REVIEW

CME CREDIT

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Celiac disease: More common than you think

ABSTRACT

Celiac disease—a chronic immune-mediated disorder primarily affecting the gastrointestinal tract—is being increasingly recognized, but because half of all cases present atypically or silently, awareness needs to be high, especially in primary care. The diagnosis is based on clinical suspicion combined with laboratory testing and can be established by a primary physician. Early diagnosis will likely improve outcome. A gluten-free diet is necessary but difficult to follow, and patients are more likely to adhere to it if a dietician and support group are involved.

KEY POINTS

The prevalence of celiac disease is 0.5% to 1% in North America and Western Europe.

The disease has a strong genetic component. From 90% to 95% of patients with celiac disease possess the HLA-DQ2 allele, and the other 5% to 10% possess the HLA-DQ8 allele.

Symptoms can vary, from diarrhea, weight loss, and abdominal pain to a variety of extraintestinal manifestations, including recurrent fetal loss, bone fractures and osteoporosis, psychiatric syndromes, dental enamel defects, and other manifestations.

Nutritional deficiencies are very common in celiac disease and are due to malabsorption in the small intestine.

PATIENT INFORMATION
If you have celiac disease, page 216

CELIAC DISEASE, also known as celiac sprue, gluten enteropathy, and nontropical sprue, is more common than you think. Indeed, up to 1% of the American population may have it,[1] a large increase from previous estimates.

A reason that the disease has been underrecognized until now is that about half of people with it do not have the classic gastrointestinal symptoms. Instead, they may present with nonspecific manifestations of nutritional deficiency or have no symptoms at all.

Because celiac disease can have devastating consequences, primary care physicians should be aware of it and consider it in the differential diagnosis if the symptoms suggest it. Serologic tests are now available to follow up your clinical suspicion. Patients typically improve when they follow a strict gluten-free diet, which usually requires the help of a dietitian and a support group.

This article reviews the epidemiology, pathogenesis, clinical features, associated disorders, management, and complications of celiac disease. We hope that as physicians become more aware of this disease and more patients are diagnosed and adopt a gluten-free diet, its complications will become fewer.

CELIAC DISEASE IS COMMON

Celiac disease was once thought to be rare in the United States, affecting about 1 in 3,000 people.[2] However, based on large population-based screening studies with serologic testing and small-bowel biopsies,[1] the prevalence is now thought to be from 1 in 300 to 1 in 100.

Celiac disease mainly affects people of European descent; the prevalence is lower in

India, South America, the Middle East, Africa, and Asia.[1] Some studies suggest that approximately twice as many women as men are affected.

AN IMMUNE RESPONSE IN SUSCEPTIBLE PEOPLE

Celiac disease is multifactorial, involving a combination of genetic susceptibility, environmental exposure (gluten ingestion), and an immunologic response that causes inflammation of the small intestine, loss of intestinal villi (the main absorptive units), and hence, malabsorption of nutrients.

Genetic factors. From 90% to 95% of patients with celiac disease possess the HLA-DQ2 allele, and the other 5% to 10% possess the HLA-DQ8 allele.[3] HLA-DQ2 is involved in the pathogenesis of the disease (see below).

The genetic basis of this disease is reflected in concordance rates of 30% to 50% among HLA-identical siblings and 75% among monozygotic twins.[4] Of practical importance, from 10% to 20% of first-degree relatives of patients with celiac disease also have celiac disease.[5]

10%–20% of first-degree relatives of patients with celiac disease also have it

Gluten, the "disease-activating protein," is found in wheat, rye, and barley. Occasionally, oats are contaminated with these other grains during processing, and hence contain gluten as well.

The immunologic response has not been fully elucidated, but a model has been proposed (FIGURE 1). When gluten is ingested, it is broken down into peptides, particularly gliadin, which are transported across the enterocyte membrane and attach to antigen-presenting cells expressing HLA-DQ2 or HLA-DQ8. Helping them attach is an enzyme, tissue transglutaminase, which converts glutamine residues of gluten to negatively charged glutamic acid, which attach preferably to the antigen-binding groove of the HLA molecules.

