Celiac Disease
Clinical Features and Diagnosis

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KEYWORDS

• Celiac disease • Celiac sprue • Diagnosis • Clinical presentation • Symptoms

KEY POINTS

- The presentation of celiac disease in adults and children is changing, with an increase in nonclassical symptoms.
- Case finding is the recommended modality to identify undiagnosed cases of celiac disease; however, there is increasing evidence that it may not be effective.
- Screening for celiac disease should be performed with serology.
- Although European pediatric guidelines recommend a serology-based diagnosis in some cases, biopsy is still recommended in diagnosis for adults.

Although virtually an unknown condition in the mid-20th century, celiac disease has since increased in both recognition and frequency.[1] The seroprevalence of celiac disease is currently approximately 1% in European[2] and US[3] populations, although the majority of these individuals have not been diagnosed.[2,4] Although the gap between undiagnosed and recognized cases may be narrowing,[4] the challenge of early diagnosis remains in both children and adults.

CELIAC DISEASE PRESENTATION
Clinical Features in the Adult Population

Celiac disease is now increasingly recognized in the adult and geriatric populations and presents with a spectrum of symptoms and associated conditions.[5] In 2013, the Oslo definitions were published, suggesting terms to classify these varied clinical presentations.[6] Celiac disease is now recognized to present as symptomatic disease, which includes gastrointestinal and extraintestinal manifestations, and subclinical

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disease, which refers to cases that do not have symptoms and signs to trigger clinical suspicion for the disease.[6] Symptomatic celiac disease can be further divided into classical and nonclassical celiac disease. Any case with malabsorption is defined as classical disease and all other cases as nonclassical.

The presentation of diagnosed celiac disease has been changing, with a shift toward older individuals with more mild disease.[5] This change has been attributed to increased awareness, better diagnostics, earlier detection through serologic testing, and environmental factors such as increased wheat consumption.[5,7] Symptomatic, classical disease was previously the most common presentation, and although it remains a prominent mode of presentation, subclinical and nonclassical cases now make up roughly 30% and 40% to 60% of new cases, respectively.[5,8] The demographics of newly diagnosed cases seem to be changing as well, with an increase in the median age at diagnosis to the third and fourth decades, although the elevated female to male ratio, estimated at roughly 3:1, has remained stable over time.[5,8] The distribution of body mass index among newly diagnosed patients has also increased, with an estimated 40% presenting as overweight/obese at diagnosis.[5]

Presentation also seems to vary between sexes and ages, with females typically diagnosed at a younger age and presenting more frequently with constipation, bloating, and iron deficiency anemia.[5,9] Additionally, females and the elderly tend to have more associated autoimmune conditions than their male and younger counterparts.[5,10] The incidence of celiac disease diagnosed in those over age 65 has been increasing, with elderly men being diagnosed more frequently than elderly women. The most common symptom in this age group is anemia, and micronutrient deficiencies may be the only presenting feature. Gastrointestinal symptoms are less prevalent in the elderly and, if present, tend to be mild.[10]

More than one-half of adults will have gastrointestinal symptoms and weight loss at presentation.[8,9] Diarrhea remains the most common gastrointestinal symptom at presentation, although it has been significantly decreasing in frequency over time.[5] In order of decreasing frequency, other gastrointestinal symptoms include bloating, aphthous stomatitis, alternating bowel habits, constipation, and gastroesophageal reflux disease.[8] Less common gastrointestinal symptoms include persistent vomiting and chronic abdominal pain. However, gastrointestinal symptoms are common in the general population and there is poor correlation between the presence of common gastrointestinal symptoms and undiagnosed celiac disease.[11]

Celiac disease can affect almost any organ system, which leads to numerous extraintestinal symptoms that are present in roughly one-half to two-thirds of cases, and that some studies suggest may be more prevalent than gastrointestinal symptoms[5,8] (**Table 1**). The most common extraintestinal symptoms in order of frequency have been identified as osteoporosis, anemia (most commonly secondary to iron deficiency), celiac hepatitis, and recurrent miscarriages.[8]

