CLINICAL PRACTICE

Celiac Disease

Joseph A. Murray, M.D.,[1] and Steffen Husby, M.D., D.M.Sc.[2]

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

SUMMARY

Celiac disease, a common autoimmune condition affecting approximately 1% of the population, can develop with exposure to gluten at any age. Diagnosis involves serologic testing, especially for IgA antibodies against tissue transglutaminase, and may include tests to confirm the presence of endomysial antibodies or even duodenal biopsies, although the latter are becoming less necessary. The presence of genes encoding HLA-DQ2 or HLA-DQ8 is a prerequisite for the disease. A gluten-free diet is the mainstay of treatment, but some adults have nonresponsive celiac disease, which warrants closer monitoring because of an increased risk of malignant conditions. Celiac disease also frequently co-occurs with other autoimmune disorders, such as type 1 diabetes mellitus and autoimmune thyroid disease.

At presentation, an 18-year-old woman reports a 1-year history of daily abdominal bloating and malodorous flatulence. She also reports fatigue and recurrent mouth ulcers. Her complete blood count shows a normal hemoglobin level but a low mean corpuscular volume (65 fl [reference range, 76 to 100]) and a low ferritin level (6 ng per milliliter [reference range, 6 to 175). Additional blood tests reveal mild iron deficiency without anemia and mildly elevated liver-enzyme levels (alanine aminotransferase level, 70 U per liter [reference range, 7 to 45], and aspartate aminotransferase level, 56 U per liter [reference range, 8 to 43]). Oral iron therapy is initiated, but her symptoms and hypoferritinemia persist. Her family history is notable for a 10-year-old brother with type 1 diabetes mellitus and celiac disease. A celiac serologic test for IgA antibodies against tissue transglutaminase (tTG-IgA) is performed, and the results are positive (150 IU per milliliter [reference value, <15). How would you proceed?

Author affiliations are listed at the end of the article. Joseph A. Murray can be contacted at murray.joseph@mayo.edu or at the Department of Gastroenterology, Mayo Clinic Rochester, 200 First St. SW, Rochester, MN 55905.

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CME

THE CLINICAL PROBLEM

Celiac disease is a chronic, small-intestinal, immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed persons.[1] The disease is increasingly common, affecting persons of all ages, and has a wide geographic distribution,[2,3] seemingly with a North–South gradient.[4] The prevalence of celiac disease is approximately 1% and may be higher in northern European countries such as Sweden, where the prevalence is estimated to be 2 to 3%.[5,6] The age-specific peak incidence has shifted from 1 to 2 years of age to 5 to 8

years of age,[7] with many patients presenting in adulthood. Celiac disease may remain undiagnosed for years, even decades, and is a common cause of malabsorption of key nutrients, such as iron and vitamin D.

In patients presenting with signs and symptoms suggestive of celiac disease, serologic testing for tTG-IgA is the first step for making the diagnosis, and if positive, the next step is to confirm the diagnosis. For decades, celiac disease has been defined and the diagnosis confirmed by histologic changes in the proximal small intestine. The increasing accuracy of celiac-specific serologic testing has enabled strategies (especially in children) of diagnosing celiac disease without histologic confirmation. However, biopsy-avoidance strategies have yet to be recommended for adults. The need for high specificity in making the diagnosis is based on the lifelong, burdensome treatment for this disease.

CLINICAL FEATURES

The clinical picture of untreated celiac disease varies from asymptomatic to severe. Gastrointestinal symptoms are the result of intestinal inflammation and include nausea, vomiting, stomach pain, bloating, and chronic diarrhea and are accompanied by weight loss and, in children, growth failure.[8] The damage to the lining of the proximal small intestine produces maldigestion and malabsorption of carbohydrates, lactose, fats, and proteins and deficiencies of micronutrients such as fat-soluble vitamins, iron, and vitamin B_{12}. The classic clinical picture of a stunted child with a large belly and flat buttocks who has steatorrhea is rare. Oligosymptomatic or monosymptomatic manifestations such as growth failure, anemia, or nonspecific gastrointestinal symptoms, including constipation, are now more common than the classic clinical features. The consequences of malabsorption include iron-deficiency anemia, which may not resolve with oral iron supplementation, and bone disease with osteoporosis. Extraintestinal symptoms, including dermatitis herpetiformis and other organ-specific effects, may occur in the absence of gastrointestinal symptoms, and celiac disease can manifest with a wide variety of extragastrointestinal symptoms (Table 1).

