Clinical reviews in allergy and immunology

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Celiac disease

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Activity Objectives

1. To describe the epidemiology of celiac disease.
2. To understand the pathophysiology of celiac disease.
3. To use appropriate screening and confirmatory tests for celiac disease.

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This review will focus on the pathogenesis, clinical manifestations, diagnosis, and management of celiac disease (CD). Given an increasing awareness of gluten-related disorders, medical professionals of all varieties are encountering patients with a diagnosis of CD or who are thought to have food intolerance to gluten. The prevalence of CD among the general population is estimated to be 1% in Western nations, and there is growing evidence for underdiagnosis of the disease, especially in non-Western nations that were traditionally believed to be unaffected. The development of serologic markers specific to CD has revolutionized the ability both to diagnose and monitor patients with the disease. Additionally, understanding of the clinical presentations of CD has undergone a major shift over the past half century. Although it is well understood that CD develops in genetically predisposed subjects exposed to gluten, the extent of other environmental factors in the pathogenesis of the disease is an area of continued research. Currently, the main therapeutic intervention for CD is a gluten-free diet; however, novel nondietary agents are under active investigation. Future areas of research should also help us understand the relationship of CD to other gluten-related disorders. (J Allergy Clin Immunol 2015;135:1099-106.)

Key words: *Celiac disease, gluten intolerance, food allergy*

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Food sensitivities are increasing in prevalence within the general population, and wheat-related proteins play a prominent contributing role in this trend.[1] Wheat is composed of 4 classes of proteins divided on the basis of their solubility in different solvents: water (albumins), dilute salt solutions (globulins), aqueous alcohol (gliadins), and dilute alkali or acid (glutenins).[2] The role of these various proteins in the development of disease is an expanding area of study. Currently, there are 3 major wheat-related food illnesses: celiac disease (CD), nonceliac gluten sensitivity (NCGS), and wheat allergy. Although there might be an overlap in the symptoms associated with NCGS, wheat allergy, and CD, the conditions have distinct characteristics.

CD is an autoimmune disorder involving both an innate and adaptive immune response that occurs among genetically predisposed subjects who are exposed to gluten-containing foods and other environmental factors. Unlike food allergies, the pathogenesis of CD is not mediated by an immediate hypersensitivity reaction through an IgE-dependent mechanism. Instead, gluten protein is the pathogenic agent activated by the enzyme tissue

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Abbreviations used
AN-PEP: *Aspergillus niger* prolyl endoprotease
CD: Celiac disease
DH: Dermatitis herpetiformis
EMA: Endomysial antibody
GFD: Gluten-free diet
NCGS: Nonceliac gluten sensitivity
TTG: Tissue transglutaminase

transglutaminase (TTG), allowing its presentation to $CD4^+$ T cells in the lamina propria of the small intestine. The release of cytokines results in histologic changes in the intestinal mucosa (eg, intraepithelial lymphocytosis and villous atrophy) and a resulting variety of clinical manifestations (eg, abdominal pain, diarrhea, anemia, osteoporosis, and failure to thrive).[3]

At the same time that CD is becoming more common, the entity of NCGS is also gaining recognition.[4-7] NCGS is a term that refers to a spectrum of clinical phenotypes in which ingestion of gluten or other wheat-related proteins is thought to produce gastrointestinal and other extraintestinal symptoms that often overlap with symptoms seen in patients with CD (eg, abdominal pain, diarrhea, fatigue, rash, and depression). However, unlike CD, there are no characteristic histologic or serologic abnormalities identified. Indeed, there is much disagreement as to what extent NCGS is a true clinical entity.[8]

Wheat allergy is distinct from both CD and NCGS in that it is an IgE-mediated hypersensitivity response that occurs within minutes to hours of wheat ingestion.[3] The main routes of sensitization are through oral ingestion of wheat products or inhalation of wheat flour.[9] The clinical spectrum of wheat allergy includes gastrointestinal and respiratory symptoms (also referred to as baker's asthma), exercise-induced anaphylaxis, and contact urticaria. The gastrointestinal symptoms that develop after wheat ingestion can include abdominal pain, bloating, and flatulence, and these occur more often in children than in adults, with a peak at age 1 year. The protein of wheat responsible for allergic reactions resides in the albumin/globulin fraction (nongluten). The amylase trypsin inhibitors present in wheat are considered the main culprit.[2,10-13] Respiratory symptoms caused by wheat allergy occur in certain subjects after inhalation of wheat flour triggers rhinitis, conjunctivitis, and contact urticaria. Finally, exercise-induced wheat allergy is a condition in which wheat ingestion and exercise trigger an anaphylactic-type reaction, leading to angioedema, dyspnea, and shock. Omega-gliadins in particular are thought to play a central role in this reaction.[14]

