



Disease in a Nutshell

Celiac disease and nonceliac gluten sensitivity

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Introduction

Celiac disease (CD) is an increasingly common chronic autoimmune disease caused by permanent gluten sensitivity that occurs in people carrying the HLA-DQ2 or HLA-DQ8. It causes both gastroenteropathy (demonstrated by duodenal biopsy) and extra-intestinal pathologic conditions (Fig 1A and B). The disease is often diagnosed by the discovery of positive autoantibodies (anti-tissue transglutaminase [anti-tTG] IgA and anti-endomysial antibody [EMA] IgA) in a patient, which might trigger an intestinal biopsy that reveals villous atrophy. A strict gluten-free diet (GFD) is the ultimate treatment.

Epidemiology and Risk Factors

CD was first described in 1888 by Gee.¹ The role of gluten was identified in the 1940s by Dicke.¹ It was not until the 1980s when it was recognized that CD involves not only intestines but also extraintestinal systems and organs.² Prevalence of CD is estimated to be 0.6% to 1% worldwide. In the United States, it is approximately 0.7% to 0.8% and higher in whites of Northern European descent than in African Americans, Hispanics, and Asians. The prevalence of CD has been increasing steadily during the past few decades, and the rate doubles approximately every 20 years. The incidence of diagnosed CD is estimated to be 3 to 13 cases per 1000, with an estimated 4% to 17% increased risk among first-degree relatives of people with CD than general population. This risk is increased to 26% if individuals are homozygous for HLA-DQ2.^{2,3} A total of 90% of patients with CD express HLA-DQ2 and 5% express HLA-DQ8. However, the incidence of CD among monozygotic twins is approximately 85%, suggesting that factors other than genetic predisposition also play an important role in the development of CD. It remains controversial whether gluten ingestion during early

infancy contributes to the development of CD. One US study suggests that *Helicobacter pylori* colonization in the gut may have a protective role against developing CD. However, earlier studies on the correlation between early-life gastrointestinal infection and development of CD are inconclusive. The role of smoking in the development of CD is also inconsistent. Some studies have found a protective role, whereas others found very little association.^{2,3}

Medication-Induced Enteropathy

Several medications have been associated with the development of an enteropathy resembling CD. These medications include azathioprine, mycophenolate mofetil, methotrexate, neomycin, colchicine, and, more recently, the oral angiotensin-receptor blocker olmesartan medoxomil. Patients taking these medications who develop intestinal symptoms need to discontinue use of the medications before duodenal biopsy is considered to avoid misdiagnosis.⁴

Pathophysiology

Gluten is the storage protein of cereal grains, including wheat, rye, and barley. The toxic fractions in gluten are called gliadins, which are rich in glutamine and proline residues, neither of which can be completely digested by peptidases from the stomach, pancreas, and intestinal brush borders.

Innate immunity plays an important role in the pathogenesis of CD. Among patients with CD, intraepithelial lymphocytes are increased, and interleukin (IL) 15 and type 1 interferons are upregulated in the intestinal mucosa. IL-15 and type 1 interferons, alone or in synergy, might be responsible for loss of oral tolerance to gluten and activation of intraepithelial lymphocytes in patients with genetic susceptibility.^{5,6}

Adaptive immunity also plays a very important role in the pathogenesis of CD. Incompletely digested gliadin fragments are deamidated by tissue transglutaminase, an enzyme residing within the lamina propria. As a result, the immunogenicity of the gliadin fragments is increased by the increase of their negative charges. This alteration facilitates the interaction between the gliadin fragments