Other less common manifestations of celiac disease may include seizures associated with occipital lobe calcifications,[11] myocarditis, and pulmonary hemosiderosis, as well as an increased risk of spontaneous abortion.[12] Celiac disease is associated with an increased risk of gastrointestinal cancer, especially cancer affecting the small intestine, the esophagus, or both. Gastrointestinal and nongastrointestinal lymphoproliferative disease is more common among patients who receive a diagnosis later in life, occurring particularly in the first year after diagnosis.[10,13] Refractory celiac disease is a condition that does not respond to a gluten-free diet. Refractory celiac disease type I is a condition without malignant potential, whereas refractory celiac disease type II has clonal aberrations that can progress to enteropathy-associated T-cell lymphoma, a rare condition that arises from the development of aberrant lymphocytes in the context of long-standing inflammation and is often preceded by refractory celiac disease. Simple immunohistochemical staining for intraepithelial lymphocytes that maintain cytoplasmic staining of CD3 but lack surface staining of CD8 may suggest refractory celiac disease type II.[14] Confirmation requires molecular testing and flow cytometry to determine aberrancy. The presence of clonality alone is not enough to make this diagnosis.

PATHOGENESIS

Celiac disease occurs in a small percentage of genetically susceptible persons who have an HLA type that puts them at risk and who eat gluten as part of their diet. What triggers the disease is less clear. Observational studies suggest that the amount of gluten in the diet during the first years of life influences the risk of celiac disease.[15] However, two studies investigated whether the introduction of gluten in minute amounts during the first year of life in infants with a hereditary risk of celiac disease would affect the later occurrence of the disease, and both studies had a negative result.[16,17] This negative outcome could be due to the small amounts of gluten that were chosen or the high risk of celiac disease in the selected patient groups. Disrupted microbiota of the gastrointestinal tract may be a risk factor, although breastfeeding is neither protective nor a risk factor. Frequent antibiotic use in early childhood may be associated with an increased risk of celiac disease.[18] Mode and season of birth have been widely studied but are not clearly responsible.[19] Several studies, although methodologically limited,

suggest a role for viral triggers leading to loss of tolerance if it overlaps with the introduction of gluten.[20]

Celiac disease is driven by gluten from wheat, rye, and barley and is caused by a reaction to gliadins and analogous proteins that have not degraded completely in the gastrointestinal tract (Fig. 1). Celiac disease has features of an autoimmune disease that is triggered by known exogenous antigens.[21] When incompletely digested gliadin peptides pass through the gut wall, the ubiquitous enzyme tissue transglutaminase 2 (TG2) selectively deaminates specific glutamine residues. This interaction results in highly antigenic epitopes that are recognized by T cells and B cells. The B cells produce antibodies against both deamidated gliadin peptides and activated TG2 and also enables antigen uptake through the B-cell receptor and presentation to the gliadin-reactive CD4 T cells central to the immune response. HLA-restricted presentation occurs specifically through HLA types HLA-DQ2.5 (encoded by DQA05* with DQB02*) or DQ8 (encoded by DQA03 DQB0302),[22] which orchestrate a further cascade of events. CD8 T cells are recruited to drive cytotoxic effects directed against epithelial cells, and an innate immune response takes place at the epithelial cells with engagement of unconventional HLA antigens.[23]

These inflammatory reactions lead to mucosal changes with an influx of lymphocytes into the surface epithelium, crypt hyperplasia due to expansion of the lamina propria with inflammatory cells, and villous atrophy, producing variable degrees of damage.[24] TG2 is recognized as the primary autoantigen in celiac disease,[25] triggering antibody formation mainly, but not solely, of the IgA isotype. It is notable that TG2 does not elicit a T-cell response without companion gliadin peptides. Assays for tTG-IgA are widely available and are often used as the first step for the detection of celiac disease. Selective IgA deficiency occurs in 2 to 4% of patients with celiac disease and may lead to a false negative screening result for celiac disease with tTG-IgA. Measurement of serum IgA levels in the initial screening for celiac disease should avoid a false negative result.

