ORIGINAL ARTICLE

Celiac Disease: an emerging disease?

Carlos Castañeda-Guillot

Abstract
Celiac disease criteria are reviewed, disease characteristics in children and adults, epidemiology, clinical manifestations, associations and complications. Methods of immunological and anatomo-pathological diagnosis and treatment are presented. Attention is drawn to its diagnostic importance as an emerging disease in the Latin American region, as it is a poorly diagnosed condition in the Central American and Andean countries.

Key words
celiac disease, epidemiology, diagnosis, treatment

■ INTRODUCTION

Celiac disease (CD) can be considered an ancient disease. It was described in England in 1888 by Samuel Gee, considered one of the forefathers of European Pediatrics and Pediatric Gastroenterology, as a digestive disease of childhood with predominance of diarrhea and emaciation. However, it was not until the end of World War II that the Dutch pediatrician Dicke associated this condition with the ingestion of wheat. (1,2) Today it is distributed worldwide and is evaluated as a chronic autoimmune disease with clinical variations regarding the classic intestinal form, which explains the high frequency of diagnostic reports in different latitudes (3–6).

The objective of this article is to disseminate the most important aspects related to the diagnosis of CD for the medical community of Belize and neighboring countries.

CONCEPT

CD is a chronic autoimmune systemic disorder triggered by permanent gluten intolerance in individuals with genetic predisposition (mainly HLA). It is characterized by various intestinal and extra-intestinal clinical manifestations, association to immune and non-autoimmune diseases and severe gluten-dependent complications. The recovery from the symptoms, nutritional status and degree of change of the jejunum histopathology as main clinical feature of the disease occur when a diet free of gluten-containing foods is established.(3–7)

1 MD, Specialist in Pediatric Gastroenterology,
Full Professor and Research Analyst.
Faculty of Medical Sciences, Regional Autonomous
University of the Andes, Ambato, Tungurahua, Ecuador.
Consulting Professor. Senior researcher.
Calixto García Faculty of Medicine. Havana
University of Medical Sciences, Cuba.
Email: ccastanedag14@gmail.com

CD, considered until a few years ago as a gluten-sensitive enteropathy, is now defined as a systemic immune process mediated by T lymphocytes due to alterations caused by gluten and related prolamins in genetically susceptible individuals and enteropathy is not a primary clinical element.(1)

CD has received different names. The most well-known term is 'celiac sprue', coming from the eighteenth century Dutch word 'spruw', to designate the condition by the presence of oral thrush or aphthous stomatitis.(1,8)

Different diagnostic guides have been established by the most prestigious international scientific medical societies (European, North American, Latin American) related to Pediatrics and Gastroenterology, providing the current criteria based on updated sources for its study, diagnosis and treatment.(9–12)

■ EPIDEMIOLOGY

In the first half of the 20th century, CD was a rare, scarcely known disease. Dicke's observation that his patients in the Netherlands showed clinical improvement during the war years, despite nutritional shortages, because they did not eat wheat-based foods such as bread and derived products was decisive for its diagnosis and treatment. When the war ended and wheat was again harvested and consumed, clinical symptoms reappeared in the children, causing it to be considered the disease trigger because of its presumably toxic effect. This analysis was transcendental for the disease knowledge. Years later, together with colleagues Van de Kamer and Weijers, the involvement of gluten, a protein fraction of wheat, was established, as the determinant of intestinal malabsorption in CD.(1) In 1955, Shiner, by designing a kit to obtain a biopsy sample of jejunal mucosa,

and Crosby in Puerto Rico, by making the models of peroral capsules for adults and children, initiated a new stage in the understanding of the intestinal effect of CD.(8)

In the following years, studies of CD incidence and prevalence started to generalize, since it was important in countries with predominance of wheat consumption. It was reported to have high frequency from the second half of the twentieth century in the European continent and Australia, in populations of Caucasian ancestry. In North America before the 1990s, it was rarely diagnosed (1: 10,000), but research in the US later made it possible to assert its high prevalence (1: 111 to 1: 250) at the onset of the New Millennium, similar to Europe.(6,13,14)