Autoimmune conditions can be found in 35% of patients of celiac disease, and individuals with celiac disease are more likely to have more than 1 autoimmune disease.[12] Hashimoto's thyroiditis is the most commonly associated autoimmune disorder, found in roughly 20% to 30% of patients; however, its frequency in celiac disease has been decreasing over time.[5,8,12] Of adults with autoimmune thyroid disease, 2.7% have celiac disease and celiac disease is more common in hyperthyroidism than hypothyroidism.[13] Psoriasis is the second most commonly associated autoimmune condition (4.3%) followed by type 1 diabetes mellitus, which is found in roughly 4% of cases of celiac disease (6% of adults with type 1 diabetes mellitus have celiac disease), and Sjogren's syndrome (2.4%).[5,8,12,14]

Table 1
Extraintestinal manifestations of celiac disease

	Demographics/ Prevalence	Pathophysiology	Treatment	Notes
Hematologic				
Anemia	Common (20%–30%)[8,9,71] Adults > children Common in elderly	Most commonly secondary to iron deficiency (which may be due to malabsorption and occult bleeding)[72] Vitamin B_{12} and Folate deficiency also are common Anemia of chronic disease[71]	Nutritional supplementation	Macrocytic anemia uncommon[71] Possible sign of more severe disease[73] Up to ~9% of iron deficiency anemia may be due to celiac disease[74] Lack of response to intravenous iron supplementation is a clue to underlying celiac disease[75]
Hyposplenism	Common (19%–80%)[76] More common when autoimmune conditions present	Hemodynamic changes Reticular–endothelial dysfunction	Pneumococcal vaccinations	Increased risk for infections, specifically by encapsulated bacteria such as pneumococcus[77]
Other hematologic findings: IgA deficiency(1.9%),[8] low cholesterol, thrombocytosis, thrombocytopenia, leukopenia, venous thromboembolism, lymphoma (particularly intestinal)[72]				
Musculoskeletal				
Osteoporosis	Common (10%–50%)[8,9]	Malabsorption ↑ Cytokines Autoimmune	Gluten-free diet Calcium and vitamin D supplementation	Worse in cases with gastrointestinal symptoms Unclear if ↑ fracture risk Test for celiac disease in those with osteoporosis of unclear cause
Arthritis/arthralgia	Common (22%–30%)[78]	Autoimmune	Gluten-free diet	Both axial and peripheral
Other: fibromyalgia-like symptoms (2.2%)[8]				

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Table 1
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	Demographics/ Prevalence	Pathophysiology	Treatment	Notes
Skin				
Dermatitis herpetiformis	Common (4%–20%)[8,79] More common in men Typically younger individuals (15–40)	Autoimmune (antibody deposition in skin)	Gluten-free diet Symptomatic treatment: dapsone, sulphapyridine[80]	Recovery after initiation of gluten-free diet can take months Considered pathognomonic for celiac disease Typically gastrointestinal symptoms are absent
Oral findings				
Aphthous ulcers	Common (18%–25%)[8,81]	Unknown	Gluten-free diet	
Dental enamel hypoplasias	Common (50% of cases of celiac disease)[82]	Immune mediated Nutritional deficiencies	None	Could be only manifestation of celiac disease Develops in those who have celiac disease during tooth mineralization (<7 y old)
Other oral findings: geographic tongue				
Neurologic				
Gluten ataxia	Rare May have slight male predominance Onset commonly during middle age[83]	Autoimmune (antibody deposition in brain tissue)	In patients with cerebellar ataxia, celiac disease antibodies, and no other diagnosis → trial gluten-free diet (response suggests gluten ataxia diagnosis)[75]	Can have either slow onset or be rapidly progressive Gastrointestinal symptoms rare[83] Presents with cerebellar ataxia Damage cannot be reversed, so early diagnosis is crucial
Peripheral neuropathy	Common (≤30%)[84]	Unknown: thought to be related to autoimmunity or inflammation	Gluten-free diet	If not treated quickly, may have permanent damage