GENETICS

A family history of celiac disease, when obtained, is key to detection. Celiac disease is strongly

Table 1. Extragastrointestinal Manifestations of Celiac Disease.

Manifestation (Special Features)
Common manifestations
Neuropsychiatric system
Peripheral neuropathy (distal, symmetric, predominantly sensory neuropathy)
Cerebellar ataxia
Migraine
Seizure disorder (associated with occipital calcification)
Movement disorder (associated with myoclonus)
Cognitive impairment (ranging from brain fog to dementia)
Depression, anxiety, eating disorders, attention deficit–hyperactivity disorder, autism spectrum disorders, and irritability
Reproductive system
Delayed menarche
Unexplained female or male infertility
Premature menopause
Miscarriage
Secondary amenorrhea
Mucocutaneous system
Dermatitis herpetiformis
Recurrent aphthous ulceration
Xerosis
Urticaria
Alopecia
Skin pigmentation
Musculoskeletal system
Arthralgias
Muscle pain or weakness
Increased fracture risk
Rickets and osteoporosis
Hepatic system
Hepatic steatosis
Isolated elevation of liver enzymes
Portal hypertension
Granulomatous hepatitis
Hematologic system
Anemia (iron deficiency, vitamin B_{12} deficiency, folate deficiency, copper deficiency)
Hyposplenism
IgA deficiency
Neutropenia
Hemophagocytic lymphohistiocytosis
Rare manifestations
Cardiovascular system
Myocarditis
Pericarditis
Deep venous thromboembolism
Dyslipidemia
Respiratory system
Lane–Hamilton syndrome (pulmonary hemosiderosis)
Bronchiectasis
Pneumococcal pneumonia[9]
Interstitial lung disease
Nocardia infection
Oncologic conditions[10]
Enteropathy-associated T-cell lymphoma
Adenocarcinoma of the small intestine
Head and neck cancers
Esophageal cancer