In the Latin American context, in Argentina, a country with a high wheat consuming population, CD diagnosis started at the end of the '60s and the beginning of the '70s of the twentieth century, followed by Uruguay and Brazil. (6) At that time Charlotte Anderson, the Australian expert pediatric gastroenterologist at the Birmingham Children's Hospital in the United Kingdom, postulated this was "a disease of blue-eyed blond children". However, in other countries such as Cuba, the diagnosis of CD began in the early '70s,(6,16–20) which was a great impact, because the Cuban people are a highly mixed population from a racial viewpoint, The result of the interaction and racial mixing of whites of Spanish origin, African blacks and American aborigines since the sixteenth century and later Chinese, in the twentieth century, has determined that the population is not homogenous from an anthropological point of view. Cuba has a high number of mulattoes and mestizos, so that it is defined as a heterogeneous population.(21)

At present CD is reported in a 1% to 2% ratio in the Western European and American populations, affecting children and adults of any age, including the elderly, over 65 years of age. There is a predominance of female over male cases of 2 to 1 and a worldwide prevalence of 1/266.(1,4,5,14).

In light of its diagnosis, CD has been reported in different regions of the world. The country with the highest prevalence in the world is the Saharawi Arab Democratic Republic, in the north-west of the African continent, a population of Arab-Berber origin with CD prevalence of 5.4%,(6,22) followed by Finland with 5% prevalence.

In Latin America, in the southern cone, Argentina reports the highest prevalence, with one celiac case per 80 children and per 100 adults,(24), and in Uruguay, 1 per 100 inhabitants. (25) In addition, the diagnosed/undiagnosed celiac ratio is 1/8, according to figures reported in 2014 by the Argentine Celiac Association.(14) In Mexico, the studies performed report a range between 0.72% and 2.7%, which is similar to European countries.(26)

In the Andean and Central American countries it is still poorly diagnosed and evaluated as of low prevalence,(27,28) but it is becoming an "emerging disease",(29,30) because of its appearance in different countries of the region.(28,31,32)

In other continents, such as Africa, there is a high prevalence in the Arab countries of its northern region, which are high wheat consumers, and in some countries of Sub-Saharan Africa, such as South Africa and Burkina Faso.(6) In the Middle East, where cereal consumption is also important, high prevalence is reported, as is also the case in the Asian continent in India.(6) In Oceania, the prevalence in Australia and New Zealand is similar.(6,33) However, in countries of the Asia-Pacific region, as China it is scarcely reported; it is not diagnosed at all only in the northern provinces, and in Japan.(6)

■ PHYSIOPATHOLOGY

There are three factors involved in the physiopathology of CD. They are the environmental factor, represented by the ingestion of wheat because of its gluten content and other cereals such as barley and rye for their prolamin content, with similar effect to gliadin, protein portion contained in gluten. (1,2) The immune factor triggered by gliadin is characterized by the presence of autoantigen, production of antibodies and activation of lymphocytes in the intestinal lamina propria with cytokine release, events caused by innate and adaptive genetic mechanisms. The genetic factor is expressed by the presence of genes DQ2 and DQ8 of the HLA class II histocompatibility complex that activate specific intestinal T lymphocytes, which are determinants of the destructive lesions in the intestine, characteristic of CD.(1–5)

■ CLINICAL FEATURES

In recent years new criteria have been described concerning the presentations of the disease, following the representation of an iceberg, where the prominent portion is the expression of typical clinical symptoms of intestinal malabsorption and the hidden portion is the atypical disease expression of extra-intestinal symptoms of the disease and subclinical, asymptomatic and potential forms. It has been argued that extra-intestinal manifestations are related to the presence of antibodies and abnormal immune responses (Table 1).
The clinical manifestations expressed by symptoms and signs vary depending on whether the patients are children, adolescents or adults (Tables 2 and 3).(1,35)

Table 1. Celiac disease presentations - Oslo Criteria, 2013

- Classical: full-blown symptoms of intestinal malabsorption
- Symptomatic: with intestinal and extra-intestinal symptoms
- Non-classical: with symptoms, but no intestinal malabsorption
- Asymptomatic: absence of clinical symptoms, equivalent to the silent form
- Subclinical: few symptoms, with altered laboratory tests
- Potential: positive serology and normal duodenum-jejunum biopsy

Source: Ludvigsson JF, Leffler DA, Bai C, Biagi J, Fasano A, Green PHR, et al. The Oslo definitions for coeliac disease and related terms.(34)

■ LABORATORY TESTS

Hemoglobin, serum iron and folate determinations evidenced the characteristics of anemia. Total protein,

