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Review

Diagnosis and classification of celiac disease and gluten sensitivity

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ABSTRACT

Celiac disease is a complex disorder, the development of which is controlled by a combination of genetic (HLA alleles) and environmental (gluten ingestion) factors. New diagnostic guidelines developed by ESPGHAN emphasize the crucial role of serological tests in the diagnostic process of symptomatic subjects, and of the detection of HLA DQ2/DQ8 alleles in defining a diagnosis in asymptomatic subjects belonging to at-risk groups. The serological diagnosis of CD is based on the detection of class IgA anti-tissue transglutaminase (anti-tTG) and anti-endomysial antibodies. In patients with IgA deficiency, anti-tTG or anti-deamidated gliadin peptide antibody assays of the IgG class are used. When anti-tTG antibody levels are very high, antibody specificity is absolute and CD can be diagnosed without performing a duodenum biopsy. Non-celiac gluten sensitivity is a gluten reaction in which both allergic and autoimmune mechanisms have been ruled out. Diagnostic criteria include the presence of symptoms similar to those of celiac or allergic patients; negative allergological tests and absence of anti-tTG and EMA antibodies; normal duodenal histology; evidence of disappearance of the symptoms with a gluten-free diet; relapse of the symptoms when gluten is reintroduced.

Contents

1. Introduction

Celiac disease (CD) is a chronic, immune-mediated, gluten-induced gut disorder that manifests itself with a range of clinical symptoms in genetically susceptible subjects. Immune reaction to wheat, barley and rye gliadin fractions and glutenins [1] triggers an inflammatory state of the duodenal mucosa: the result is reduced intestinal villus height and hyperplastic cryptae that may lead to complete villus atrophy. The critical role played by gluten is demonstrated by the fact that in CD patients on a gluten free diet (GFD) clinical symptoms disappear, anti-transglutaminase 2 antibodies (anti-tTG2, the serological markers of the disorder) normalize, and villus atrophy recedes. As to the role of genetic factors, CD development has been demonstrated to be closely associated with MHC class II HLA-DQ2 and HLA-DQ8 molecules; in fact, virtually all CD patients express at least one of these HLA molecules compared to the general population in which about 30–35% have either DQ2 or DQ8 [2,3].

A new gluten-associated clinical condition, named 'non-celiac gluten sensitivity' (NCGS) [4], also described in literature as gluten hypersensitivity or gluten intolerance, has been recently identified. NCGS is characterized by gastrointestinal or extraintestinal symptoms comparable, in many cases, to those of CD patients; however, to date no specific immunological mechanisms or serological markers have been identified for this disorder. The diagnosis is made by exclusion of CD or IgE-mediated allergy to wheat, and is based on the direct association between gluten ingestion and symptom onset.

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2. Pathogenesis

CD is initiated by the ingestion of gliadin which is present in foods containing wheat, barley and rye. It is well established that the pathogenic mechanism is related to an alteration in the integrity of the tight junction system of intestinal epithelium cells, enabling the passage of macromolecules such as gluten in the submucosa. Gluten is an excellent substrate for transglutaminase 2 (TG2, also known as tissue transglutaminase). This enzyme converts glutamine residues into negatively charged glutamate residues in a process termed deamidation, thus facilitating the binding of gliadin peptides to HLA antigens of class II DQ2 or DQ8 expressed on antigen presenting cells. HLA DQ2- or DQ8-restricted CD4 T cells are critical to the pathogenesis of CD. These cells recognize gluten selectively in the context of HLA-DQ2 or DQ8 molecules and are present only in the small intestinal mucosa of individuals with CD. A high number of cytotoxic intraepithelial T lymphocytes (IELs) that express activating NK cell receptors are also present in these patients. These cells, which are responsible for intestinal mucosal damage, are found in higher numbers in the presence of villus atrophy. CD patients develop autoantibodies against TG2 as well as to gluten (antibodies against deamidated gliadin peptides — DGP) suggesting that CD has an autoimmune component [5]. The relationship between CD and autoimmunity is further supported by epidemiological studies that show a link between CD and autoimmune disorders as type I diabetes and autoimmune thyroiditis [6].

Unlike CD, patients with NCGS are not affected by alterations of mucosal tight junctions or cytokine increases; conversely, there is evidence of overexpression of Toll-like receptor 2, a marker of innate immunity activation. It has therefore been proposed that NCGS and CD are different clinical syndromes and that NCGS may be associated with gluten-induced activation of innate, rather than adaptive, immune response [7].

