieLO, January 2000-July 2022, using the following terms: celiac disease, pathogenesis, intestinal microbiota, intestinal barrier and intestinal permeability.

Analysis and interpretation of results: Studies report evident development of intestinal microbiota dysbiosis influenced by early intestinal infection, particularly viral, and the influence of antibiotic consumption as new possible mechanisms that increase the appearance of celiac disease in children with genetic predisposition to gluten ingestion, suggesting a microbiota role together with intestinal barrier alteration and permeability involved in pathogenesis.

Conclusion: Celiac disease is an autoimmune condition that in recent years it has been evaluated in pathogenesis association to intestinal microbiota dysbiosis and sequelae in barrier and intestinal permeability. These facts could play new mechanisms together with genetics and gluten that would be promising for therapeutics.

Keywords: *Celiac Disease; Pathogenesis; Microbiota Intestinal; Intestinal Barrier; Intestinal Permea*

Introduction

Celiac disease (CD) is a chronic autoimmune disorder triggered by the ingestion of gluten in genetically predisposed individuals. It is a condition of multisystemic manifestation that presents an inflammatory enteropathy, caused by permanent intolerance to gluten, by the consumption of wheat, barley and rye cereals in the diet [1].

The objective of the editorial is to review the most current criteria related to celiac disease and the participation of the intestinal microbiota in its pathogenesis by evaluating the arguments that have been put forward in recent years.

History of the disease

It is an ancient disease described by Aretaeus of Cappadocia in the 2nd century BC, designating it as a condition "of the one who suffers from the intestine". It was Samuel Gee, a pediatrician at St. Bartholomew's Hospital in London, who published his famous article in 1888 with a brilliant description of the clinical manifestations of the symptoms and signs of the disease in children. Likewise, he suspected it was due to a diet disorder; but it was not until 1950 that William Dicke, a Dutch pediatrician, discovered the relationship with foods containing gluten [1].

Since the 1970s, contributions have been made on new knowledge for the proper management of the disease. The development of serological markers anti-gliadin antibody, anti-endomysial antibody (EAA) and tissue anti-transglutaminase antibody IgA (tTG IgA) were decisive for the diagnosis. On the other hand, another contribution resulted: the discovery of the human leucocyte antigens (HLAs) DQ2/DQ8 susceptibility genes necessary for the development of the disease and the discovery of the tissue transglutaminase autoantigen. About 95% of the people with celiac disease have HLA DQ2 [1].

The disease presents a wide spectrum of clinical manifestations and damage to the small intestine mucosa with specific T cell immune responses, whose treatment consists of a lifelong gluten-free diet. However, it can be asymptomatic. It is also known as celiac sprue or gluten-sensitive enteropathy.

Epidemiology

At present, the increasing prevalence in different areas of the world is considered to be progressive, in relation to the global trend of increased consumption of wheat. This is significant in Europe and the United States, classic regions of high incidence, with spread to new Asian regions, in different countries, probably due to changes in eating habits.

CD is common worldwide, estimated at 0.5 - 1% in the general population in most countries, with higher occurrence in Caucasians, with high prevalence in Finland and Sweden at 2 - 3%. Since the 1970s, contributions have been made on new knowledge for the proper management of the disease. The development of serological markers (anti-gliadin antibody, anti-endomysial antibody and anti-transglutaminase antibody) were decisive for the diagnosis. On the other hand, another contribution resulted: the discovery of the HLA DQ2/DQ8 susceptibility genes necessary for the development of the disease and the discovery of the tissue transglutaminase autoantigen.

The prevalence in Europe and the USA varies in a range of 1:80 to 1:300 in children and more frequently in women than in men in a ratio of 2:1. In the countries with the highest incidence, it is estimated for each diagnosed case, there are 6 - 7 undiagnosed cases. In India, a prevalence of 1:96 is reported, but it is estimated that there may be between 5 and 8 million people with the disease, however, the number of diagnosed patients is low. Studies reported in the Latin American region suggest it is common, according to reports from Brazil (0.5% in children), Argentina (1:167 prevalence in adult population), Chile, Uruguay, Cuba, Mexico, and Peru. Likewise, it has been described in North African countries, with the possibility of underdiagnosis in many countries of the region. Serological research studies have reported a high incidence in the population of countries in North Africa, South Asia and the Middle East.