Table 2. Clinical manifestations

Clinical symptoms		
Children	**Adolescents**	**Adults**
Chronic diarrhea Abdominal pain Vomiting Low size Anorexy Apathy, sadness Irritability	Asymptomatic Abdominal pain Arthralgia Constipation Headache Delayed menarche Menstrual disorders	Dyspepsia Chronic diarrhea Abdominal pain Irritable bowel syndrome Bone and joint pain Infertility Recurrent abortions Paresthesia, tetany

Source: Polanco I. Enfermedad celíaca. Presente y futuro. Madrid (1)

Table 3. Clinical manifestations

Clinical signs		
Children	**Adolescents**	**Adults**
Malnutrition Abdominal distension Muscle hypotonia Weight-height delay Iron deficiency anemia	Oral aphtae Tooth enamel hypoplasia Abdominal distension Short stature Arthritis Osteopenia Follicular keratosis Iron deficiency anemia Dermatitis herpetiformis	Malnutrition with or without weight loss Dermatitis herpetiformis Peripheral edemas Short stature Peripheral neuropathy Iron deficiency anemia Hypertransaminasemia Hyposplenism

Source: Polanco I. Enfermedad celíaca. Presente y futuro (1)

serum calcium, phosphorus, magnesium and alkaline phosphatase quantitation are useful as indicators of malabsorption. Studying the excreted fat balance will allow establishing fat malabsorption. Hypertransaminasemia may be an asymptomatic form of disease presentation in up to 40% of cases.(1,8)