The antigen-presenting cells then present these peptides to mucosal T lymphocytes, which become activated and produce multiple antibodies and cytokines, such as interferon gamma, interleukin 4, and tumor necrosis factor alpha.[6,7] These cytokines result in enterocyte damage and increased expression of the HLA-DQ2 genes.[7]

GASTROINTESTINAL FEATURES ARE THE TIP OF THE ICEBERG

Celiac disease is typically detected when the patient is either 8 to 12 months old or in his or her 20s or 30s.

Infants and children develop the signs and symptoms of celiac disease after gluten is introduced into their diet. As the disease affects the absorption of nutrients essential for growth, its signs include failure to thrive and short stature. Other signs and symptoms include anemia, abdominal pain, vomiting, and diarrhea. Children may also have pubertal delay, rickets, iron and folate deficiency, and behavioral problems.

Adults can have a wide variety of symptoms. The classic gastrointestinal manifestations include diarrhea, flatulence, abdominal distention, weight loss, malaise, steatorrhea, and recurrent aphthous ulcers. However, recent studies suggest that approximately 50% of adults with celiac disease do not present with the classic gastrointestinal manifestations.[7,8]

Atypical presentations of celiac disease are becoming increasingly recognized, usually in older children and adolescents. Thus, the latest estimates suggest that the prevalence is much higher than we used to think. The classic gastrointestinal symptoms may really be just the "tip of the iceberg."[9]

Because its clinical presentation is so variable, celiac disease can easily be missed. But the situation is improving: in a large case series, Green[8] found that the average duration from the onset of symptoms until the patient was diagnosed with celiac disease decreased from 9 years before 1993 (when serologic testing became available) to 4 years afterward.