Pathogeny

In the pathogenesis of the disease the intervention of factors of a genetic nature, immunity factors, represented by the immunological response for the appearance of the disease and environmental factors are essential; due to gluten, as a specific trigger factor, together with the consumption of breast milk and the introduction of gluten.

In recent years, changes in the natural history of the disease, pathogenesis, and diagnosis have been of interest to the scientific community. Arguments about novel intestinal microenvironment factors involved in the development of CD have been described, such as a viral intestinal infection and the use of antibiotics.

The Oslo classification, in 2011 referred to the presentation of CD phenotypes in classic, non-classical, subclinical, potential and refractory, was changed in recent years by groups of experts who modified the classic/non-classical categories used, Intestinal/extraintestinal form or their combination [1-3].

Among these new contributions, the interest in the participation of IM in the pathogenesis of the disease stands out. Studies of the gut microenvironment have reported intestinal Rotavirus infections in children and *Campylobacter* infections in adults, which seem to increase the risk for the development of CD. Likewise, the use of antibiotics and proton pump inhibitors has also been associated with an increased risk of developing the disease. In the pathogenesis of the disease, the intervention of factors of a genetic nature, immunity factors, represented by the immunological response for the appearance of the disease, and environmental factors are essential; due to gluten, as a specific trigger element, together with the consumption of breast milk and the introduction of gluten.

Early disruption of the intestinal barrier coupled with intestinal microbiota dysbiosis have been suggested as inducers in the pathogens intestinal microbiota of CD [4-6]. On the other hand, it has been stipulated that the variations in the course of the disease, independent of compliance with gluten free diet, may be dependent on the integration of the intestinal barrier and its microbiota. The onset of CD in childhood is classic, but it can present in young adults over 30 years of age or in the elderly, which may be related to the loss of barrier function.

Dysbiosis and CD

Studies related to the dysbiosis of the intestinal microbiota in CD have been reported for more than 10 years [7,8] demonstrating evidence of the imbalance in its composition in different series. In infants, a significant decrease was found in the proportions of unclassified *Bifidobacteria* and *Bifidobacteriaceae*. A higher number of *Bacteroides* and a lower proportion of the number of *Bifidobacterium* spp and *B. longum* were also demonstrated [9]. These results support the changes in the ecology of the intestine in relation to controls due to dysbiosis in celiac patients with repercussions on the local microenvironment of the intestine.

The reports in celiac patients allow us to affirm that dysbiosis has repercussions in three directions: 1) marked increase in the inflammatory process of the intestinal mucosa, 2) decreased gluten degradation, and 3) increased intestinal permeability. Among the consequences, the role of immunotoxic peptides and a greater load of antigens for immune cells stand out.

Diagnostic guides

The European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) in 1969 established the criteria of three jejunal biopsies for the diagnosis of the disease, which was modified in 1990 to a single biopsy, with new arguments in more recent years that have modified the initial criteria. Similarly, the initially test challenge postulated as mandatory for all cases, was reduced only to children under 2 years of age and is currently an exceptional study.

In 2012 ESPGHAN published the new Diagnosis Guide for the disease in children and adolescents, which for the first time defined it as "an immunologically-based systemic disorder" and also contemplated for the first time the possibility of diagnosis without biopsy based on 4 requirements: 1) symptoms compatible with the disease with: 2) anti-transglutaminase antibody, at levels 10 times normal, 3) positive anti-endomysium antibody (EAA), and 4) HLA DQ2 and DQ8 haplotypes, results that did not require an intestinal biopsy for diagnosis. Enteropathy was considered as an element more of the diagnosis, not as an indispensable criterion [4,10].