CELIAC DISEASE

Epidemiology

CD was once considered a rare condition characterized predominately by intestinal symptoms that led to a malabsorption syndrome and stunted growth in young children of European ancestry. However, it is now appreciated that CD has a worldwide and increasing incidence among persons of various ethnic groups and among both adults and children.[15-18]

Numerous studies in which serologic screening was performed among the general population indicate that CD has a prevalence of nearly 1% among Western nations. One of the earliest studies in the United States found a prevalence of CD near 0.8%.[15] Among

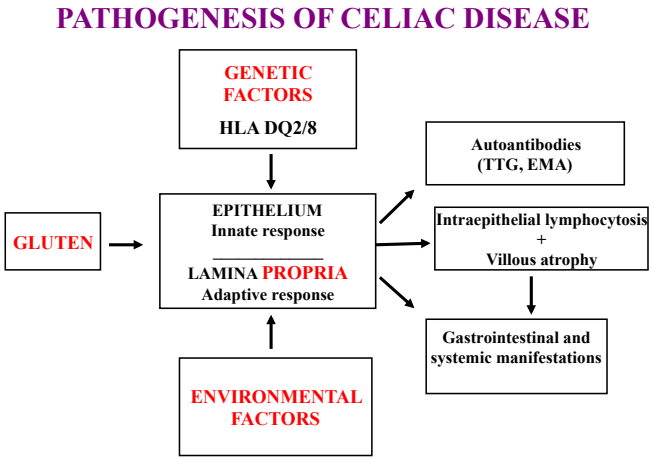

FIG 1. The pathogenesis of CD involves a triad of predisposing genes, gluten, and environmental factors. The main genes in CD are the HLA-DQ2 and/or HLA-DQ8 haplotypes. Dietary gluten is the major exposure among patients with CD. Numerous other environmental factors influence the development of CD but are less well defined than gluten. The reaction to gluten fragments occurs at the small intestinal epithelium, with both an innate and adaptive immune response. The results are characteristic autoantibodies, histologic changes (intraepithelial lymphocytosis and villous atrophy), and clinical symptoms (eg, diarrhea or iron deficiency anemia).

several European countries, the overall prevalence is also near 1%, although exact percentages vary by country (eg, 0.3% in Germany, 0.7% in Italy, 1.2% in England, and 2.4% in Finland).[19,20] The distribution of CD also extends beyond persons primarily of European ancestry, with significant prevalence identified in such disparate populations as the Middle East, Asia, South America, and North Africa.[21-25] One proposed reason for this trend is that, with a globalizing world market, developing nations that traditionally relied on gluten-free grains, such as rice and maize, are increasingly incorporating wheat-based foods into their diets.[26] As more mass screening studies are performed in different populations, more cases of previously undiagnosed CD are identified. Particularly on a global scale, there is evidence that CD is a missed diagnosis in many children in whom infection and malnutrition are quite common and the presumed cause for diarrheal illness.[27,28]

Sex differences also exist with respect to the rate of diagnosis of CD. One study found a female/male ratio of 2 to 3:1. The sex difference was true only in diagnoses made in adulthood, in which iron deficiency anemia was a significant presenting manifestation among women.[29] However, there is indication that the prevalence among male and female subjects based on serologic screening is comparable at about 1%.[15,30] The differential rates of diagnosis among sexes is thought to reflect several factors, including a higher rate of autoimmune disease among women in general, more regular health care interaction in female than male subjects, and a higher likelihood of symptomatic disease among women than men.[30]

Among the pediatric population, diarrhea and malabsorption syndrome are seen in the very young, whereas growth issues (failure to thrive and short stature) occur in children of all ages. Recurrent abdominal pain and screening of high-risk groups account for the other clinical presentations and are more common in older children.[31] The age at diagnosis has also increased over