

Celiac disease for the allergist: Who and how to screen

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ABSTRACT

This article is meant to guide the allergist in clinical practice. Current understanding of the pathogenesis and epidemiology of celiac disease is reviewed. Issues of screening and genetic testing are discussed and current controversies and additional resources are highlighted.

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Key words: Celiac disease, screening, transglutaminase

Celiac disease also is called gluten sensitivity, sprue, celiac sprue, and gluten sensitivity enteropathy. It is an immune non-IgE-mediated enteropathy caused by a permanent sensitivity to gluten and related proteins. The disease occurs in a minority of genetically susceptible individuals. Gluten, the water-insoluble fraction of wheat flour, includes two main groups of proteins: glutenins (ethanol insoluble) and gliadins (ethanol soluble). Individuals with celiac disease are intolerant to the gliadin fraction of gluten, as well as equivalent prolamins found in rye and barley. Recent evidence suggests that some individuals with celiac disease also may be intolerant to the glutenin fraction of gluten.¹ Given the wide and often subtle range of clinical symptoms along with increased public perception, the allergist may be tasked with distinguishing between celiac disease and intolerance and IgE-mediated allergy to wheat or other grains.

PATHOGENESIS AND GENETICS

Celiac disease is unique among autoimmune diseases in that the three major elements are known: a genetic restriction, a required environmental exposure, and an autoantigen (Fig 1).² Currently, the only effective long-term therapy is the gluten-free diet.

Between 90 and 95% of individuals with celiac disease express human leukocyte antigen (HLA) DR3-DQ2, and the remaining 5–10% express HLA DR4-DQ8.³ The strong HLA restriction in celiac disease is related to the characteristics of gluten, which is rich in proline and glutamines. Proline residues help confer resistance to proteolysis by digestive enzymes, and glutamine is targeted by the ubiquitous enzyme tissue transglutaminase (tTG) for deamidation. This deami-

dation of glutamine to glutamic acid results in a modified gluten peptide that effectively binds DQ2 and enhances T-cell recognition, resulting in gluten-specific T cells. In particular, a 33 amino acid sequence in gliadin has been found especially resistant to intestinal digestion and has been suggested as the major gluten epitope in celiac disease.⁴

In patients with celiac disease, even though antibodies to gliadin appear, they do not reliably indicate the presence of disease, because a large number of normal healthy individuals also have antibodies to gliadin. A much more reliable serological test for celiac disease is the measurement of IgA autoantibodies to tTG. New tests for antibodies to modified gliadin peptides also show promise, such as those measuring actin and deamidated gliadin peptides.^{5,6}

The contention that celiac disease is truly an autoimmune disease is based on the following evidence: there is HLA restriction, autoantibodies exist (tTG), and there is a strong association with other autoimmune diseases. However, when applying classic criteria to establish an autoimmune disease, data for celiac disease are lacking with respect to demonstration of the existence of autoreactive T cells, identification of the T cell autoantigen involved, and the ability to induce disease in an animal model with the autoantigen. Gluten-reactive T cells, but not autoreactive T cells, have been identified in patients with celiac disease. For this reason, the disease is sometimes characterized as a food allergy or food intolerance disorder. Characteristic of food allergies, the disease waxes and wanes with gluten intake and gluten-free diet. However, it is clear that celiac disease is a T cell-mediated disorder with a known environmental trigger that occurs in genetically predisposed individuals.

PRESENTATION

The clinical presentation of celiac disease is quite variable and age dependent.⁷ Often, it is helpful to consider intestinal and extraintestinal features of celiac

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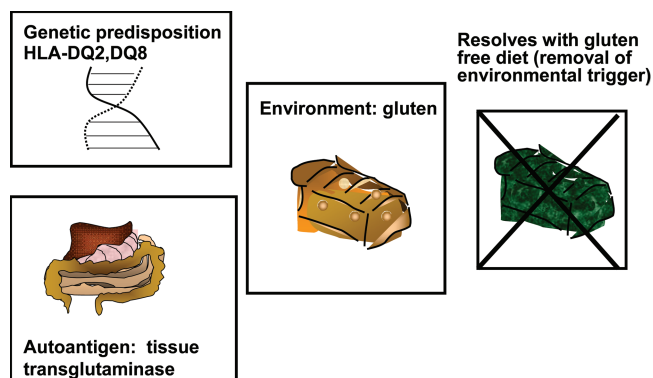


Figure 1. Celiac disease is unique among autoimmune diseases in that three elements, a genetic predisposition, environmental exposure, and an autoantigen, are known.

disease because the differential diagnoses may be quite different.