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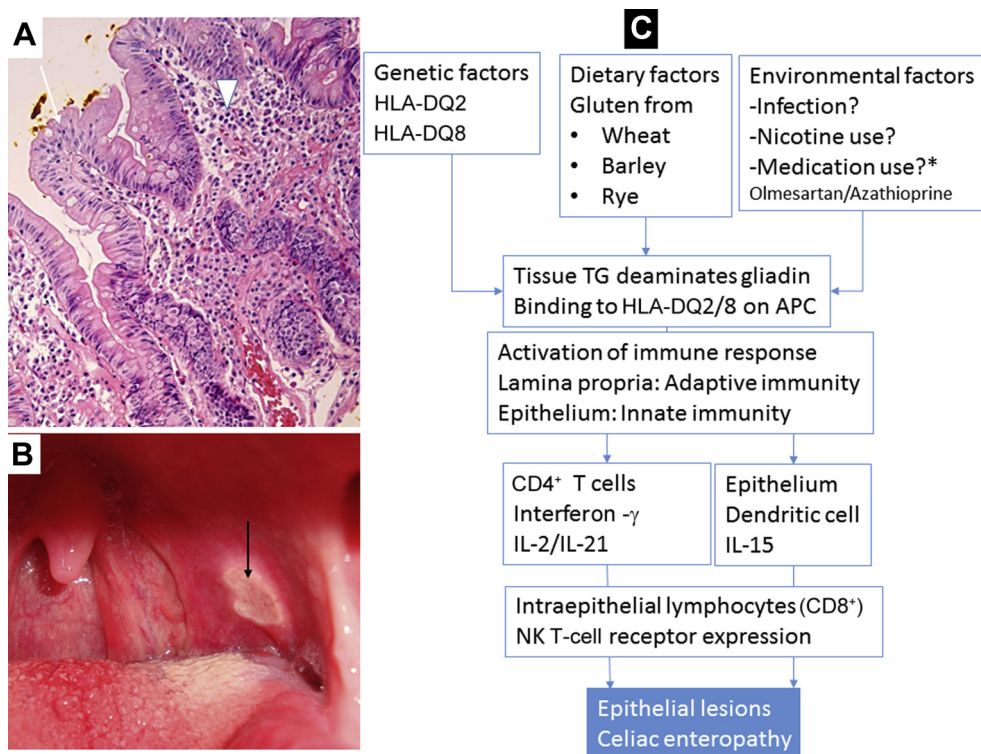


Figure 1. Celiac disease findings. A, Ileal biopsy reveals villous blunting (white arrow), crypt elongation, and increased intraepithelial lymphocytes (inflammatory response indicated by black arrowhead) in a patient with documented seropositive celiac disease. B, Oral ulcers (black arrow) with surrounding erythema located on the soft palate or elsewhere may be a presenting feature of celiac disease, as in this patient. Biopsy of the ulcer may reveal inflammation, granulation tissue, and scarring. C, Presumed mechanisms operative in celiac disease centered around the pivotal cytokine interleukin (IL) 15. The interactions between gluten and the innate and adaptive immune response, HLA haplotypes, and the collaborative cytokines IL-2, IL-21, and IL-15 are shown. Refer to the text for more details. Asterisk indicates that several medications have been reported to be associated with the development of an enteropathy resembling celiac disease, including azathioprine, mycophenolate mofetil, methotrexate, and olmesartan medoxomil (angiotensin II receptor antagonist). APC indicates antigen-presenting cell; NK, natural killer; TG, transglutaminase.

and HLA-DQ2 and HLA-DQ8 on the antigen-presenting cells and further activates CD4 T cells, resulting in the production of proinflammatory cytokines.^{2,3} The interactions among innate and adaptive immunity, HLA haplotypes, and gluten are shown in Figure 1C.

Clinical Presentation

CD affects persons of any age, races, and ethnic groups. The presentation of CD varies greatly from minor or absent gastrointestinal symptoms to major extraintestinal symptoms.

Abdominal pain and chronic or intermittent diarrhea are the most common gastrointestinal symptoms in patients with CD. Other symptoms include vomiting, chronic constipation, abdominal distention, weight loss, and severe malnutrition.^{3,7}

Among extraintestinal associations, fatigue and iron deficiency anemia are the most common ones. The others include dental enamel hypoplasia, short stature, delayed puberty in children, unexplained infertility and miscarriages, dermatitis herpetiformis, isolated transaminitis, aphthous stomatitis, low bone mineral density, and even osteoporosis in 60% of patients. Neurologic manifestations include recurrent headaches, peripheral neuropathy, cerebella ataxia, and idiopathic epilepsy. Psychiatric issues, especially common in adolescents, include depression, hallucinations, and anxiety. Suicidal ideation might be slightly higher among these patients as well.^{3,7}

Other Important Aspects: Associations and Comorbidities

CD, but not nonceliac gluten sensitivity (NCGS), is associated with other comorbidities summarized in Table 1. Table 2 outlines the differential diagnosis commonly encountered in patients presenting with bowel symptoms.