Epilepsy	Rare	Unknown	Gluten-free diet[85]	~6% of epileptics may have celiac disease[85] People with celiac disease have 2.7-fold increased risk of epilepsy[86] May be associated with cerebral calcifications
Headache	Common (5%–46%)[8,84]	Unknown: postulated that ↑ proinflammatory cytokines leads to vascular tone disorder	Gluten-free diet	Includes migraine, tension, and mixed headaches
Other neurologic/psychiatric symptoms: schizophrenia,[87] dysthymia,[84] chronic fatigue				
Cardiopulmonary				
Lane-Hamilton syndrome	Rare[88]	Autoimmune	Supportive Gluten-free diet	Celiac disease presenting with pulmonary hemosiderosis Fewer than one-half the cases have gastrointestinal symptoms[88]
Gastrointestinal system (excluding luminal)				
Hypertransaminasemia ("celiac hepatitis")	Common (≤40% of adults)[89]	Increased intestinal permeability and inflammation Malnutrition Bacterial dysbiosis[90]	Gluten-free diet (normalization in 6–12 mo)	Celiac disease present in up to 9% of people with unexplained hypertransaminesemia[91] Mild nonspecific histologic changes on liver biopsy
Pancreatitis (acute and chronic)	Acute pancreatitis → uncommon Chronic pancreatitis → common among those undergoing endoscopic ultrasound (26%)[92]	Duodenal inflammation causing recurrent sphincter of Oddi obstruction	Sphincterotomy	People with celiac disease have a 3-fold increased risk of pancreatitis[93]

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Table 1
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	Demographics/ Prevalence	Pathophysiology	Treatment	Notes
Pancreatic exocrine insufficiency	Common (estimates range from 4%–80%)[94]	Loss of intestinal brush border proteins Low cholecystokinin levels	Gluten-free diet Pancreatic enzyme replacement therapy	Common cause of persistent diarrhea in those with celiac disease on gluten-free diet
Other less commonly associated liver conditions: autoimmune hepatitis, autoimmune cholangitis, primary biliary cirrhosis, primary sclerosing cholangitis, vital hepatitis, fatty liver, nonalcoholic steatohepatitis, severe cryptogenic hepatopathy[90] People with celiac disease are 2–6 times more likely to develop liver disease, and people with liver disease are 4–6 times more likely to develop celiac disease				
Reproductive				
Infertility[95] Miscarriage[95] Intrauterine growth restriction[95] Preterm delivery[95] Low birth weight[95]	Common	Nutrient deficiency (ie zinc, selenium, folic acid) Autoimmune	Gluten-free diet significantly reduces risk	Test women with unexplained infertility, recurrent miscarriage, and intrauterine growth restriction for celiac disease (an up to 8-fold increased risk of having celiac disease) Often no other symptoms of celiac disease Higher risk in untreated patients than treated[95]
Other reproductive symptoms: delayed menarche; early menopause; amenorrhea; shorter duration of time when fertile (improved with gluten-free diet); short breastfeeding period (improved with gluten-free diet)[95]; decreased ovarian reserve[96]				

Other conditions associated with celiac disease include connective tissue disorders, several genetic conditions, as well as inflammatory bowel disease. Commonly associated connective tissue disorders include Sjogren's syndrome and systemic sclerosis (1.7%).[8] Celiac disease is also more prevalent in Down syndrome (5.8%),[15] Turner syndrome, and William syndrome. Inflammatory bowel disease has a higher prevalence in the celiac disease cohort as compared with the general population, and in 1 study was estimated at 3%.[16]

Although celiac disease is increasing in incidence, most cases remain undiagnosed. A recent case-control study found that this undiagnosed population has a similar frequency of classical and extraintestinal symptoms as the general population, and in fact is less likely to have chronic diarrhea and dyspepsia.[17] The undiagnosed population is more likely to have hypothyroidism, and over time to develop osteoporosis, autoimmune conditions, chronic fatigue, and thyroiditis. It may be that the undiagnosed population is asymptomatic or that their symptoms are too mild to rise to clinical attention; regardless, a large proportions of the undiagnosed population seems to be clinically silent.