In 2020, a new version was published with novelties for the diagnosis without biopsy in children and adolescents that replaced the previous one from 2012, considering that in some asymptomatic patients with specific diagnostic criteria for CD, the intestine biopsy could be omitted. Likewise, the HLA haplotype is not necessary for diagnosis without intestinal biopsy in IgA deficiencies and asymptomatic patients with type 1 diabetes mellitus, intestinal biopsy is mandatory.

Conclusion

CD is an autoimmune condition with a historically recognized cause, however, in recent years the addition of a new mechanism in favor of its appearance has been stipulated, which postulates the genetic condition and gluten as a trigger are not enough and support the microbiota dysbiosis of the disease. Intestinal microbiota and alterations in the intestinal barrier and permeability are associated with the pathogenesis. There is evidence that the host-microbiota homeostasis is disrupted in CD patients.

The ESPGHAN Diagnostic Guidelines (2012 and 2020) established decisive criteria for children and adolescents, with modifications resulted from of the experiences of the experts with the aim of achieving an accurate and early diagnosis of the condition.

Studies in the first years of life report exposure to an early infection, especially intestinal, presumably viral, and the consumption of antibiotics as conditions that favor the development of microbiota dysbiosis, which suggests the possibility of increased CD in the child, holder of the conditions of susceptibility to suffer from the disease.

Further research on this criterion and manipulation of the intestinal microbiota by biotherapy with probiotics and prebiotics [11,12] to restore the imbalance of microbial composition that determines its dysbiosis and the interrelationship with gluten will outline future strategies for the treatment of CD.

Bibliography

1. Alkalay MJ. "Update on celiac disease". *Current Opinion in Pediatrics* 32.5 (2020): 654-660.
2. Nellikkal SS., *et al*. "High prevalence of celiac disease among screened first-degree relatives". *Mayo Clinic Proceedings* 94 (2019): 18071813.
3. Ludvigsson JF., *et al*. "The Oslo definitions for coeliac disease and related terms". *Gut* 62 (2013): 43-52.
4. Chander AM., *et al*. "Cross-Talk Between Gluten, Intestinal Microbiota and Intestinal Mucosa in Celiac Disease: Recent Advances and Basis of Autoimmunity". *Frontiers in Microbiology* 9 (2018): 2597.
5. Lebwohl B and Sanders DS. "Green P.H:S. Coeliac disease". *Lancet* 391 (2018): 78-81.
6. Cukrowska., *et al*. "Intestinal epithelium, intraepithelial lymphocytes and the gut microbiota - Key players in the pathogenesis of celiac disease". *World Journal of Gastroenterology* 23 (2017): 7505-7518.
7. Cardoso-Silva D., *et al*. "Intestinal Barrier Function in Gluten-Related Disorders". *Nutrients* 11.10 (2019): 2325.
8. Cenit MC., *et al*. "Intestinal Microbiota and Celiac Disease: Cause, Consequence or Co-Evolution?" *Nutrients* 7.8 (2015): 6900-6923.
9. Olivares M., *et al*. "Double-blind, randomized, placebo-controlled intervention trial to assess the effects of *Bifidobacterium longum* CECT 7347 in children with newly diagnosed celiac disease". *Journal of Nutrition* 112 (2014): 30-40.

10. Husby S., *et al*. "European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for diagnosing coeliac disease in children and adolescents. An evidence based approach". *Journal of Pediatric Gastroenterology and Nutrition* 54 (2012): 136-160.

11. Román Riechmanna E., *et al*. "National application of the new European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) 2020 criteria for the diagnosis of celiac disease". *AN Ped* 92.2 (2020): 110e1-110e9.

12. Rueda GH y and Pinto-Sánchez MI. "Probióticos para enfermedad celíaca ¿estamos listos para su aplicación en la enfermedad celíaca?" *Revista ACTA Gastroenterológica Latinoamericana* 51.4 (2021): 394-402.

Volume 10 Issue 1 January 2023