For allergists, it is important to recognize that asthma is associated with CD. Recent research by Yaqoob et al⁸ found that CD is associated with increased risk and severity of asthma based on a large US registry study of 26 major health care systems covering 50 million patients in 50 states. It was suggested that aggressive screening of asthma in patients with CD may be warranted. However, it is unclear whether GFD will decrease the risk and severity of asthma in such patients.

NCGS is a poorly defined syndrome characterized by a combination of intestinal and extraintestinal symptoms that occurs soon after consumption of gluten-containing foods and disappears quickly with removal of gluten from routine diet. It is a diagnosis of exclusion. NCGS is not associated with HLA-DQ2 and HLA-DQ8, although both are positive in more than 30% of the general population. Autoantibodies to tTG and EMA are not present, and the intestinal biopsy result is negative for typical pathologic findings. Given the indistinguishable clinical presentation of CD and NCGS and the association of CD with long-term health consequences, it is important to reliably exclude CD.⁹

Poorly Responsive CD

Recurrent symptoms may occur in a patient with diagnosed CD and after a GFD. Continuing gluten exposure is likely, but other diagnoses, including irritable bowel syndrome, food intolerances (eg, lactose and fructose), microscopic colitis, bacterial overgrowth, or malignant tumor, may have to be entertained.

Diagnosis

Patients with CD most commonly will present with signs of malabsorption or chronic gastrointestinal symptoms. However,

Table 1
Comorbidities and Associations Seen in Patients With Celiac Disease

Condition	Manifestations
Malignancy	Non-Hodgkin lymphoma Small intestinal adenocarcinoma
Immune disorders	Systemic lupus erythematosus Adrenal insufficiency Type 1 diabetes mellitus Hashimoto thyroiditis Selective IgA deficiency
Neurologic disease	Cerebellar ataxia Peripheral neuropathy Dementia Seizures
Dermatologic disease	Dermatitis herpetiformis Alopecia areata
Gastrointestinal disease	Autoimmune hepatitis Primary biliary cirrhosis Primary sclerosing cholangitis NASH Pancreatic disease Stomatitis Abnormal liver function test results
Respiratory disease	Asthma
Cardiovascular disease	Ischemic heart disease Cardiomyopathy
Renal disease	IgA nephropathy
Obstetrics related	Adverse pregnancy outcomes Recurrent fetal loss
Miscellaneous	Primary hyperparathyroidism Osteoporosis Chromosomal disorders ^a Endometriosis Cataracts Menstrual abnormalities ^b Iron deficiency anemia B ₁₂ or folate deficiencies

Abbreviation: NASH, nonalcoholic steatohepatitis.

^aChromosomal disorders that may coexist include Down, Turner, and Williams syndromes.^bAmenorrhea, early menarche, early menopause, and infertility have been reported.

other presentations should warrant CD screening, such as dermatitis herpetiformis, short stature, recurring headaches, and failure to thrive. In some patients, laboratory evidence may be the only abnormality, including elevated alanine aminotransferase or aspartate aminotransferase, iron deficiency anemia, and vitamin B₁₂ or folate deficiency. Concurrent autoimmune conditions,

mainly type 1 diabetes and autoimmune thyroiditis, as well as a family history of CD should always prompt screening.^{2,3}

Serologic Testing

Patients with high clinical suspicion of CD should then be tested for tTG IgA while on a gluten-containing diet. The sensitivity and specificity of tTG IgA approach 98%. This is often adequate to proceed to duodenal biopsy; however, other comorbid conditions may affect the validity of the test. For example, patients with CD are 5 to 10 times more likely to have a selective IgA deficiency compared with the general population; thus, serum total IgA levels should always be obtained.¹⁰ If the serum IgA level is less than 0.2 g/L, the test of choice is IgG to anti-deamidated gliadin peptide. IgG and IgA to deamidated gliadin peptide is also preferred in children younger than 2 years because tTG has a lower sensitivity in this age group. False-negative serologic test results should always be considered in patients who have reduced or eliminated gluten from their diet or less commonly from the use of corticosteroids or immunomodulatory drugs.¹¹