Clinical Features in Children

As in adult populations, over time there has been an evolution in disease presentation in children.[18] Early literature pertaining to celiac disease or "sprue" characterized the condition as one marked by wasting and steatorrhea.[19,20] Before the recognition of gluten as a key component to disease pathogenesis, mortality was observed to be as high as 36% in children.[21]

Although celiac disease is no longer viewed as a lethal condition of childhood, the classic presentation of celiac disease as a malabsorptive and stunting syndrome of early childhood has been noted to be predominant even as recently as 30 years ago,[22] and remains a common mode of presentation for very young children (infants or preschool age).[23] Very young children may also be more likely to have total villus atrophy on small bowel biopsy.[24]

Despite some features remaining consist with time, there has more generally been a shift in pediatric disease presentations of celiac disease, with children now diagnosed more commonly at an older age and with less frequent classical or gastrointestinal complaints.[25,26] Abdominal pain is now a common mode of presentation in children.[18] Extraintestinal manifestations of celiac disease may include oral aphthous ulcerations or other oral manifestations, such as dental enamel defects.[27] Headaches, arthralgias or arthritis, and nutritional deficits including iron deficiency anemia and bone fragility may prompt diagnosis.

In recent years, some investigators have noted less variability in disease presentation in children, suggesting a plateau in these observed shifts.[28] The gradual change in celiac disease presentation has been attributed at least in part to an evolution of available serologic testing methods enabling disease recognition in more subtle or asymptomatic cases.[29,30] Cases of children diagnosed owing to screening, many asymptomatic, have become more common with time.[18,31] Relatives of individuals with celiac disease are at increased risk of developing this condition and may be diagnosed owing to screening in the absence of clear symptoms.[31,32] Those with IgA deficiency are both at greater risk of developing celiac disease, and also pose a diagnostic challenge given the lack of sensitivity of tissue transglutaminase (tTG) antibody for diagnosing these individuals.[33] Other associated conditions, such as type 1 diabetes and trisomy 21, may also prompt serologic screening given the increased prevalence of celiac disease in these populations.

DIAGNOSIS OF CELIAC DISEASE IN CHILDREN AND ADULTS

The diagnosis of celiac disease relies on clinical features and serologic and histologic findings (**Fig. 1**). The current guidelines for diagnosis of celiac disease in adults and children recommend case finding, which involves screening populations felt to be at high risk for the disease owing to associated symptoms, signs, conditions, or family history.[34–36] However, there is increasing evidence to suggest that this method may not be effective.[17] Although there are some proponents for mass screening, the US Preventive Services Task Force recently released a statement against testing for celiac disease in asymptomatic individuals owing to the lack of evidence showing benefit.[37] Although more effective methods are needed to identify who should be tested for celiac disease, case finding remains the recommended strategy.

Given the invasive nature and expense of endoscopy and biopsy, serologic testing is used as a screening test for celiac disease. The original antibodies were targeted against native gliadin; however, owing to low sensitivity and specificity, testing for these antibodies has since been abandoned. Since then, more specific and sensitive antibodies have been discovered, targeted against endomysium (EMA) and tTG as well as against synthetic deamidated gliadin peptides (DGP). Although the guidelines differ, tTG-IgA is the most commonly recommended screening test owing to its reported high sensitivity (**Table 2**). However, there is increasing concern that the true sensitivity of this test may be lower than previously estimated. Sequential testing with tTG-IgA and EMA or DGP-IgG, the latter combination being recommended by the British Society of Gastroenterology, may be more sensitive screening tests.[35] Point-of-care tests are now available; however, further data are needed on their diagnostic accuracy.[38]

Diagnosis in the Adult Population

In the adult population, endoscopy with small intestinal biopsy remains the gold standard and is required for diagnosis. There are several endoscopic findings that suggest celiac disease, such as a mosaic tile pattern, prominent submucosal capillary fissures, loss of circular folds, and scalloping; however, these findings are not sensitive and their absence should not affect the decision to biopsy (**Fig. 2**).[39] Chromoendoscopy may highlight mucosal changes, although 1 study estimated that one-third of newly diagnosed cases of celiac disease had a normal endoscopic appearance.[40] The majority of cases of celiac disease will have patchy mucosal changes, with more significant injury in the proximal intestine. Additionally, roughly 10% of cases will only have mucosal changes in the duodenal bulb. It is therefore crucial for endoscopists to collect 4 to 6 biopsy specimens from the duodenum including 1 or 2 biopsies from the duodenal bulb, and to note the location that the specimens were collected to increase the diagnostic yield.[41] A single biopsy collected per pass has been recommended to improve orientation.[42] However, adherence to these recommendations is low in clinical practice and studies suggest significant variability in performance between endoscopists, likely stemming from insufficient specimens, failure to biopsy the duodenal bulb, or failure to biopsy at all.[41]

