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CELIAC DISEASE

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■ **Abstract** Celiac disease is an autoimmune disease that occurs in genetically predisposed individuals as the result of an immune response to gluten. This immune response occurs in both the lamina propria and the epithelium of the small intestine. There is a close link to HLA DQ2 and DQ8, although these HLA genes account for only 40% of the genetic influence. Environmental factors, such as the amount and timing of gluten administration in infancy, as well as breastfeeding, influence the disease. Serologic screening studies that use sensitive and specific antibody tests have revealed the disease to be common, occurring in ∼1% of the population. Clinical presentations are diverse and atypical; the majority of patients lack diarrhea. Therapy is a gluten-free diet that requires avoidance of wheat, rye, and barley, although there is potential for other therapies based on our understanding of the pathophysiology of the disease.

INTRODUCTION

Celiac disease was originally considered a rare malabsorption syndrome of childhood, but it is now recognized as primarily an adult disease. It is closely related to specific HLA alleles (DQ2 and DQ8) and requires the ingestion of gluten.

Gluten is the term for the storage proteins of wheat. The alcohol-soluble fraction of gluten, gliadin, is toxic in celiac disease, along with similar proteins in barley (hordeins) and rye (secalins) (1). Dermatitis herpetiformis (DH), an intensely pruritic, vesicular rash, is the dermatologic manifestation of celiac disease.

There have been major advances in the knowledge of celiac disease over the past few decades. These include a greater understanding of the pathologic mechanisms of the disease, knowledge of the diverse clinical and pathologic spectrum of the disease, and development of sensitive and specific serologic markers. These serologic tests have allowed epidemiologic studies that have demonstrated that the disease is common in the general population, and have allowed the diagnosis to be entertained by any physician.

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EPIDEMIOLOGY

Screening studies have revealed that the incidence of celiac disease approaches 1% of the population (2–6). It is recognized on every continent—in Asia (7), the Middle East (4, 8), North Africa (9), and South America (10). Most individuals with celiac disease are currently undiagnosed (2), although the rate of diagnosis is increasing (11). The disease is considered to be underdiagnosed (12); patients have a long duration of symptoms prior to diagnosis (13). This has been attributed to physicians' delay in diagnosis rather than patients' delay in seeking health care (14).

GENETIC FACTORS

Celiac disease is a polygenic disease. The human major histocompatibility complex (MHC) molecules DQ2 and DQ8 are essential genetic factors for the development of celiac disease, with the majority of patients carrying DQ2 (DQA1*05/DQB1*02). In the remaining patients, an association with DQ8 (DQA1*0301/DQB1*0302) is found (15). These HLA genes confer up to 40% of the genetic risk; the rest is attributable to non-HLA genes (15).

About 30%–40% of Caucasians carry DQ2 or DQ8, but <3% of these people will develop celiac disease. These figures suggest that although necessary, DQ2 and DQ8 molecules are not sufficient to cause celiac disease. Concordance in monozygotic twins (70%) is much higher than in MHC-identical siblings (30%). Overall, ∼10% of first-degree relatives of affected individuals have celiac disease. This increases to 20% if the family includes sib pairs with celiac disease, and even extends to second-degree relatives, demonstrating that there are families at high risk for the development of the disease (16).

Many studies have attempted to identify non-HLA genes. There is evidence for strong linkage at 5p31–33 (17), and also, albeit to a lesser degree, at 19p13.1 (18) and 11q (19). A small and controversial effect of the non-HLA gene CTLA-4 located on chromosome 2q33, which encodes a molecule involved in the inhibition of T cell activation, has been reported (20, 21). It is difficult, because of the linkage disequilibrium effect, to identify associations with non-MHC class II genes that are encoded within the HLA locus. However, there are indications that the MICB*10 gene, which codes for MIC B molecules, is associated with celiac disease (22). There is also evidence for an association with TNF2, also encoded within the HLA locus in the MHC class III region (23).