Genetic Testing

In patients whose serologic and histologic results may not be consistent, genetic testing of HLA-DQ2 and HLA-DQ8 can be useful, which are expressed in approximately 95% of patients with CD. This testing is also helpful in patients who have eliminated gluten from their diet before seeking medical attention because both serologic and histologic test results may be negative. Thus, genetic testing can be seen as an excellent tool for excluding a diagnosis of CD.¹²

Duodenal Biopsy

Patients with a positive genetic or serologic test result will then undergo upper endoscopy with biopsy. One or 2 samples should be obtained from the duodenal bulb and at least 4 samples from the rest of the duodenum. As seen in Figure 1A, a biopsy can yield varying presentations from mild distortion of crypt architecture to villous atrophy often with lymphocyte infiltration in the lamina propria.¹³ These findings often reverse after adherence to treatment; however, follow-up endoscopy with biopsy to confirm this remains controversial. The gold standard for diagnosis of CD is villous atrophy on biopsy plus clinical remission while on a GFD.⁹ Modified Marsh criteria provides a grading system of intestinal

Table 2
Disorders Associated With Wheat- and Gluten-Related Sensitivities

Feature	Celiac disease	Nonceliac gluten sensitivity	Wheat allergy	Irritable bowel syndrome
Genetics	Strong association; a negative test result makes disease unlikely	Negative association	Negative association	Negative association
HLA-DQ2/8				
Immunopathology	Dendritic cell activation, intraepithelial lymphocytes, cytokines IL-2, IL-15, IL-21	Uncertain	T cells, T _H 2 cytokines, IgE, mast cells	Negative
Manifestations	Children: diarrhea (only in 10%), failure to thrive, abdominal pain, short stature; adults: diarrhea, anemia, osteoporosis, dermatitis herpetiformis, abdominal pain, neuropsychiatric disease, aphthous stomatitis	Abdominal pain, bloating, diarrhea, headaches, fatigue, arthralgia, eczema, anemia, depression, neuropsychiatric disease, including "foggy mind"	Food allergy, urticaria, anaphylaxis, WDEIA, eosinophilic esophagitis	Abdominal pain, constipation or diarrhea, postprandial urgency, fibromyalgia, GERD
Autoantibody to tTG, endomysial, gliadin, deamidated gliadin peptide	+++	Negative	Negative	Negative
Autoimmunity	Gluten ataxia, dermatitis herpetiformis, many other autoimmune disorders	Negative	Negative	Negative
Enteropathy	Crypt distortion, villous atrophy and infiltration by T cells	Negative	Negative or eosinophilic esophagitis	Negative
Malignancy	Increased risk for lymphoma, intestinal adenocarcinoma	Negative	Negative	Negative

Abbreviations: GERD, gastroesophageal reflux disease; IL, interleukin; tTG, tissue transglutaminase; WDEIA, wheat-dependent exercise-induced anaphylaxis.

Table 3
Foods That Are Considered Safe or Unsafe in Patients With Celiac Disease^a

Category	Vegetable	Fruit	Nuts	Poultry, meat, or fish	Grains
Safe	Beans Soy Tea Coffee Olive/oils Seeds	All fruits Juices Seeds	Unprocessed nuts	Eggs Fresh meat Fish Poultry	Rice/cakes Amaranth Buckwheat Corn Millet Quinoa Sorghum Teff Oats
Unsafe					Wheat and wheat surrogates, including semonlina, Kamut, and triticale Rye Barley/malt Oats Drug filler
Hidden	Soy sauce Marinades Shared equipment			Processed meat Shared equipment	