The characteristic histologic changes consistent with celiac disease involve the superficial small intestinal mucosa and include increased intraepithelial lymphocytes, crypt elongation (also called hyperplasia or hypertrophy), and loss of villus height in the form of partial or complete villus atrophy (**Fig. 3**). The lamina propria often has an infiltrate of plasma and lymphocytic cells. The increased intraepithelial lymphocytes tend to localize in the tips of villi and are predominantly $CD8^+$ T cells; this characteristic is often quantified as the lymphocyte count per 100 enterocytes. The degree of

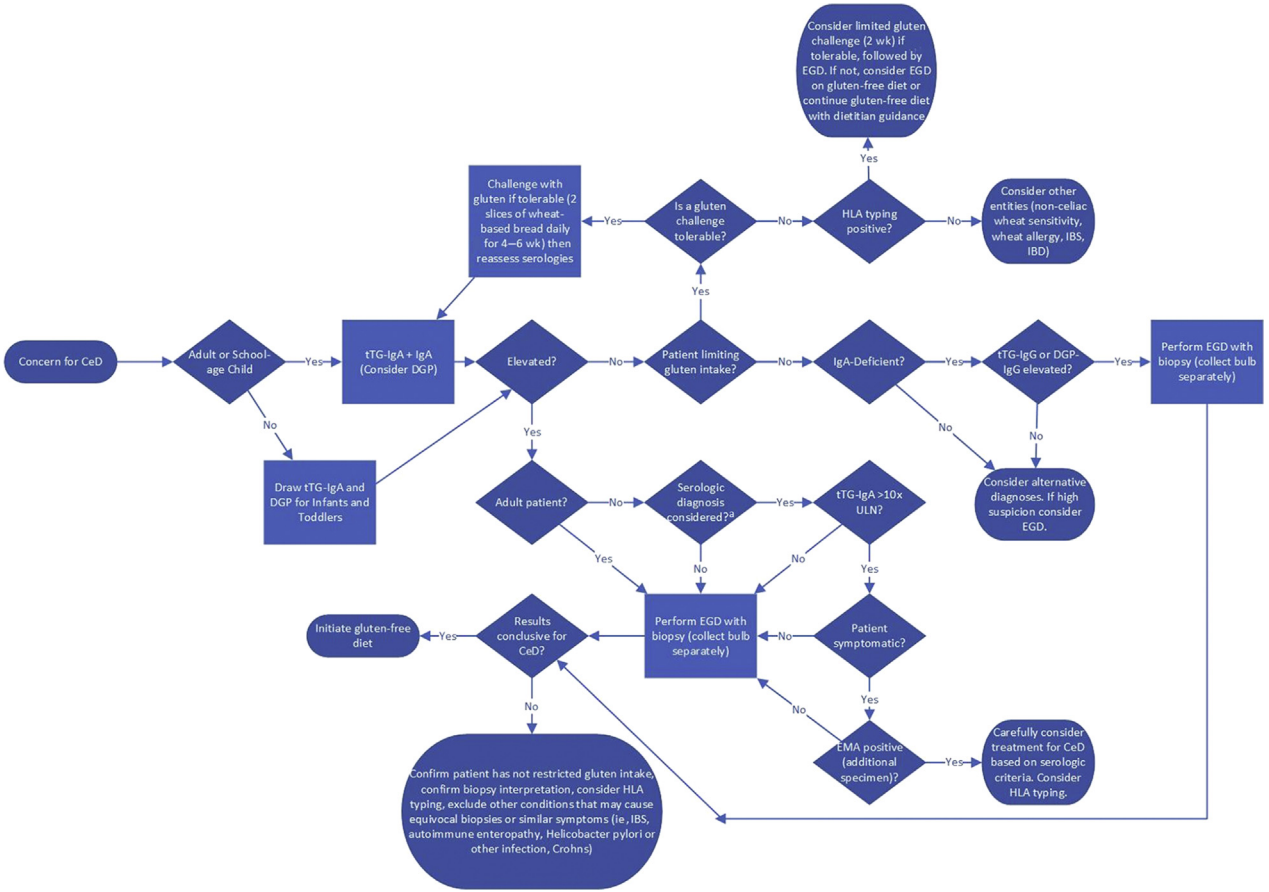

Fig. 1. An algorithm to approach the diagnosis of celiac disease (CeD). [a] A serologic diagnosis for a child should be considered carefully and in the context of local guidelines and laboratory standards. Even among children technically fulfilling criteria for a serologic diagnosis, this method may not be appropriate in all cases. DGP, deamidated gliadin peptides; EGD, esophagogastroduodenoscopy; EMA, endomysium; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; tTG, tissue transglutaminase; ULN, upper limit of normal.

Table 2
Sensitivities and specificities of serologic testing in celiac disease

	Sensitivity (Range), %	Specificity (Range), %
Antigliadin antibody	IgA: 85 (57–100) IgG: 85 (42–100)	IgA: 90 (47–94) IgG: 80 (50–94)
Antideamidated gliadin peptide	IgA: 88 (74–100) IgG: 80 (63–95)	IgA: 95 (90–99) IgG: 98 (90–99)
Endomysial antibody	95 (86–100)	99 (97–100)
Antitissue transglutaminase	IgA: 98 (78–100) IgG: 70 (45–95)	IgA: 98 (90–100) IgG: 95 (94–100)