ENVIRONMENTAL FACTORS

Considerable knowledge concerning environmental factors important in the development of celiac disease was obtained from studies of an epidemic of infantile celiac disease in Sweden in the early 1980s (24, 25). Lack of breastfeeding, a large

amount of gluten in the infant formula, and ≥3 infections markedly increased the risk of celiac disease (26, 27). The greatest protection occurred when a small amount of gluten was ingested while breastfeeding was undertaken. As well as protecting against the development of celiac disease, breastfeeding delays the onset and alters the clinical presentation of celiac disease in children (28, 29).

PATHOGENESIS

Gluten is not fully digested by man. A 33-amino-acid peptide molecule (33mer) and probably other immunogenic peptides remain after the action of gastric, duodenal, and pancreatic enzymes. It is this fragment that is considered to elicit the immune response in susceptible individuals (30). It is unclear how gliadin peptides enter the mucosa, but tissue damage caused by gastrointestinal infections or alteration in tight-junction permeability by upregulation of zonulin (a protein that induces tight-junction disassembly and a subsequent increase in intestinal permeability) may be important (31).

Celiac disease can be viewed as a T cell–mediated inflammatory disorder with autoimmune features. The gliadin-induced T cell response comprises a specific and an innate component. The first is an antigliadin DQ2/DQ8-restricted CD4 T cell response in the lamina propria (reviewed in Reference 32). In adults, the CD4 T cell response is mainly directed against the α-gliadin 33 amino acid peptide. Gliadin is a good substrate for the enzyme tissue transglutaminase (33), which can transform glutamine residues into negatively charged glutamate residues by deamidation. In this process gliadin becomes negatively charged, facilitating binding to the groove on the surface of DQ2 and DQ8 molecules on antigen-presenting cells. Deamidation markedly enhances the CD4 antigliadin T cell response (34, 35); however, it may not be actually required to initiate the antigliadin CD4 T cell response, especially in children (36). As the antigliadin response develops in the gut, antitransglutaminase antibodies appear. Their role in the pathogenesis of the disease is not apparent, but serum IgA antibodies do inhibit crypt epithelial cell differentiation (37), and immune complexes can trigger inflammatory responses by activating the complement system and Fc receptors.

The second component of the antigluten T cell response is the intraepithelial CD8 T cell response involving the innate immune system. It has been proposed that the CD8 T cell response in the epithelium is directed against stressed epithelial cells (38). There are several lines of evidence supporting this model. First, intraepithelial CD8 T cells, which express the natural killer receptor NKG2D, can kill epithelial cells that express the stress-induced MIC molecules (39, 40). Second, studies suggest that peptides not recognized by CD4 T cells can induce early epithelial changes (40, 41) and induce IL-15 and MIC molecules on epithelial cells that arm the cytolytic NKG2D pathway to kill stressed epithelial cells (39, 40). It is unclear how gluten triggers the expression of stress molecules and IL-15 on epithelial cells and how the CD4 T cell response in the lamina propria relates to the CD8 T cell process in the epithelium.

CLINICAL PRESENTATION

The clinical classification of celiac disease is based on the presence of gastrointestinal symptoms. "Symptomatic" or "classical" celiac disease refers to presentations with diarrhea, with or without a malabsorption syndrome, whereas in "asymptomatic," "atypical," or "silent" celiac disease gastrointestinal symptoms are lacking or not prominent. It is unclear why the phenotypic expression of celiac disease is so variable. The presence of DQ8 as opposed to DQ2 does not account for differences in clinical or histologic severity (42).

In most studies, females predominate over males, in a ratio of 3:1 (13); however, men may have a more severe form of the disease at presentation (43). Although the peak age of diagnosis is in the fourth and fifth decades (13), population-based screening studies from the United Kingdom reveal that 1% of both seven-year-olds and adults have celiac disease, which suggests that it occurs in children and may remain undetected until adulthood (2, 6).

Younger children present with diarrhea and failure to thrive, whereas older children are more likely to present with anemia, short stature, neurologic problems, and other atypical symptoms such as constipation (29).