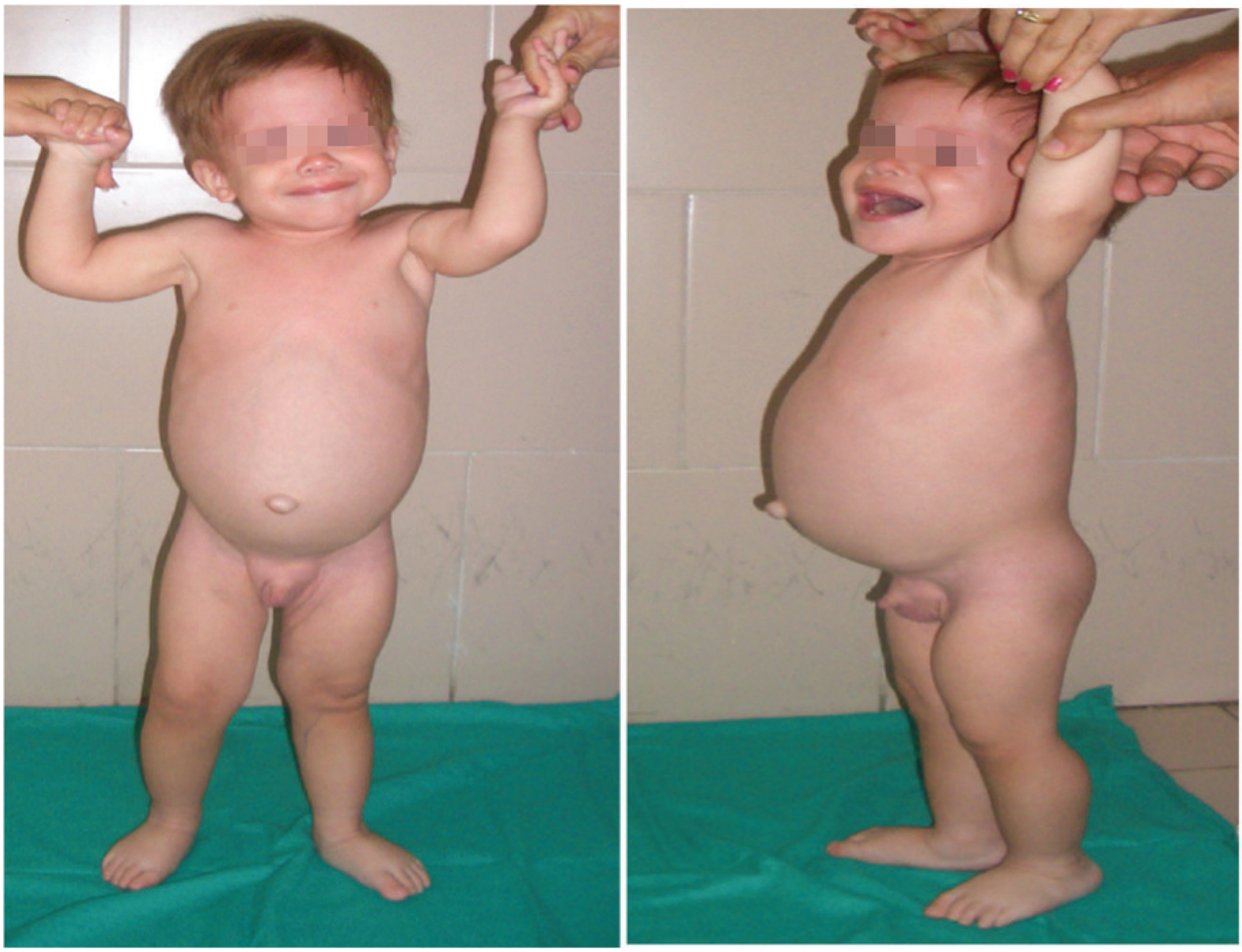
Bone studies

The degree of osteopenia, osteoporosis and bone mass measured by bone mineral densitometry may demonstrate bone involvement caused by intestinal malabsorption of calcium and vitamin D.(8)

Immunological tests

Immunological tests to determine antibody presence have provided a wide range of tools to guide diagnosis and screening studies in risk groups and first-degree relatives with a predictive value of interest.(35)

Antibody detection is performed by different methods: enzyme immunoassay (Elisa) and indirect immunofluorescence. (36) Immunoglobulins of IgA and IgG classes are used with variable degrees of sensitivity and specificity. IgA type tissue anti-transglutaminase antibody is now the most accepted for its management, cost, sensitivity (61%–100%, average 87%} and specificity (86%–100%).(37,38) Others, such as the anti-



Figures 1a and 1b. Classical presentation, 16 month-old child. Marked abdominal distension. Photo of author's case. Patient of the Pediatrics Section of the National Institute of Gastroenterology. Havana, 2009.

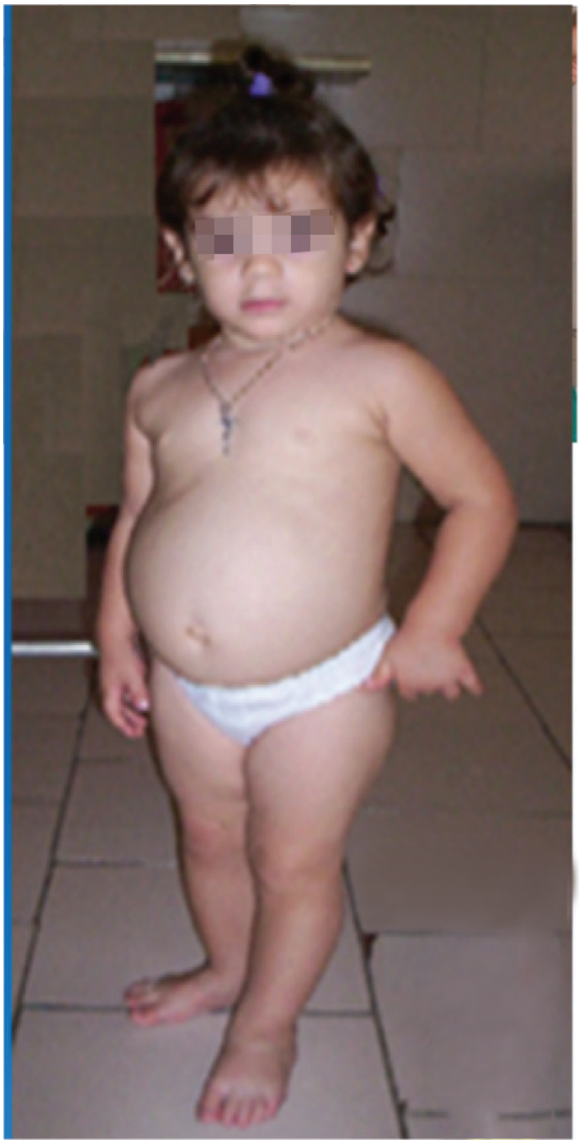


Figure 2. Classical presentation. 4 year-old girl. Marked abdominal distension. Photo of author's case. Patient of the Pediatrics Section of the National Institute of Gastroenterology. Havana, 2009.

gliadin antibody, is now less used due to its lower sensitivity. The anti-endomysium antibody has high sensitivity and specificity, but the interpretation of its immunofluorescence requires specialized personnel and sections of endomysial tissue of monkey esophagus or umbilical cord as substrate, where the antibodies become fixed.(39) Gliadin deamidated peptides (IgG and IgA) that appeared in recent years also provide high sensitivity and specificity(40) and their negative predictive value is very high. In childhood, absence of these antibodies rules out CD. Serum IgA decrease in up to 10% of celiac cases advises the determination of serum immunoglobulin to prevent a false-negative result in specific immunological studies to demonstrate CD.