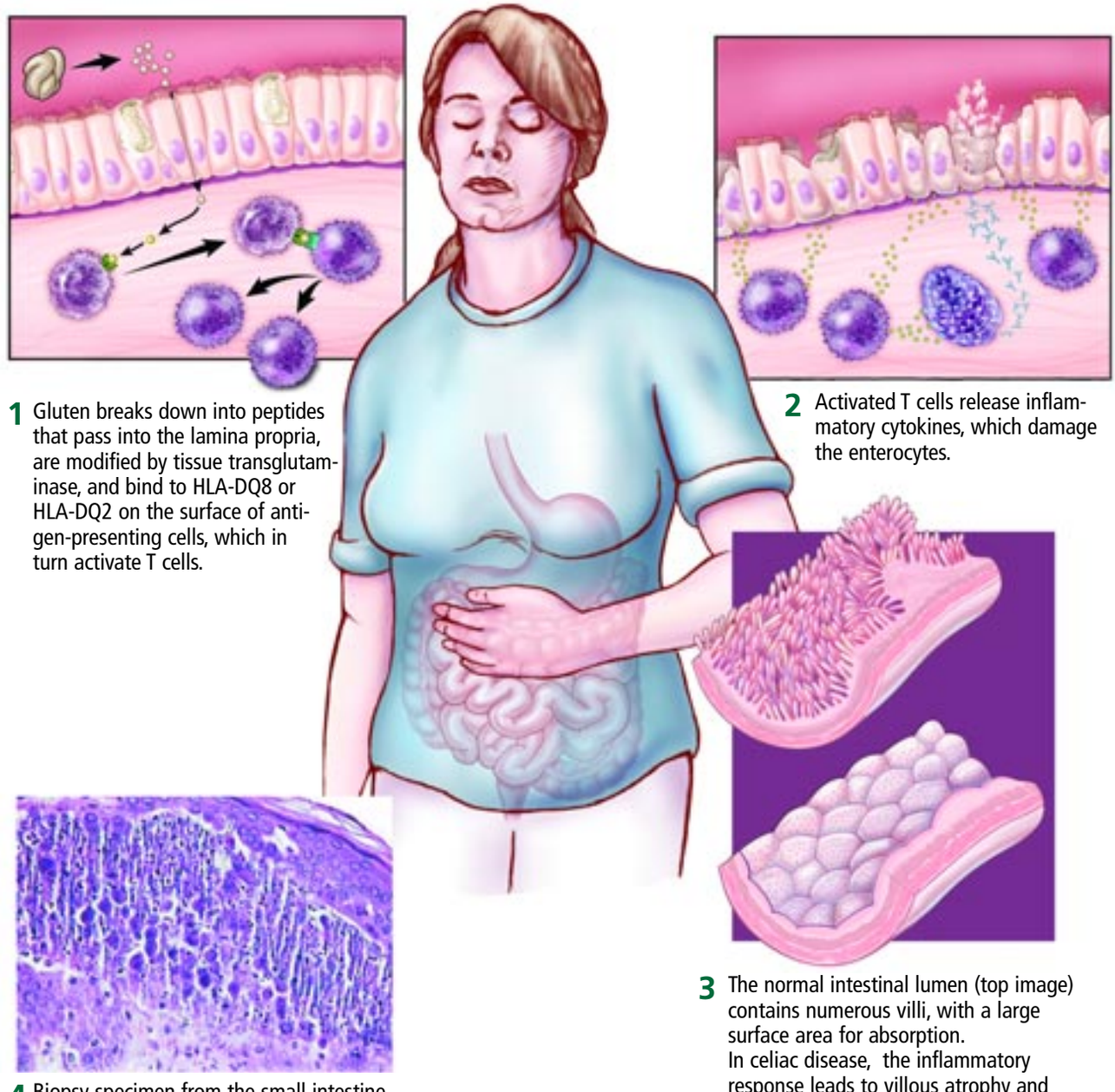
Subtypes of celiac disease

Silent (asymptomatic) celiac disease can be detected by serologic tests and by biopsy of the small intestine.[1] Most silent cases are discovered when the patient undergoes testing because a family member has celiac disease, or incidentally during esophagogastroduodenoscopy performed for other purposes.

Latent disease includes cases in which patients had celiac disease at one point but currently have normal results on small-

Pathogenesis of celiac disease: The gluten factor

It is believed that patients with celiac disease mount a T-cell-mediated immune response to gluten in the wall of the small intestine. The resulting damage leads to chronic malabsorption of key nutrients and a host of possible intestinal and extraintestinal manifestations.



1 Gluten breaks down into peptides that pass into the lamina propria, are modified by tissue transglutaminase, and bind to HLA-DQ8 or HLA-DQ2 on the surface of antigen-presenting cells, which in turn activate T cells.

2 Activated T cells release inflammatory cytokines, which damage the enterocytes.

3 The normal intestinal lumen (top image) contains numerous villi, with a large surface area for absorption.
In celiac disease, the inflammatory response leads to villous atrophy and malabsorption (bottom image).

4 Biopsy specimen from the small intestine of a patient with celiac disease, showing villous atrophy, crypt cell hyperplasia, and increased intraepithelial lymphocytes.

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Medical Illustrator: David Schumick ©2007

FIGURE 1

TABLE 1

Subtypes of celiac disease

SUBTYPE	SYMPTOMS	SEROLOGIC TESTS	SMALL-BOWEL BIOPSY RESULTS
Atypical	Atypical	Positive	Suggested positive
Silent	None	Positive	Suggested positive
Latent	None	Positive	Normal

bowel biopsies. Other cases involve patients who have not yet developed clinical symptoms.[1]

Atypical (ie, presenting with atypical features) celiac disease is also diagnosed with serologic tests and small-bowel biopsy (**TABLE 1**). Common atypical presentations may be iron deficiency anemia (most common in adults) or decreased bone density.[1,10]

Common atypical presentations of celiac disease in adults are iron deficiency anemia and low bone density

Extraintestinal clues to the diagnosis of celiac disease

Extraintestinal features that may be clues to the diagnosis of celiac disease include:

- Recurrent fetal loss and infertility
- Delayed puberty
- Bone fractures and osteoporosis
- Psychiatric syndromes
- Neurologic disorders such as ataxia, peripheral neuropathy, and seizures
- Dental enamel defects
- Macroamylasemia
- Short stature
- Alopecia areata.