It has been noted in the United States that fewer patients are presenting with the malabsorption syndrome or diarrhea (11, 45). Diarrhea is still the most frequent mode of presentation, but others include iron deficiency (46), osteoporosis (47), and the recognition of mucosal changes in patients undergoing endoscopy for either esophageal reflux or dyspeptic symptoms (48, 49). Other patients are identified as a result of screening of high-risk groups, including relatives of patients with celiac disease (5), type 1 diabetics (50), and patients with Down syndrome (51). There is increasing recognition of celiac disease as a cause of various neurologic syndromes, including small-fiber peripheral neuropathy (52), epilepsy with occipital calcifications (53), and ataxia (54). A prior diagnosis of an irritable bowel syndrome is common (13), and in one study 5% of patients who fulfilled strict criteria of an irritable bowel syndrome had celiac disease (55). In addition, atypical presentations include rheumatologic symptoms, abdominal pain, macroamylasemia, hypoalbuminemia, abnormal liver tests, and evidence of hyposplenism (56).

DIAGNOSIS

Traditionally the diagnosis of celiac disease is made in an individual in whom a biopsy of the upper small intestine demonstrates the characteristic findings of villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis, and in whom there is an unequivocal response to gluten withdrawal. Patients come to biopsy because of a clinical suspicion of the disease, positive serologic tests, or the recognition of abnormalities in the duodenum at endoscopy (57). Serologic testing for celiac disease should occur under various clinical settings (Table 1).

TABLE 1 Clinical indications for serologic testing

Chronic diarrhea with and without malabsorption
Irritable bowel syndrome
Unexplained weight loss
Iron deficiency anemia
Folate deficiency
Vitamin E or K deficiency
Osteoporosis
Hypocalcemia or vitamin D deficiency, secondary hyperparathyroidism
Unexplained elevation of transaminases
First-degree relatives with celiac disease
Associated autoimmune diseases: type 1 diabetes, Sjogren's syndrome, primary billiary cirrhosis
Down and Turner syndromes
Neurologic disorders: unexplained peripheral neuropathy, epilepsy in children, and ataxia

SEROLOGIC TESTING

The most sensitive serologic tests are based on the use of IgA isotypes. The available tests include antigliadin antibodies as well as connective tissue antibodies: endomysial and tissue transglutaminase antibodies. The antigliadin antibodies have been available for many years; however, because of their lower sensitivity and specificity compared to the tissue transglutaminase and endomysial antibodies, their use for the diagnosis of celiac disease has been challenged (12).

The current standard is the IgA endomysial antibody (EMA) because of its very high specificity, which approaches 100%. The majority of reports indicate >90% sensitivity (58). [This topic is thoroughly reviewed in a paper commissioned for the 2004 National Institutes of Health Consensus Development Conference (58).] The titer of EMA correlates with the degree of mucosal atrophy (59); as a result, the sensitivity is lower when a greater number of patients with lesser degrees of villous atrophy are included in studies (60, 61).

The recognition of the enzyme tissue transglutaminase 2 (tTG) as the autoantigen for the EMA (33) allowed development of enzyme-linked immunoassays, which are less expensive and less observer- dependent than the EMA immunofluorescence test (62). Different commercial kits for assaying tTG have different characteristics and resultant sensitivities and specificities (63). Overall the sensitivity of IgA anti-tTG is >90% (58). The tTG test does not achieve the EMA's near-100% degree of specificity. There are many reports of positive tTG results in the absense of celiac disease (64–66).

Selective IgA deficiency occurs more commonly in patients with celiac disease than the general population (67). In order to detect celiac disease in those with selective IgA deficiency, a total IgA level should be incorporated into the testing for celiac disease, as well as a test based on IgG antibody, preferably IgG-tTG (68).

Alternatively, a very low IgA-tTG should trigger determination of total IgA and IgG-tTG. However, this needs to be determined in the laboratory because it is unlikely that the practicing physician would consider it in the face of a negative (normal) test result.

Several studies have revealed lack of sensitivity of the serologic tests in the clinical setting (55, 69, 70). This low sensitivity is probably due to inclusion of patients with lesser degrees of atrophy; such patients may not express an EMA or tTG (60, 71). Due to the presence of selective IgA deficiency, apparent lack of specificity of the tTG test and the lower sensitivity of both the tTG and EMA in clinical practice we consider a panel of tests that include the tTG-IgA, tTG-IgG, EMA and total IgA level would be optimal for case finding.