Intestinal Manifestations

There is good evidence for a number of intestinal manifestations of celiac disease (Table 1).⁸ These represent the “classic” form of the disease but the majority of cases no longer present this way. The intestinal manifestations of celiac disease are not specific for celiac disease and are common in the general population.

Extraintestinal Manifestations

Celiac disease may manifest distant from the intestinal tract (Table 1). These manifestations include short stature, delayed puberty, aphthous ulcers, decreased bone mineralization, and abnormal liver function tests. Weaker evidence associates celiac disease with other conditions such as dental enamel hypoplasia, epilepsy with occipital calcifications, arthritis, and, in adults, iron deficiency anemia not responsive to oral iron supplementation.

Dermatitis Herpetiformis

A well-described form of celiac disease presents usually ~30–40 years of age with intensely pruritic papulovesicles with excoriation, called dermatitis herpetiformis.⁹ The areas most often involved are the elbows, knees, scalp, and buttocks, although other areas such as the palms may be involved. Newer entities, such as gluten ataxia, are being considered, but evidence still is circumstantial.

Asymptomatic Cases

Presently, asymptomatic celiac disease may be the most common form of the disease. This “silent” form is identifiable only by screening because these individuals have no symptoms or mild symptoms. Silent celiac disease should be considered in those individuals at higher risk. This includes patients from a family with celiac disease or patients with conditions associated with an increased risk of celiac disease (Table 2).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis depends on the presentation (Table 3). For a malabsorption type of presentation (diarrhea, fatty stools, weight loss, and/or distention) considerations include Crohn’s disease, intestinal parasites, food allergy, and intestinal malignancy. For abdominal pain and epigastric discomfort, acid-peptic diseases such as ulcer, gastroesophageal reflux disease, *Helicobacter pylori* infection, pancreatitis, and gall bladder disease may be considered. For the dermatitis herpetiformis presentation, eczema and food allergies may be considered. The diagnosis of dermatitis herpetiformis is made by skin biopsy revealing granular IgA deposits in the dermal papillary tips in the uninvolved areas adjacent to a lesion. Celiac-related antibodies usually are present, but the actual titer may be low. Granular IgA deposits may be seen in Henoch-Schon-

Table 1 Evidence for intestinal and extraintestinal manifestations of celiac disease

Classic GI Manifestations, Strong Evidence	Extraintestinal Manifestations	
	Stronger Evidence	Weaker Evidence
Chronic diarrhea	Elevated LFT	Epilepsy with cerebral calcifications
Abdominal distention	Short stature	Dental enamel hypoplasia
Poor weight gain, weight loss	Pubertal delay	Arthritis
Irritability	Iron deficiency anemia, resistant to oral iron (adults)	
Anorexia	Aphthous ulcers	
Constipation	Dermatitis herpetiformis	
Abdominal pain	Osteopenia/osteoporosis	
Vomiting		

GI = gastrointestinal; LFT = liver function tests.

Table 2 Risk groups for celiac disease

Risk Group	Frequency (%)
Type 1 diabetes	4–10
Williams syndrome	8
Down syndrome	4–20
Autoimmune thyroid disease	8
Secretory IgA deficiency	7
First-degree relative of celiac disease patient	~5
General population	1

lein purpura and lupus erythematosus, but these diseases present very differently. When there is delayed puberty and short stature, considerations include Crohn's disease, growth hormone deficiency, and hypothyroidism, as well as nutritional deficiencies from increased intestinal losses or poor absorption. When the complaints are nonspecific or vague, depression, irritable bowel syndrome, specific nutritional deficiencies including vitamin B12, folate, and iron may be considered.¹⁰

CELIAC DISEASE AND ALLERGIC CONDITIONS

There is some evidence that adults with celiac disease do not have increased frequency of allergy compared with a control group of spouses and relatives.¹¹ Celiac disease affects ~1% of atopic patients. This prevalence is about the same as found in the general population.¹²

SCREENING BECAUSE OF CLINICAL SUSPICION USUALLY IS STRAIGHTFORWARD

Screening because of a clinical suspicion of celiac disease is straightforward for the majority of cases. A single test, tTG antibody, or endomysial antibody has

very high sensitivity and specificity in the range of 95–100%.⁸ Because of rare cases of IgA deficiency with celiac disease, a quantitative IgA level also may be drawn and if normal, increases the confidence in a negative test. Most guidelines and experts recommend that a positive screening test be followed by small bowel biopsy to confirm the diagnosis of celiac disease. Our experience is that a small proportion of seropositive individuals will have a different condition causing their symptoms, and, in our department, we require a small bowel biopsy to make the diagnosis of celiac disease. In developing countries, biopsy may be viewed as mandatory to exclude other entities such as tropical sprue.