Adapted from Leffler D, Schuppan D. Update on serologic testing in celiac disease. Am J Gastroenterol 2010;105(12):2523; with permission.

alteration of the villus architecture and crypt elongation may also be described as the ratio of the villus height to crypt depth, with decreasing values indicating greater histologic change. Two grading schemes have been developed to classify, trend, and compare histologic changes: the Marsh-Oberhuber and the Corazza-Villanacci systems (**Table 3**).[43,44] The Marsh-Oberhuber system is more qualitative and subjective than the Corazza-Villanacci system and may have less concordance among pathologists.[45] Studies suggest that these 2 systems are rarely used in practice and, when they are, there is poor agreement between pathologists in grading, although not in respect to the presence or absence of disease. Perhaps because of these limitations, there has been a movement in research toward more quantitative scoring mechanisms.[46]

It is important to counsel patients on consuming a gluten-containing diet before serologic and/or histologic testing. The amount of daily gluten intake and the duration of time required to avoid false-negative testing is not clear. Classically, 10 g of gluten per day for 6 to 8 weeks was recommended. However, more recent data suggest that a shorter course of at least 3 g/d for 2 weeks may be effective in the majority of adults

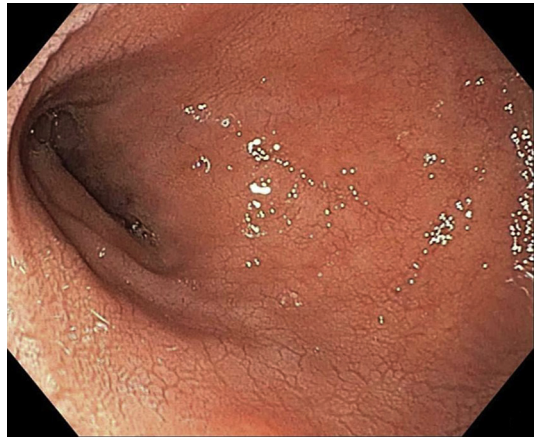

Fig. 2. Endoscopy findings in celiac disease showing the characteristic loss of circular folds, fissuring, and cobblestone appearance of the duodenal mucosa.