Histopathological examination

Over the years the duodenum-jejunum biopsy has been considered the gold standard test. At present obtaining different samples of duodenum and jejunum mucosa by digestive endoscopy is recommended. There are variations of mucosal and lamina propria lesions with varying degrees of severity. The features include mainly partial to total atrophy, elongated crypts, decreased villus/crypt ratio, increases in epithelial lymphocyte infiltrate that will make it possible to demonstrate compatibility with the intestinal damages of the disease.(1,9) The Marsh classification, modified by Oberhuber, known as Marsh-Oberhuber Criteria (42,43) is accepted and recommended by the Diagnostic Guides of the International Scientific Societies,(9–12) especially the criteria weighted by the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN). (1,2,9)

■ ASSOCIATED DISEASES

Dermatitis herpetiformis (DH) or Duhring's disease, also known as 'skin celiac disease' is an external sign of gluten intolerance. It can present as an associated autoimmune condition or a dermatological expression of CD itself. They are vesicular scabby rashes, symmetrical, grouped in the form of plaques, which are very itchy. They appear anywhere in the body, especially in the arms and legs. It occurs in adolescents and young adults. DH is an unequivocal sign (100%) of associated CD. In 90% of the cases, it is not associated with digestive symptoms and only 75% present damage of the intestinal mucosa (atrophy of intestinal villi). (1,44)

Associated diseases may have an autoimmune cause, due to identical HLA haplotype shared. The most frequent ones are type 1 diabetes mellitus (8%), autoimmune thyroid diseases (Hashimoto's thyroiditis), selective IgA defect (4%), Addison's disease, Sjögren's syndrome and different forms of arthritis. Autoimmune cholangitis, autoimmune hepatitis, primary biliary cirrhosis and IgA nephropathy have also been described. Many of the autoimmune diseases associated with celiac disease have a higher rate in these patients than in the normal population.(1) Other non-autoimmune associations of CD are with Down syndrome (5–16%), Williams syndrome (8%), Turner syndrome and cystic fibrosis.(1,8) Several neurological disorders such as epilepsy and bilateral occipital intracranial calcifications (Gobbi syndrome: celiac disease, epilepsy and intracranial calcifications, described in 1992),(45) cerebellar syndrome and dementia with brain atrophy have been described.(2) Association studies in diabetes mellitus and Down syndrome conducted in Cuba reported a prevalence of 2.4% and 2.2%, respectively.(46)

■ COMPLICATIONS

Celiac crisis is the most frequent complication, but it is not common, it consists of a severe crisis of the disease. Refractory celiac disease is present when the patient does not respond to the gluten-free diet treatment, which is also uncommon. Both severe presentations are characterized by the impact on the patient's general condition.(1,8)

In childhood, malignant diseases are exceptional and rare in the young adult. The age of onset is over 40 years. Intestinal

T-cell non-Hodgkin's lymphoma is the most frequent and the remaining are epithelial neoplasias of the digestive system such as small bowel adenocarcinomas (jejunum), squamous cell carcinomas of the mouth, pharynx and esophagus. Thyroid papillary carcinoma has also been described.(1,3–5,8)

Compliance with a gluten-free diet for more than 10 years renders the risk of developing neoplasms or autoimmune diseases similar to the risk of the general population, which emphasizes the importance of performing the diagnosis in childhood and adolescence.(8)

■ DIAGNOSIS

Suspicion of the disease due to clinical manifestations advises serological testing (anti-transglutaminase antibody, tTGA and endomysium antibody, EMA) and confirmation of intestinal involvement by duodenum and/or jejunum biopsy to establish the CD diagnosis. The intestinal lesion shown by biopsy is characteristic of the condition, but not pathognomonic.(1) The diagnostic guidelines established in recent years by different international scientific medical societies, especially those recommended by the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), guide the fundamental aspects approved.(9) Historically, ESPGHAN postulated that diagnosis is based on the anatomopathological findings of the biopsy when a gluten-containing diet is consumed and the clinical and histological normalization after its exclusion. Today, the need for the initial intestinal biopsy is questioned in those cases in which the quantitative value of the tTGA is ten times higher than normal.(1,2) The performance of the second biopsy and the gluten overload test, recommended in 1969, have been relegated only to uncertain cases by ESPGHAN in 2012.(9)