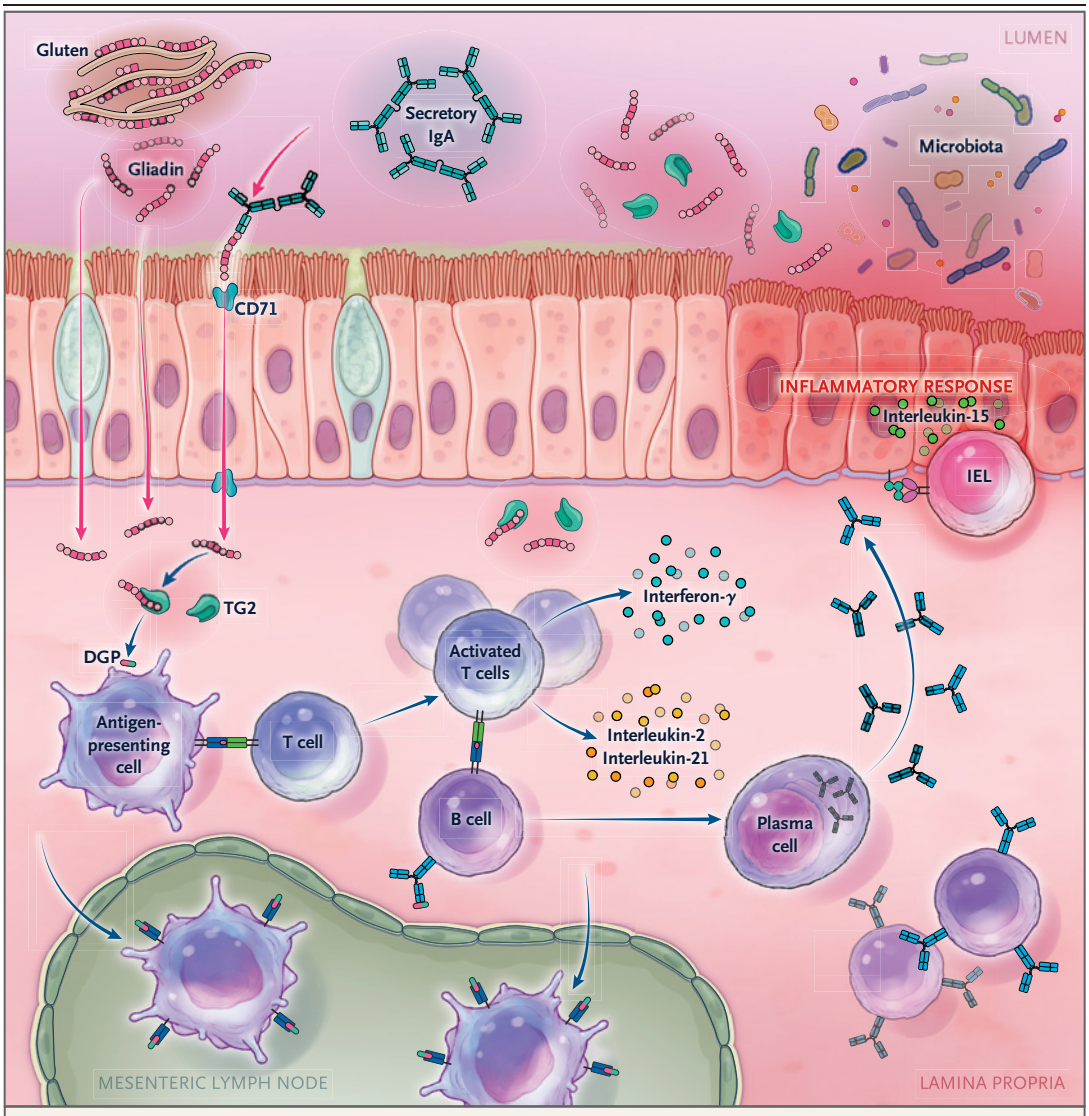

Figure 1. Elements of the Pathogenesis of Celiac Disease in the Small Intestine.

Gluten is incompletely digested into peptide fragments. These peptides transit the epithelium by several pathways and interact with tissue transglutaminase 2 (TG2). The peptides are deamidated and taken up by antigen-presenting cells (especially B cells) to engage with CD4 T cells driving the release of cytokines, including interleukin-2 and interferon-γ, and expansion of inflammatory cells. B cells develop into plasma cells that produce primarily IgA antibodies. Intraepithelial lymphocytes (IELs) expressing the natural killer cell receptors NKG2D and NKG2C recognize HLA-E and class I major histocompatibility complex–related molecules and target enterocytes for cytolysis, which leads to mucosal destruction. DGP denotes deamidated gliadin peptide.

genetically determined. Beyond the essential HLA types,[26] celiac disease is related to a multitude of genes involved in barrier function, innate immunity, and T-cell activation, including those coding for interleukin-2, interferon-γ, and cytotoxic T-lymphocyte antigen 4 (CTLA-4). Clinicians should be aware that the risk of celiac disease for first-degree family members (parents, siblings, and children) is 10 to 20%.[27] The risk of celiac disease is increased among patients with other autoimmune diseases — among those with type 1 diabetes, the risk is 7 to 12%[28]; among those with autoimmune thyroid disease, the risk is 5 to 7% [29]; and among those with autoimmune liver disease,

the risk is 5%.[30] Most studies have shown that celiac disease precedes the onset of type 1 diabetes mellitus, but this may depend on the regional strategy for celiac disease detection. Furthermore, the prevalence of celiac disease is increased among patients with Down's syndrome or Turner's syndrome (2 to 5%), probably owing to abnormal immune responses related to chromosomal instability.[31]