BIOPSY AND HISTOLOGY

Biopsy of the small intestine remains the gold standard in the diagnosis of celiac disease. Biopsy of the descending duodenum, rather than the more distal intestine, is sufficient (72). The recognition of the spectrum of histologic changes in celiac disease, as classified by Marsh (73), has provided a major advance in its diagnosis. The earliest lesion, Marsh I, is characterized by normal villous architecture with an intraepithelial lymphocytosis. A Marsh II lesion is identified when the intraepithelial lymphocytosis is accompanied by crypt hypertrophy. Ninety percent of patients diagnosed with celiac disease fall into the category of Marsh III, which includes partial, subtotal, and total villous atrophy. The histologic changes are not specific for celiac disease and may be seen in tropical sprue, autoimmune enteropathy, giardiasis, and HIV enteropathy.

Pitfalls in the diagnosis of celiac disease include both over- and underinterpretation of villous atrophy due to poorly oriented biopsies. Histologic findings may be milder than expected if the patient is on immunosuppressant medications, or if the patient's diet is low in gluten (as is often the case if a family member has celiac disease).

ASSOCIATED DISEASES

There are many conditions associated with celiac disease (Table 2). These include autoimmune diseases, which occur 3–10 times as frequently as in the general population (74–76). The relationship between the increased frequency of autoimmune diseases and celiac disease is attributed to a common genetic and immunologic mechanism as well as the presence of celiac disease itself. Gluten withdrawal does not prevent the development of autoimmune diseases (75); however, diabetes and thyroid-specific autoantibodies may disappear in children and adolescents after they start a gluten-free diet, suggesting a relationship between the autoimmune process and gluten exposure (77, 78). Improvement may occur in

TABLE 2 Disorders associated with celiac disease*

Endocrine disorders
Type 1 diabetes (8%–10%)
Autoimmune thyroid disorders
Addison's disease (8%)
Neurologic disorders
Cerebellar ataxia
Neuropathy (5%)
Epilepsy in children
Migraine
Cardiac diseases
Idiopathic dilated cardiomyopathy (2%–4%)
Autoimmune myocarditis (4%)
Liver diseases
Primary biliary cirrhosis (5%–10%)
Elevated transaminase values (9%)
Autoimmune hepatitis (6%)
Autoimmune cholangitis (3.5%)
Others
Iron deficiency anemia (3%–15%)
Hyposplenism
Sjogren syndrome (10%)
Osteoporosis (2%–7%)
Arthritis
Turner syndrome (6%)
Down syndrome (5%–10%)
Alopecia areata
Dental enamel defects
Inflammatory bowel disease
Ulcerative colitis
Crohn's disease (18%)
Microscopic colitis

* In parentheses: percent with celiac disease when these populations are screened.

the cardiomyopathy (79), hypothyroidism (80), or peripheral neuropathy (52) on a gluten-free diet, but generally the associated autoimmune disorders do not improve with a gluten-free diet after celiac disease is treated.

Various malignancies also appear to be a direct result of celiac disease, in that the increased incidence seen in patients with celiac disease returns to that of the general population after several years on a gluten-free diet (81). The malignancies include esophageal and head and neck squamous carcinoma, small intestinal adenocarcinoma, and non-Hodgkin lymphoma (81–83). Dermatitis herpetiformis (DH) also carries an increased rate of non-Hodgkin lymphoma (84). The non-Hodgkin lymphomas are of both T and B cell type and occur at both intestinal

and extraintestinal sites (83–85). Several studies have demonstrated that the increased risk for the development of lymphoma is less than previously considered (86–88), only two- to fourfold (89).

REFRACTORY CELIAC DISEASE/SPRUE

Refractory celiac disease or sprue is defined by persistent diarrhea and villous atrophy despite a gluten-free diet for at least six months. The term refractory sprue was coined because it was unclear whether all patients had celiac disease; some lack the crucial component of the diagnosis of celiac disease, that is, a response to the gluten-free diet. Recent studies have demonstrated that some patients who are refractory to the diet have an aberrant intraepithelial T cell population that lacks surface expression of CD8, CD4, and other T cell receptors. They have intracytoplasmic but not surface CD3 epsilon chains and exhibit restricted TCR gamma gene rearrangements (90). These patients are considered to harbor a cryptic T cell lymphoma. They have a high mortality rate and a high rate of progression to enteropathy T cell lymphoma, and they frequently require immunosuppressant therapy (91). The poor prognosis has motivated a search for alternative therapies such as biologic agents as well as stem cell transplantation.

