Diagnosis and Updates in Celiac Disease

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KEYWORDS

• Gluten • Villous atrophy • Celiac disease • Enteropathy • Celiac sprue

KEY POINTS

- Patients who should be tested for celiac disease include those with classic gastrointestinal manifestations or those deemed at high risk based on genetic susceptibility.
- Diagnosis of celiac disease is usually initiated by serologic testing with anti-tTG, anti-DGP, or EMA and confirmed with duodenal biopsy.
- Generally, patient nonresponse to gluten-free diet is typically caused by either unintentional gluten exposure or by a secondary cause, such as inflammatory bowel disease or small intestinal bacterial overgrowth.
- Patients with refractory celiac disease may benefit from further radiologic or endoscopic evaluations including MRE, CT enterography/enteroclysis, capsule endoscopy, or device-assisted enteroscopy to evaluate for complications including ulcerative jejunoileitis or malignancy.

INTRODUCTION

Celiac disease (CD) is an autoimmune disorder induced by gluten in genetically susceptible individuals characterized by intraepithelial lymphocytosis, crypt hyperplasia, and villous atrophy of the small bowel. It is a chronic inflammatory state that heals on exclusion of gluten-containing foods from the diet. The prevalence of CD is about 1% of the general population worldwide.[1] Gluten from wheat, barley, and rye are enriched in glutamines and prolines, which undergo partial digestion in the small bowel resulting in peptide derivatives that are deamidated by tissue transglutaminase, which renders them immunogenic to those with CD.[2] Active CD can result in intestinal and extraintestinal manifestations of disease including diarrhea, weight loss, anemia, osteoporosis, arthritis, hepatitis, or malignancy. Some patients are also asymptomatic.[3]

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Diagnosis of CD is generally initiated through serologic testing with antitissue transglutaminase IgA antibodies (anti-tTG), gliadin-derived peptide antibodies IgA/IgG (anti-DGP), endomysial IgA antibodies (EMA), and/or antigliadin antibodies (AGA). Given the lower sensitivity and specificity of AGA tests for CD, the EMA, anti-tTG, and anti-DGP have largely replaced other serologic testing.[4] Following positive serologic testing, diagnosis should generally be confirmed by histopathologic examination of duodenal biopsies.

Generally CD is a benign disorder with a good prognosis in those patients that can adhere to a gluten-free diet. However, in those with refractory disease, complications may develop, which warrant additional testing with more advanced radiologic and endoscopic methods including magnetic resonance enterography/enteroclysis (MRE), PET/computed tomography (CT), capsule endoscopy, and device-assisted enteroscopy.[5]

PATHOGENESIS

CD develops in genetically susceptible individuals who are exposed to gluten. The clinical presentation of CD can vary greatly including the age of onset, presenting symptoms, the level of antibody titers, and a range of histopathologic findings, which can likely be explained by the interaction between genetic predisposition and environmental exposure.

Genetic Predisposition

Sibling studies in CD have demonstrated a disease concordance of about 80% in monozygotic twins and less than 20% in dizygotic twins indicating a genetic link. The major genetic determinants in CD involve the HLA, which is estimated to contribute to about 36% of the hereditability between siblings.[6–9]

HLA-DQ molecules are made up of two subunits, α and β, which are encoded by two different genes of the class II MHC molecule: HLA-DQA1 and HLA-DQB1, respectively. In CD, it has been found that 90% of patients carry the alleles *DQA1*05* and *DQB1*02*, which make up the HLA-DQ2 heterodimer. More specifically, they tend to have the HLA-DQ2.5 variant, which involves the *DQA1*05:01* and *DQB1*02:01* genes in *cis* configuration on the DR3 haplotype.[10] This molecule has a high affinity for the peptides that are formed from incomplete digestion of gluten, which results in their presentation and resultant intestinal inflammation. HLA influence on CD susceptibility also demonstrates a dose effect. Homozygous HLA-DQ2 individuals, for example, may have an increased risk for CD and enteropathy-associated T-cell lymphoma (EATL).[11–13]

Of the 10% who have not inherited the HLA-DQ2.5 molecule (*DQA1*05:01* and *DQB1*02:01* alleles), most have inherited the *DQA1*03* and *DQB1*03:02* alleles of the HLA-DQ8 molecule.[6] In addition, there are also non-HLA genetic factors that play a role in the development of disease. In Western countries about 40% of the general population possess one or both of the HLA-DQ2/HLA-DQ8 heterodimers, yet only 1% of individuals develop CD.[6] This indicates that there must be other genetic and environmental factors that contribute to the development of disease. Through genome-wide association studies, several different non-HLA alleles associated with risk of CD have been discovered.[14] Currently there are about 40 loci outside of HLA that have been determined through genome-wide association studies that have been found to either protect or predispose to CD, although they contribute little when compared with HLA.[10]

Environmental Exposure and Trigger Factors

In addition to genetic predisposition, patients with CD need to be exposed to gluten to develop the disease. Gluten is the storage protein for the cereal grains of wheat, rye,