Nutritional deficiencies

Nutritional deficiencies are very common in celiac disease and are due to malabsorption in the small intestine.

- Vitamins A, D, E, and K (the fat-soluble vitamins) can become deficient due to fat malabsorption
- Iron and folate deficiency can occur due to involvement of the proximal small bowel
- Vitamin B_{12} deficiency occurs if the inflammation affects the ileum, but this is rare
- Calcium, magnesium, and albumin deficiencies also occur in some patients.

MANY ASSOCIATED CONDITIONS

Celiac disease is associated with many other conditions, some of which may contribute to many of the complications encountered in this disease.

Dermatitis herpetiformis, a skin disorder exclusive to celiac disease, is characterized by symmetric pruritic papulovesicles and excoriations, most often on the elbows, knees, buttocks, and scalp (**FIGURE 2**). Nearly 100% of people with this skin disorder have abnormalities in the intestinal mucosa that are characteristic of celiac disease. It is diagnosed by skin biopsy, in which granular IgA deposition is visualized with immunofluorescence at the dermoepidermal junction. Management includes a gluten-free diet and dapsone (Aczone) 50 to 100 mg/day.[11]

Enteropathy-associated T-cell lymphoma, a rare, aggressive non-Hodgkin lymphoma, is also very specific to celiac disease.[12,13] It is characterized by clonal proliferation of intraepithelial lymphocytes, most commonly in the jejunum, although it can also be found in the ileum, lymph nodes, stomach, and colon, and it is often disseminated at diagnosis.[13] The mean age of incidence is in the sixth decade of life.[13] It is diagnosed by endoscopic or laparoscopic biopsy, and treatment includes surgery and chemotherapy. The prognosis is dismal despite treatment, with a 13% survival rate at 30 months.[14]

Other malignancies with increased incidence in patients with celiac disease include small-bowel adenocarcinoma, oropharyngeal and esophageal adenocarcinoma, liver cancer, and melanoma. Some suggest that the incidence rates of non-Hodgkin lymphoma of any origin and colorectal adenocarcinoma may also be increased.[13]

Autoimmune disorders that are associated with celiac disease include type 1 diabetes mellitus[15,16] and autoimmune thyroiditis.[17] Approximately 3% to 8% of patients with type 1 diabetes have celiac disease,[15,16] and unexpected episodes of hypoglycemia or diarrhea should alert the physician to the possibility of coexisting celiac disease in patients with type 1 diabetes. Celiac disease has also been reported in association with psoriasis, autoimmune liver disease, autoim-

mune cardiomyopathy, Sjögren syndrome, rheumatoid arthritis, and systemic lupus erythematosus.[8]

Other conditions that have been associated with celiac disease include Down syndrome, Turner syndrome, William syndrome, and selective immunoglobulin A deficiency. Of note: patients with this deficiency will have negative immunoglobulin A antibody studies, and therefore, antibody testing will not be helpful in this population.

TO DIAGNOSE CELIAC DISEASE, FIRST SUSPECT IT

The diagnosis of celiac disease is based on clinical suspicion and is confirmed with laboratory tests.

Who should be tested?

Current guidelines suggest that anyone with chronic diarrhea, malabsorption, weight loss, and persistent abdominal distention should be tested. Others who should be tested include those with unexplained iron-deficiency anemia, short stature, infertility, recurrent fetal loss, and aminotransferase elevations. Patients with irritable bowel syndrome, autoimmune disease, persistent aphthous stomatitis, unexplained peripheral neuropathy, unexplained cerebellar ataxia, and dental enamel hypoplasia can be considered for testing.[18]

Serologic tests

All laboratory testing must be done while the patient is on a gluten-containing diet.