GLUTEN-FREE DIET

The treatment for celiac disease is a lifelong gluten-free diet. Patients are advised to avoid all gluten (wheat, rye, and barley), but there is lack of unanimity about what this entails (92). Wheat is ubiquitous in the western diet. Washed wheat starch, which contains trace amounts of gluten, is allowable in the diet in some European countries, but not the United States. There is a minimal amount of gluten that appears to be tolerated without an inflammatory reaction (93), but there is probably a variability in sensitivity to small amounts, because 1 mg daily, in the form of a fraction of a communion wafer, prevented mucosal recovery over a two-year period in one patient (94). In Finland, where the "gluten-free" diet contains trace amounts of gluten, most patients do well. The biopsies normalize (95), and overall patients who follow a gluten-free diet have no increased mortality rate (96). However, in New York, mucosal abnormalities may persist despite a gluten-free diet (97), suggesting that a gluten-free diet may be more difficult in large urban areas in the United States.

Patients require knowledge of the flours and grains that are naturally gluten-free. These include rice and corn, as well as potato and chestnut flour, teff, millet, quinoa, buckwheat, and amaranth. Flour from wheat, rye, and barley is usually fortified with iron, thiamin, riboflavin and niacin; however, the gluten-free substitutes are frequently rice-based and are not usually fortified. As a result, the gluten-free diet is low in B complex vitamins and iron (98), and patients on a gluten-free diet frequently have evidence of poor B vitamin status (99).

Oats remain a dilemma for some patients who desire them. Multiple studies have demonstrated that most patients with celiac disease or DH tolerate oats (100, 101). However, a few people with celiac disease mount an immune response to oats (102), and gastrointestinal symptoms, due to an increase in fiber, are more frequent when oats are consumed. In addition, oats may be contaminated with other gluten-containing grains, even brands considered to be gluten-free (103). Oats, however, add both fiber and diversity to the gluten-free diet.

Those diagnosed with celiac disease in developing countries have tremendous difficulties obtaining a gluten-free diet. In developed countries, patients face problems such as increased cost of food, inadequate food labeling, lack of information while eating in restaurants, use of gluten-containing products in medications, and conflicting information from physicians, nutritionists, support groups, and the Internet (104).

Because of the restraints encountered with adherence to a gluten-free diet, quality of life is an important issue. Patients surveyed in the United States reported an improvement in quality of life after diagnosis of celiac disease and commencement of a gluten-free diet (13). This occurred even in those diagnosed in Finland through screening programs (105). However, other studies report a negative effect on aspects of quality of life. The disease and diet impact quality of life in females rather than males (106) and in those with gastrointestinal symptoms, lower compliance, and more comorbid diseases (107, 108). An impact was also reported in activities such as dining out, social functions, and travel (109, 110). As a result, compliance with the diet remains an issue, especially in those without symptoms and in the social setting (13).

THE FUTURE

There are several unanswered questions. What is the significance of silent celiac disease in the vast number of currently undiagnosed people with the disease? Who should be screened for the disease? What is the maximal level of gluten tolerated by people with celiac disease? However, with the widespread availability of serologic testing and physicians' increasing awareness of the diverse clinical presentations of the disease, it is anticipated that the rate of diagnosis will continue to increase. This will result in an increasing demand for gluten-free foods. Another result will be the search for new, nondietary therapies based on the understanding of the pathogenesis of celiac disease.

The discovery that ancient wheat lacks the toxic immunodominant 33mer fragment of gliadin indicates that genetic manipulation of wheat, bred to lack this fragment, is feasible (111). Possible drug therapies are being researched; these include oral administration of bacterial endopeptidases that digest the toxic 33mer of gliadin (30), inhibitors of the zonulin pathway (31), and peptides that block the binding groove of DQ2 and DQ8 (112). These therapies may help ease the burden of a life-long gluten-free diet.

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