Differential diagnosis

Differential diagnosis varies according to the clinical manifestations and age. In the child presenting chronic diarrhea with or without intestinal malabsorption, other causes such as parasitic diseases (giardiasis and cryptosporidiosis), environmental diarrhea, persistent diarrhea, allergy to cow milk protein, autoimmune enteropathy and cystic fibrosis should be evaluated.(8) Steatorrhea also requires distinguishing from exocrine pancreatic insufficiency and intestinal bacterial overgrowth. It is important to rule out irritable bowel, especially in the adolescent and young adult.(47) Among mono-symptomatic presentations, iron deficiency anemia occurs more frequently in childhood and adulthood. In short stature school-children and adolescents, it is a non-digestive cause to be considered. (1,8) The association with *Giardia lamblia* is frequent and can cause diagnostic error if not excluded.(8)

■ THERAPY

The only treatment consists of a strict diet free of foods containing wheat, barley and rye cereals, since they contain gluten and prolamins, proven to cause CD. The elimination of toxic cereal ingestion is for life. Oats can be administered, although there are criteria about the risk that they may be contaminated with gluten when harvested, ground or transported.(1) The diet should be based on natural foods and forbidden cereals should be substituted by corn, rice and sorghum. Clinical response is remarkable, with rapid resolution of the clinical manifestations in the various forms of the condition. Normalization of the nutritional status is evident expression of diet compliance. Histological lesions of the jejunum occur for 12 to 16 months in 90% of patients with gluten free-diet.(9–12)

Diet compliance will determine the quality of life, which can be complex due to conscious or inadvertent transgression. (1,48) Lack of awareness of gluten presence in manufactured products is a factor to be avoided. It is necessary to achieve that they are labeled regarding the presence or absence of gluten in all countries. Thickeners, flavorings or preservatives may contain gluten. Gluten-free food should not exceed 200 ppm, according to the Codex Alimentarius. (1,2) Many patients, when diagnosed, can tolerate small amounts of lactose; although, in the severe form, lactose should be suppressed until clinical and histological recovery is achieved. Regarding treatment, administration of vitamins and minerals will enable correction of their deficiencies until recovery.(1, 9–12)

■ PROGNOSIS

Undiagnosed CD in childhood and adolescence presents greater severity of long-term morbidity and mortality. Unperformed or delayed diagnosis or non-compliance with the gluten-free diet are determinants of poor prognosis. Intestinal non-Hodgkin's lymphoma is the leading cause of death.

■ CONCLUSIONS

CD diagnosis is a challenge for the general practitioner and related medical specialties, such as Pediatrics and Gastroenterology, especially in those countries where it is a poorly diagnosed or inadequately known condition.

Diagnostic criteria guided by clinical manifestations will be confirmed by immunological tests and the histology of the small intestine (duodenum-jejunum) mucosa. The determination of the HLA haplotypes DQ2 and DQ8 is of importance, since their absence discards CD in more than 98% of cases.

The importance of the studies that have been performed in recent years in the Andean and Central American countries leading to the demonstration of CD, make it a challenge as an emerging disease in these regions, since most celiac cases remain undiagnosed.

Today it is crucial to spread the criteria for diagnosis and treatment of the 'celiac condition', to accomplish with proper medical care that they are "healthy people, who eat different."(1)

Enfermedad celíaca ¿enfermedad emergente?

Resumen

Se revisan los criterios de la Enfermedad Celíaca, sus rasgos en la infancia y el adulto, la epidemiología, las manifestaciones clínicas, las asociaciones y las complicaciones. Se exponen los métodos de diagnóstico inmunológico y anatomopatológicos y el tratamiento. Se llama la atención sobre la importancia diagnóstica como enfermedad emergente en la región de Latinoamérica al ser una afección poco diagnosticada en los países centroamericanos y andinos.

Palabras clave

enfermedad celíaca, epidemiología, diagnóstico, tratamiento

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