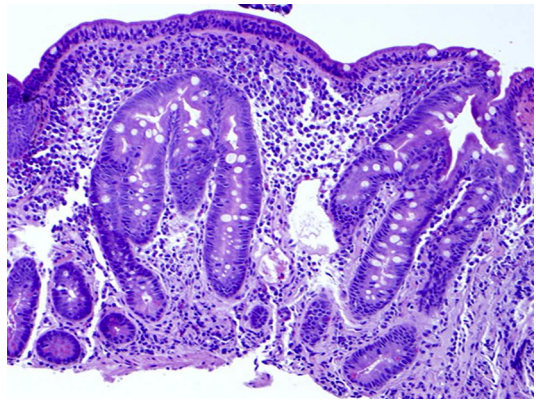

Fig. 3. Characteristic histologic findings in celiac disease. This specimen shows total villus atrophy, increased intraepithelial lymphocytes (80 intraepithelial lymphocytes per 100 epithelial cells), and crypt hyperplasia (stain: hematoxylin and eosin; original magnification ×40).

with celiac disease.[34,47] If a patient is already on a gluten-free diet, baseline serologic testing should be obtained. If this is negative, HLA typing can be performed to check for permissive genetics. If positive, a gluten challenge can be performed.

Clinicians may be faced with individuals who have villus atrophy on duodenal biopsy but negative serology. These cases can represent either an alternative disease process or seronegative celiac disease (**Box 1**). The tTG antibodies have been found in

Table 3
Marsh-Oberhuber and Corazza-Villanacci systems for classification of small bowel histology

Marsh-Oberhuber System	Villus Architecture	Crypts	Intraepithelial Lymphocytosis	Corazza-Villanacci System
0	Normal	Normal	None	
I (infiltrative)	Normal	Normal	Increased[a]	Grade A (nonatrophic)
II (hyperplastic)	Normal	Enlarged, increased division[b]	Increased	
IIIa (partial villus atrophy)	Short, blunt villi[b]	Enlarged[b]	Increased	Grade B1 (atrophic)
IIIb (subtotal villus atrophy)	Atrophic[b]	Enlarged,[b] increased immature epithelial cells	Increased	
IIIc (hypoplastic)	Total atrophy, complete loss of villi	Severe hyperplasia	Increased	Grade B2 (atrophic)

[a] The threshold for the Corazza-Villanacci system of 25 intraepithelial lymphocytes per 100 enterocytes, and for the Marsh-Oberhuber system of 40 intraepithelial lymphocytes per 100 enterocytes.
[b] The ratio of villus height to crypt depth of <3:1 to meet grade B1 criteria in the Corazza-Villanacci system (no thresholds for the Marsh-Oberhuber system).

Data from Oberhuber G. Histopathology of celiac disease. Biomed Pharmacother 2000;54(7):368–72; and Corazza G, Villanacci V. Coeliac disease: some considerations on the histological diagnosis. J Clin Path 2005;58:573–4.

Box 1
Conditions aside from celiac disease that can lead to duodenal villus atrophy

Infections[a]
Whipple disease, infectious enteritis, tuberculosis, human immunodeficiency virus infection, *Helicobacter pylori*, *Giardia*

Tropical sprue[a]

Small-bowel bacterial overgrowth[a]

Common variable immunodeficiency-associated enteropathy

Autoimmune enteropathy

Collagenous sprue

Medication-associated enteropathy[a]
Nonsteroidal antiinflammatory drugs, mycophenolate mofetil, azathioprine, olmesartan (and potentially other angiotensin-receptor blocker medications)

Intestinal lymphoma

Eosinophilic enteritis

Crohn's disease

Amyloidosis

Peptic duodenitis[a]

Malnutrition

Ischemia

Radiation enteritis

[a] More commonly seen in practice.

the small bowel mucosa of seronegative cases, leading to the hypothesis that these antibodies are unable to pass into the circulation. This finding, along with the clinical features identified in case-series, suggests that seronegative celiac disease may represent more severe disease.[48] Diagnosis of seronegative celiac disease requires exclusion of alternative causes of villus atrophy, response to a gluten-free diet, and permissive HLA typing.

The converse situation, with positive serology and a normal biopsy, or increased intraepithelial lymphocytes with no atrophy, may also be seen, and may represent either potential celiac disease or a false-positive test result. HLA typing to rule out celiac disease if negative and/or a trial of a gluten-free diet can be considered to further characterize these cases.