3. Epidemiology

The development of highly sensitive immunological methods for identifying diagnostic antibodies (e.g. anti-tTG autoantibodies and anti-DGP antibodies) has enabled an increasing number of CD patients with vague or asymptomatic clinical presentations to be identified. Population-based studies now indicate that approximately 0.5–1% of the Western European and Northern American populations suffer from CD. In a recent paper, Abadie and coworkers [8] correlate gluten consumption with HLA DQ2 and DQ8 haplotype frequency in the populations of the different world countries. The authors found a significant correlation between CD prevalence and wheat consumption, and between CD prevalence and DQ2–DQ8 frequency in most countries. However, outlier countries have been observed: Finland and Russia, for example, have similar wheat consumption levels and comparable HLA haplotype frequencies, but the prevalence of CD in Finland is 1–2.4% whereas in the adjacent Russian republic of Karelia the prevalence of CD is considerably lower (0.2%). In the Maghreb area, wheat and barley are the major staple foods. Despite similar frequencies of the DR3–DQ2 and DR4–DQ8 haplotypes, the prevalence of CD in Algeria (5.6%) is by far the highest reported worldwide, whereas CD prevalence in Tunisia (0.28%) remains one of the lowest. These observations suggest that similar levels of wheat consumption and predisposing HLA expression can be associated with strikingly different levels of CD prevalence, which suggests the role of environmental factors and other genetic factors in CD pathogenesis.

NGCS epidemiological data are too scarce to provide positive information. Fasano's team [4] reports a 6% prevalence in a population of patients who presented to Maryland gastroenterology clinics; this finding obviously does not refers to the general population, but to a selected population with clinical problems of a gastrointestinal nature.

Bisiekierski [9] recently demonstrated, through a double blind study, that 30–40% of patients with inflammatory bowel syndrome diagnosed by Rome III criteria are NCGS patients, as just one week after reintroduction of gluten into their diet they experience abdominal distension and pain.

4. Clinical manifestations

CD is characterized by multiple clinical expressions. An ESPGHAN (European Society for Paediatric Gastroenterology, Hepatology and Nutrition) working group has recently developed new guidelines for the diagnosis of CD based on scientific and technical developments using an evidence-based approach [10]. The ESPGHAN working group decided to revise the classification, also taking into consideration signs and symptoms that had not been considered in the previous classification. In particular, it was deemed advisable to eliminate the distinction between classic and atypical CD based on symptoms, as atypical signs and symptoms (e.g. anemia, neuropathy, reduced bone density) may be considerably more common than classic symptoms (e.g. chronic diarrhea). Table 1 provides an extensive list of symptoms and signs of CD in children and adolescents. Conversely, the definitions of silent, latent and potential CD are still valid. Silent CD is defined as presence of positive serology (anti-tTG IgA or IgG in IgA deficient subjects), of HLA alleles compatible with CD, and of histological alterations typical of CD, in patients not affected with CD symptoms. Latent CD is defined as presence of compatible HLA without gastrointestinal symptoms in patients who have had a gluten-dependent enteropathy at some point of their life. Potential CD is defined as the presence of CD-specific antibodies and compatible HLA, without histological abnormalities in duodenal biopsies [10].

Patients suffering from certain disorders (especially Hashimoto's thyroiditis, type I diabetes, IgA deficiency and Down's syndrome) have a higher risk of developing CD than the normal population. In these patients it is advisable to perform HLA DQ2/DQ8 and serological tests for CD even in the absence of symptoms.

CD and NGCS cannot be distinguished clinically, since the symptoms experienced by NGCS patients are often seen in CD. The definition of NGCS is a gluten reaction in which both allergic and autoimmune mechanisms have been ruled out (diagnosis by exclusion criteria). Specifically: symptoms similar to those of celiac or allergic patients must be present; in vivo and in vitro wheat allergy tests (prick test and specific IgE), as well as anti-tTG and EMA antibodies must be negative; duodenal histology must be normal; the patients must also experience a disappearance of the symptoms when on a GFD and their reappearance after the reintroduction of gluten. The most frequent symptoms in NGCS patients are abdominal pain, eczema or rash, headache, blurred vision, fatigue, diarrhea, depression, anemia, numbness in the legs, arms or fingers, and joint pain (Table 2).

Table 1
Signs and symptoms of CD in children and adolescents.

Iron-deficiency anemia
Other or unspecified anemia
Anorexia
Weight loss
Abdominal distension/bloating
Abdominal pain
Vomiting
Flatulence
Diarrhea
Short stature
Growth failure
Irritability
Increase level of liver enzymes
Chronic fatigue
Failure to thrive
Constipation
Irregular bowel habits