Tissue transglutaminase, as mentioned earlier, is important in the pathogenesis of the disease. An enzyme-linked immunosorbent assay for tissue transglutaminase had sensitivities and specificities of around 98% in recent studies.[19,20]

Endomysial antibodies bind to connective tissue surrounding smooth muscle cells and can be visualized using immunofluorescence. In recent studies, the sensitivity of this test was 97%, and its specificity was 97% to 100%.[19,20]

The antigliadin antibody test is no longer recommended because its sensitivity and specificity are low.[19,20]

Dermatitis herpetiformis

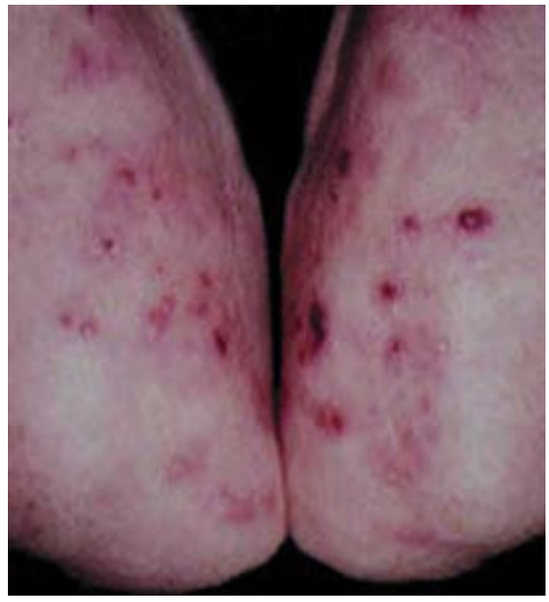

FIGURE 2. Dermatitis herpetiformis, which is characterized by symmetric pruritic papulovesicles and excoriations, is found exclusively in people with celiac disease.

Duodenal endoscopy, biopsy

Small-bowel biopsy should be performed if a patient has positive results on serologic tests or if you still strongly suspect celiac disease even though the serologic tests were nondiagnostic.

The gross characteristic mucosal changes seen on endoscopy include flattening or scalloping of the duodenal folds. These changes are not specific to celiac disease but may alert the endoscopist to the diagnosis. Multiple biopsy samples should be taken, since mucosal involvement can be patchy.

The classic histopathologic changes seen in celiac disease include crypt cell hyperplasia, villous atrophy, increased numbers of intraepithelial lymphocytes, and chronic lymphocyte and plasma cell infiltrates in the lamina propria (**FIGURE 1**). The Marsh criteria are used to grade the progression of mucosal changes in celiac disease.[21] The degree of histopathologic changes correlates with the degree of malabsorptive symptoms.

Of note: these pathologic changes can also be seen in other diseases. Therefore, it is useful to use the results of the small-bowel

Test anyone with chronic diarrhea, malabsorption, and persistent abdominal distention

TABLE 2

Commonly overlooked gluten-containing foods

Baked beans
Breading
Chocolate bars
Dry roasted nuts
Gravy
Icing and frosting
Imitation bacon bits
Imitation seafood
Licorice
Marinades
Processed meats and poultry
Roux
Salad dressings
Seasonings
Soups
Soy sauce

ADAPTED FROM CASE S. THE GLUTEN-FREE DIET: HOW TO PROVIDE EFFECTIVE EDUCATION AND RESOURCES. GASTROENTEROLOGY 2005; 128(SUPPL 1):S128–S134, WITH PERMISSION FROM THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION.

biopsy in conjunction with serologic testing and clinical suspicion. Also, if the patient truly has celiac disease, the symptoms, histopathologic changes, and degree of malabsorption should resolve with a gluten-free diet, which confirms the diagnosis.