SCREENING BECAUSE OF A RISK GROUP (FAMILY HISTORY OR ASSOCIATED CONDITION)

Recent guidelines allow screening of individuals who belong to a risk group (family history, associated condition such as type 1 diabetes)^{8,13} However, the risk and benefit of screening and early diagnosis remains unclear, and universal screening has not been recommended.¹⁴ The frequency of celiac disease in most risk groups is ~5–10% (Table 2). There are two main problems when considering screening. First, ~25–30% of individuals with positive screening serological tests may have normal biopsies. It is unclear whether these individuals have early or mild celiac disease, false positive tests, or variable production of autoantibody of unclear prognostic value (Table 4).¹⁵ This situation is the reason that, for most experts, a positive serological test is not sufficient to confirm the diagnosis and biopsy confirmation is required for the diagnosis of celiac disease. The second issue is that compliance with gluten-free diet is poor when symptoms are mild or absent and when diagnosis is made beyond childhood.¹⁶

Table 3 Differential diagnosis depends on presentation

Malabsorption	Abdominal Pain, Vomiting	Growth, Pubertal Delay	Nonspecific Complaints	DH
Crohn's disease	Acid-peptic disease (ulcer, reflux)	Crohn's disease	Depression	Eczema
Intestinal parasite	<i>H. pylori</i>	Growth hormone deficiency	Irritable bowel syndrome	Food allergy
Food allergy	Food allergy	Thyroid disease	Nutritional deficiency: B12, folate, iron	
Malignancy	Pancreatitis			
Lactose intolerance	Gall bladder disease			

DH = *Dermatitis herpetiformis*.

Table 4 Positive predictive value for biopsy confirmation of celiac disease

Presentation	Positive Predictive Value
Clinical presentation	>95%
Screening identified (family history, associated condition)	70–80%

GENETIC TESTING FOR HLA DQ2 AND HLA DQ8: HIGH NEGATIVE PREDICTIVE VALUE

Approximately 30% of the Western (European and North American) population expresses HLA DQ2 or HLA DQ8. The 1% of the population that is thought to have evidence of celiac disease resides entirely (or almost entirely) in this group because almost all celiac disease patients express DQ2 or DQ8. Genetic testing for DQ2 or DQ8 is commercially available. A positive test for DQ2 or DQ8 has a positive predictive value for celiac disease of only ~3%. The value of the test is its high negative predictive value. If a test for DQ2 and DQ8 is negative, the probability of ever developing celiac disease is very low (~<1%) and additional testing is not needed.⁸ This test might be useful in those individuals who feel better not eating wheat but who do not have standard evidence for celiac disease (seronegative or biopsy normal). Genetic counseling may be helpful because testing is easily misunderstood.

IgA DEFICIENCY

If IgA deficiency is present, IgG class endomysial, TG, and gliadin peptide antibody tests are becoming available. Alternatively, a small bowel biopsy may be performed. Celiac panels, such as testing for antibodies to tissue transglutaminase, gliadin, and endomysium do not add value over single tests for antibodies to tissue transglutaminase or endomysium.⁸ However, some guidelines do recommend screening with panels, especially in low probability situations.⁷

SUPPORT GROUPS AND MORE INFORMATION

The treatment with a gluten-free diet may be accomplished more effectively with the assistance of an experienced dietitian and support groups. Fortunately, there are many support groups and websites available in the United States (Table 5).

TO SUMMARIZE: KEY POINTS

1. The decision on whether to screen at-risk groups is controversial.

Table 5 Selected support groups and websites

www.celiachealth.org	Children's Digestive Health and Nutrition Foundation
www.nlm.nih.gov/medlineplus/ceciacdisease.html	National Institutes of Health
www.gluten.net	Gluten Intolerance Group
www.celiac.org	Celiac Foundation
www.csaceliacs.org	Celiac Sprue Association

2. The positive predictive value of endomysial antibody or tTG antibody testing is lower when screening at-risk individuals compared with testing those individuals with a clinical suspicion.
3. Experts continue to require small bowel biopsy to diagnose celiac disease.
4. Genetic testing for HLA DQ2 and HLA DQ8 has high negative predictive value for celiac disease but is not useful for confirming the presence of celiac disease.
5. A single test for IgA antibodies to TG or endomysium is sufficient for screening (except IgA deficiency).
6. Quantitative IgA levels may be obtained, primarily to add confidence in a negative test for celiac disease. If IgA deficiency is present, order IgG antibodies to TG or endomysium and/or proceed with small bowel biopsy.

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