STRATEGIES AND EVIDENCE

DIAGNOSIS

Before testing a patient for celiac disease, it is important to ascertain whether the patient is consuming a normal gluten-containing diet, since restriction of gluten intake dramatically reduces the sensitivity of both serologic and histologic testing. Histologic analysis of duodenal biopsies has long been the reference standard for the diagnosis of celiac disease (Fig. 2). Serologic analysis of celiac antibodies, particularly tTG-IgA, has been shown to have high accuracy.[32,33] There is now evidence that a no-biopsy approach can provide a reliable diagnosis when the tTG-IgA level is at least 10 times the upper limit of the normal range (ULN), which accounts for 40 to 70% of the cases in children.[34,35] The accuracy that can be obtained by combining a tTG-IgA level of at least 10 times the ULN (with high sensitivity) with a subsequent endomysial antibody–positive test (with high specificity) may lead to positive predictive values of 99.8%, which is similar to or better than that of histologic analysis.[34,36] Histologic analysis is often used as the reference standard; however, the result depends on the experience level of the pathologist,[37] and the interpretation may vary in the range of 4 to 7%. The recommendation for a tTG-IgA level of at least 10 times the ULN to be used as a cutoff value in children was based on a systematic review.[38] In all cases, biopsy is necessary in the diagnosis of IgA deficiency.

The pattern of differential diagnosis in adults differs from that in children and includes an elevated risk of gastrointestinal cancer.[39] Histologic analysis remains a crucial step for confirmation of the diagnosis when the initial tTG-IgA level is less than 10 times the ULN.[40] Persons with persistently positive serologic tests but normal biopsy results (together indicating potential celiac disease) present a challenge. Those with obvious symptoms may be offered a trial of a gluten-free diet, and if the response is positive, can be followed as if they had received a diagnosis of celiac disease. Those without obvious symptoms or with unclear symptoms may be followed while they remain on a normal, gluten-containing diet. In a study involving 280 children with potential celiac disease, one third had negative serologic tests within the first 2 years of follow-up, whereas 43% had progression to overt celiac disease by 12 years.[41]

Virtually 100% of patients with celiac disease carry either the HLA-DQ2 or HLA-DQ8 haplotype[42]; however, these haplotypes occur in 30 to 45% of persons in most populations, so only 3 to 4% of those with these haplotypes will eventually have celiac disease. These haplotypes are rare in East Asia, notably Japan, and celiac disease is also less common in these populations. Determination of the presence of HLA-DQ2 and HLA-DQ8 is useful to rule out celiac disease in persons who have already started a gluten-free diet at their first visit.

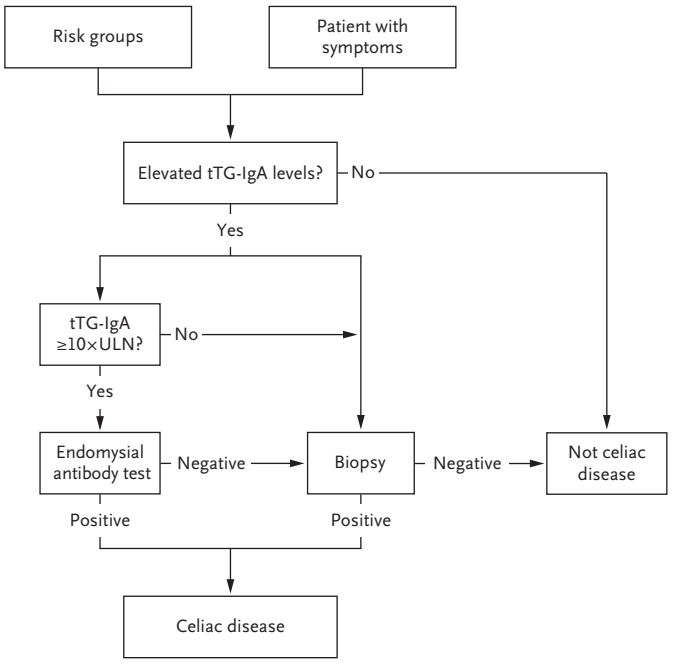

Figure 2. Flowchart for the Diagnosis of Celiac Disease.