Patients beware: many foods and drugs contain gluten

Genetic testing

Genetic testing can be performed to confirm the diagnosis or to determine which family members may develop the disease. The patient and family can be tested for HLA-DQ2 and HLA-DQ8. As stated earlier, nearly all patients carry one of these alleles; however, so does approximately 40% of the general European population. Therefore, this test is only useful if it is negative, ie, it has a high negative predictive value.[22]

MANAGEMENT IS MULTIDISCIPLINARY

Management of patients with celiac disease is multidisciplinary.

Gluten-free diet

Once celiac disease has been diagnosed, patients should immediately be referred to a dietician to start following a gluten-free diet. A support group plays an important role in helping patients understand the disease and adhere to the diet.

Patients must avoid all wheat, barley, rye, and, initially, oats (which is often contaminated with wheat during processing). There are no agreed-upon safe levels of gluten in the diet for patients with celiac disease. Patients should be aware of the potential presence of gluten in emulsifiers, medications, food stabilizers, and food additives. TABLE 2 lists some gluten-containing foods that are often overlooked. Oats may be added back into the diet at low levels (2 ounces/day) once malabsorptive symptoms have disappeared.[7]

Patients typically improve when they follow a strict gluten-free diet and relapse when gluten is reintroduced.

Lactose-containing products should also initially be avoided due to the relative lactase deficiency caused by the immunologically mediated mucosal damage. Like oats, lactose can be added back into the diet once the malabsorptive symptoms improve.[7]

Nutritional supplementation should also be considered in all patients with celiac disease, as nutritional deficiencies can occur as a consequence of the disease itself and of the gluten-free diet.[23]

Medical follow-up

Patients should have close follow-up in the first 3 to 6 months.[24]

Nutritional deficiencies should be screened for initially by checking the complete blood cell count, comprehensive metabolic profile, prothrombin time, liver enzymes, vitamin A, vitamin D, vitamin E, folate, vitamin B_{12}, and iron studies.[23] Routine bone density scanning is controversial, but some recommend it upon diagnosis in view of the increased incidence of bone disease in patients with celiac disease.[24]

Many gastroenterologists do a repeat biopsy of the small bowel approximately 4 to 6 months after the patient starts the gluten-free diet to see if the histopathologic changes have resolved, although this is not the standard of care.

First-degree relatives should be screened for celiac disease as well.

COMPLICATIONS

Complications of celiac disease include refractory sprue, malignancy, acute celiac crisis, ulcerative jejunoileitis, and collagenous sprue.

Refractory sprue. Patients with refractory sprue, as the name implies, have persistent symptoms despite at least 6 months of a truly gluten-free diet. Corticosteroids are indicated to induce remission.[25]

Malignancy is a major concern in patients with long-standing celiac disease that is poorly controlled or has been misdiagnosed. The malignancies include lymphoma of the small intestine, esophageal cancer, and squamous cell carcinoma of the small intestine.

"Acute celiac crisis" is a rare entity characterized by profuse diarrhea, metabolic acidosis, hypokalemia, and dehydration. Corticosteroids, total parenteral nutrition, and aggressive supportive measures are the main therapeutic interventions.[26]

Ulcerative jejunoileitis is also rare but can be severe, involving ulcerations and strictures of the jejunoileal area, leading to perforation, obstruction, and hemorrhage. The treatment is surgical resection, and the prognosis is dismal, with a 5-year survival rate of less than 50%.[9]

Collagenous sprue is defined as deposition of collagen in the subepithelial tissue. This results in malabsorption in spite of treatment with a gluten-free diet and steroids. As with ulcerative jejunoileitis, the prognosis is very dismal.[9]

PROGNOSIS CAN BE GOOD

The rate of death due to all causes in patients with celiac disease is two times that of the general population.[27] However, the prognosis can be quite favorable if patients adhere to a strict gluten-free diet.

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