^aThe following foods can be ingested if they are certified as being gluten free: french fries, pasta, cookies, beer, bread, cakes, pies, puddings, ice creams, and certain salad dressings. It should be noted that wheat free does not imply gluten free, and gluten can also be found in rye and barley products. Per the US Food and Drug Administration (FDA) website, on August 5, 2013, the FDA issued a final rule defining the term *gluten free* for voluntary use in the labeling of foods. The compliance date for the final rule was August 5, 2014. The final rule defines gluten free as meaning that the food is inherently gluten free or does not contain an ingredient that is (1) a gluten-containing grain (eg, spelt wheat); (2) derived from a gluten-containing grain that has not been processed to remove gluten (eg, wheat flour); (or 3) derived from a gluten-containing grain that has been processed to remove gluten (eg, wheat starch), if the use of that ingredient results in the presence of 20 ppm or more gluten in the food (<http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Allergens/ucm362880.htm>).

damage by intensity. There are 3 types: preinfiltration (normal, type 0), infiltration with increased intraepithelial lymphocytes (types 1 and 2), and destruction with villous atrophy of different degrees (type 3, 3a partial atrophy, 3b subtotal atrophy, and 3c total atrophy).^{11,14}

Management

CD commonly leads to nutritional deficiencies, such as iron, folic acid, vitamins B₁₂ and B₆, copper, and zinc. Low bone mineral density may also be present secondary to malabsorption of vitamin D. In fact, a Dutch study assessing patients before initiation of a GFD found that 87% of patients had deficiencies in at least one serum vitamin or mineral.¹⁵ CD also places patients at greater risk for certain cancers. Lymphoma, specifically T-cell lymphoma, occurs at a 2.5 times higher rate in patients with CD compared with the general population and carries a particularly poor prognosis. In addition to hematologic malignant tumors, patients with CD are also at higher risk for colon, oropharyngeal, esophageal, pancreatic, and hepatobiliary cancers, but only in the first year after diagnosis. After 1 year, there is a small risk only for small-bowel and hepatobiliary malignant tumors, and some studies have even found a protective effect against breast, ovarian, and endometrial cancers.¹²

The gold standard for CD treatment is strict adherence to a GFD, and symptomatic improvement is usually seen within 4 weeks. Serologic normalization often follows at approximately 1 year after initiation of a GFD. In the United States, the cutoff to classify a food as gluten free is 20 ppm or 20 mg of gluten per kilogram of product.¹⁵ Table 3 gives a general list of foods that are safe to eat and specifically which grains are safe and which should be avoided.

Medical care personnel must realize the difficulties inherent in strict gluten intolerance because this is the most common cause for relapse in disease. Specifically, teenagers with CD may encounter challenging situations, such as birthday parties, religious ceremonies, and dining out. One questionnaire cited that in patients with CD, the self-rated adherence to a diet was similar to that of patients with end-stage renal disease.² It is therefore no surprise that nonadherence to a GFD is the most common cause of nonresponsive celiac disease, which is defined as recurrent symptoms or laboratory abnormalities at 6 to 12 months after diagnosis. A total

of 1% to 2% of cases will have what is termed *refractory celiac disease*, which is when strict adherence to a GFD is maintained and other causes of symptoms are excluded.¹²

Therapies for CD besides a GFD are being researched and are promising. Oral enzyme supplements (glutenases) are under development, which have been found to attenuate mucosal injury in patients with biopsy-proven CD.⁹ Other novel therapies being investigated include the enhancement of tight junctions in the intestinal epithelium, a vaccine to induce gluten tolerance, and inhibitors of the HLA-DQ2 and HLA-DQ8 proteins. One study even found remission of aphthous stomatitis and improvement in quality of life in a patient with CD with the use of etanercept.¹⁶ However, these new approaches to CD are still not standard of care; thus, a lifelong adherence to a GFD is still the mainstay of treatment.

Conclusion

CD is an increasingly prevalent autoimmune condition that requires a multisystem approach for proper diagnosis and treatment. Serologic tests and duodenal biopsy help confirm the diagnosis. Irritable bowel syndrome and nonceliac gluten sensitivity need exclusion. Patients require education about which foods are safe to eat and which to avoid. Often, referral to a dietitian is necessary.

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