Risk groups are those with a family history of celiac disease or autoimmune diseases associated with celiac disease. Testing for IgA antibodies against tissue transglutaminase (tTG-IgA) is the primary serologic test in patients with normal total serum IgA. ULN denotes upper limit of the normal range.

Recently, it has been shown that in vitro gluten challenge in whole-blood samples obtained from patients with suspected celiac disease who were already following a gluten-free diet but have not received a formal diagnosis may be useful in making the diagnosis on the basis of gluten-stimulated interleukin-2 secretion, which indicates the presence of pathogenic gluten-specific CD4+ T cells.[43]

The usefulness of screening asymptomatic persons for celiac disease is controversial. Although the disease can be readily detected and treated, little is known about the ultimate outcome in asymptomatic persons and whether early detection matters. This uncertainty led the U.S. Preventive Services Task Force to conclude in 2017 that the evidence was insufficient to justify testing asymptomatic persons for celiac disease.[44] The Italian government has launched a general screening strategy for celiac disease and type 1 diabetes in schoolchildren in five regions, including Sardinia, where the incidence of type 1 diabetes is particularly high. In the United States, the Autoimmunity Screening for Kids study is currently addressing this issue in several locations.[45] The results of such studies may provide more evidence to inform a global screening policy.

MANAGEMENT

The mainstay of treatment is a gluten-free diet, in which foods and ingredients containing proteins from wheat, barley, rye, and related grains are avoided.[46] The agreed threshold for gluten contamination of gluten-free foods is 20 ppm. The diet, simple in concept, is not easy to adhere to and presents a substantial burden of care.[47] Guidance by a qualified dietician is needed to implement the gluten-free diet. Most patients can consume oats (a valuable nutritional supplement) without unacceptable side effects. A pragmatic approach to dietary management is to introduce oats when symptoms have disappeared and the tTG-IgA levels have normalized or are close to normal, which usually occurs 3 to 12 months after starting a gluten-free diet (Fig. 3). It is important to note that the preparation of oats needs to be free of contamination with wheat. In patients with continued symptoms, which can occur in up to 30% of adult patients, or persistently elevated tTG-IgA levels, the first task will be to scrutinize the gluten-free diet before seeking other explanations such as refractory celiac disease. IgG antibody levels in IgA-deficient patients with celiac disease tend to normalize at a slower pace (1 to 2 years after starting a gluten-free diet).[48]

In patients who receive a diagnosis of celiac disease later in life, concomitant complications such as malignant conditions should be considered at the time of diagnosis, given the evidence that these complications are typically detected within a year after diagnosis. For example, celiac disease–related clonal aberrations can progress to enteropathy-associated T-cell lymphoma, a condition that is associated with a very poor outcome, particularly in patients with poor performance status. Celiac disease is a chronic disease that may lead to long-term complications and deserves regular follow-up.

GUIDELINES

A number of guidelines for diagnosing celiac disease have been published during the past decade. Strict adherence to both serologic and histologic criteria is necessary, particularly for the no-biopsy approach in children with symptoms or signs of celiac disease.[8,38] Selection criteria include a tTG-IgA level of at least 10 times the ULN and a positive IgA endomysial antibody test (a fluorescence-based test) from a second blood sample (Fig. 2). Both the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) guidelines[49] and the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) guidelines[38] promote the tTG-IgA test for initial detection and address the possibility of IgA deficiency by measurement of serum IgA. The NASPGHAN guidelines and guidelines for adults consider biopsies to be essential for diagnosis, except in circumstances in which endoscopy is not feasible.[40,49] In this review, we have primarily described the 2023 American College of Gastroenterology guidelines for adults[50] and the 2020 ESPGHAN guidelines for children (Fig. 2).[38] All guidelines recommend that to increase the sensitivity of serologic tests, it is essential that testing is performed before any reduction in dietary gluten. When patients first receive a biopsy-based diagnosis, timely serologic analysis is useful for confirmation, since 5 to 10% of patients with enteropathy may have alternative diagnoses.

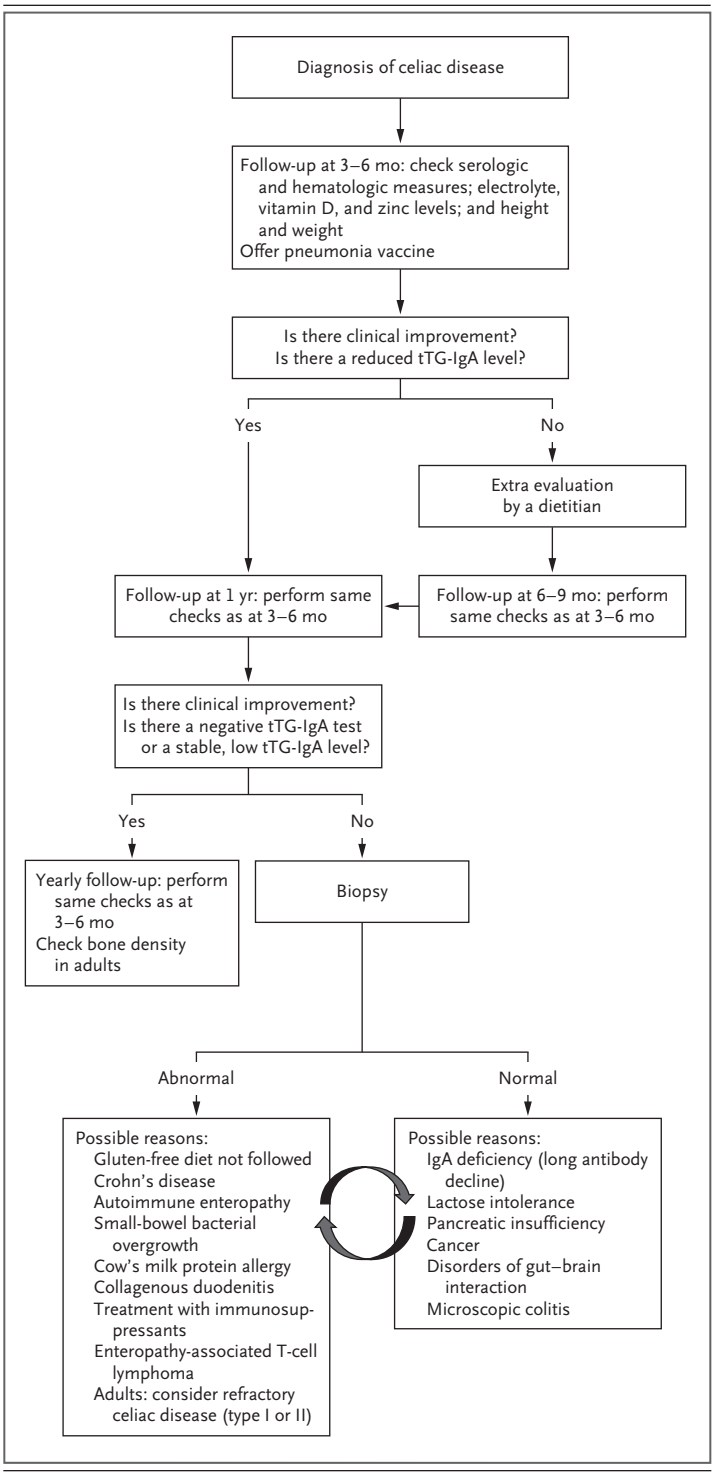

Figure 3. Flowchart for the Management of Celiac Disease.

After the 1-year follow-up, it may take 1 to 2 years for a tTG-IgA test to become negative or show a low and stable level. The symptoms of lactose intolerance may not differ from those in persons without celiac disease. The rotating arrows between the possible reasons for abnormal and normal biopsy results indicate the uncertain clinical significance of histologic findings and the fact that disorders can coexist.

AREAS OF UNCERTAINTY

The guidelines for both children and adults rely on serologic testing that may be affected by the quality of assays that are in routine use.[35] Further prospective studies may lead to a revision of the cutoff level of 10 times the ULN. In addition, biopsy evaluation is not flawless. Whereas the diagnostic guidelines are reasonably well documented, the instructions for follow-up and management are less clear. Histologic changes and antibody levels are usually normalized within 6 to 12 months. In children, lack of antibody normalization is rare, provided that a gluten-free diet is followed,[51] whereas adults may have a more protracted course warranting histologic reevaluation.[52] If severe symptoms and histologic findings of villous atrophy persist after 1 year of following a gluten-free diet, the patient may have refractory celiac disease, which occurs in 1 to 4% of adult cases.[53] Our improved understanding of the biologic processes that underlie celiac disease has provided a range of targets for potential therapies. Many of these therapies have been or are being investigated in clinical trials, but none have yet been proved to be safe and effective for celiac disease.

CONCLUSIONS AND RECOMMENDATIONS

Our practice regarding celiac disease has changed dramatically over the past decades. Health professionals now consider celiac disease in a far broader range of patients, both in terms of demographic characteristics (i.e., age, geographic region, and ethnic group) and across a much wider spectrum of clinical manifestations.

In the introductory vignette, the patient has an increased tTG-IgA level (10 times the ULN) on celiac serologic testing. On the basis of the American College of Gastroenterology guidelines, we recommend performing a gastroscopy with duodenal biopsies and, if the results are confirmatory

KEY CLINICAL POINTS

CELIAC DISEASE

- Celiac disease is a common autoimmune disease with a prevalence of approximately 1%.
- Celiac disease occurs at all ages, provided that gluten is part of the diet, and can be a major cause of malabsorption of key nutrients.
- A gluten-free diet is the mainstay of treatment.
- The presence of genes encoding HLA-DQ2 or HLA-DQ8 is a prerequisite for celiac disease.
- Celiac antibodies in serum, mainly IgA antibodies against tissue transglutaminase, are used for first-line screening in patients with symptoms consistent with celiac disease. Endomysial antibodies are more specific and are used as a confirmatory test in those with a positive screening result.
- Histologic evaluation of a duodenal-biopsy sample is needed to confirm the diagnosis in most adults and in children who do not meet nonbiopsy diagnostic criteria.
- Celiac disease often occurs in conjunction with other autoimmune diseases such as type 1 diabetes mellitus and autoimmune thyroid disease.
- Nonresponsive celiac disease occurs in adults and should be followed regularly owing to the risk of malignant conditions if refractory celiac disease occurs.

for celiac disease, prescribing a gluten-free diet. However, because the patient is still a teenager, a no-biopsy diagnostic approach is possible. This strategy involves the use of an endomysial antibody test, which, if positive, would confirm the diagnosis. If the test is negative, we would then recommend duodenal biopsy.

Many patients struggle to adhere to a gluten-free diet and are exposed to gluten at a level sufficient to cause ongoing inflammation, placing them at risk for symptoms and complications. Therefore, once the patient is confirmed to have celiac disease and placed on a gluten-free diet, we would establish regular follow-up with routine surveillance of recurrent symptoms, extragastrointestinal manifestations, and cancer surveillance as appropriate, especially if the patient does not have a response to a gluten-free diet.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

AUTHOR INFORMATION

[1]Department of Gastroenterology, Mayo Clinic, Rochester, MN; [2]Department of Clinical Research, University of Southern Denmark, Odense.

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