Serologic Testing in Children: Special Considerations

For most IgA-sufficient children beyond the toddler years, the tTG-IgA antibody is the diagnostic tool of choice to detect celiac disease,[49–51] demonstrating a sensitive and specific diagnostic tool with a sensitivity and specificity of 90% or greater.[52] It should be remembered that occasionally results may vary when tests from different manufacturers are used, however.[53] EMA-IgA antibody performs similarly in terms of sensitivity ($\geq$90%), although its specificity is even greater (98.2%),[52] which may be useful in groups such as those with autoimmune conditions such as type 1 diabetes, where tTG-IgA may sometimes lack specificity.[54] Although EMA may serve as an acceptable

first-line screening tool in low-risk populations,[55] greater cost and user-dependent accuracy make tTG-IgA preferable in most populations.

For infants and young children with suspected celiac disease, especially those less than 2 years of age, tTG-IgA or DGP antibodies are recommended.[56] DGP-IgA has a sensitivity ranging between 80.7% and 95.1% (specificity, 86.3%–93.1%) and DGP-IgG has a sensitivity of 80.1% to 98.6% (specificity, 86.0%–96.9%).[52] DGP, particularly IgG, has demonstrated comparable sensitivity to tTG-IgA in young school-aged children (<7 years), although this sensitivity may diminish for older children.[57,58] In very young children, the sensitivity of DGP-IgG antibody may be superior to tTG[59] and to DGP-IgA antibody,[60] although other studies suggest that tTG-IgA alone is comparable[49] or superior to[61] both DGP-IgG and DGP-IgA in children younger than 2 years. Most societies recommend tTG-IgA in addition to DGP antibodies when celiac disease is suspected in a child less than age 2 years.[50]

Immunoglobulin A Deficiency

The level of IgA alters the sensitivity of IgA-based serologies. IgA levels tend to be lower among the youngest children and increase with age, with adult levels present by approximately age 6 to 7 years.[62] IgA levels may also be low in those with selective IgA deficiency. Although IgA antibodies are used typically, in cases of IgA deficiency, IgG antibodies should be used. Either IgG antibody to DGP or tTG may be used, although the sensitivity of tTG-IgG may be slightly superior.[63] In isolation in general population use, however, the specificity of tTG-IgG is poor[64] and generally a low positive tTG titer in a patient who is IgA sufficient should be regarded as a false-positive result.

Confirmatory Testing for Celiac Disease in Children

Recommendations as to how to proceed after abnormal serologic testing for celiac disease in children differs by geographic region. In North America, guidelines for the management of children with suspected celiac disease recommend proceeding to a small bowel biopsy for confirmation of the diagnosis before exclusion or limitation of gluten from the child's diet.[51,65] A separate biopsy collected from the duodenal bulb has been recommended in children as in adults, given variability in mucosal lesions of celiac disease in young patients.[66]

In 2012, guidelines from the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition provided for a serologically based diagnosis of celiac disease in select cases of symptomatic children with a tTG-IgA level greater than 10 times the upper limit of normal for the laboratory, who additionally had a confirmatory positive EMA IgA antibody collected separately.[50] These guidelines seem to function well in practice among European populations,[67] and although some have suggested similar outcomes when these guidelines were applied to North American populations,[68] others have not.[69] Applying this guidance to groups outside of Europe may be acceptable, although a deeper understanding of local laboratories is warranted before reliably doing so given the heterogeneity in assays used.[68,70]

Human Leukocyte Antigen Typing

HLA typing has usefulness as a rule-out test in celiac disease owing to the high negative predictive value. Risk genes for celiac disease include HLA DQ2 (DQA1*05:01/05:05 and DQB1*02:01/02:02) and HLA DQ8 (DQA1*03:01 and DQB1*03:02). The presence of either HLA DQ2 or DQ8 is pivotal in the pathogenesis of celiac disease and therefore their absence indicates that development of celiac disease is extremely unlikely. These haplotypes are prevalent in the community (30%–40% of Caucasian

population); however, only a small percentage of individuals with those haplotypes have celiac disease (3%). Therefore, HLA typing is beneficial in ruling out celiac disease, but cannot be used for diagnosis. The identification of a risk gene for celiac disease has been suggested for those diagnosed based on serologies alone.[50] However, the value of HLA typing in symptomatic patients with elevated tTG antibody more than 10 times the upper limit of normal and subsequent positive EMA antibody in a separate serum sample is controversial. HLA typing has also been recommended as a screening measure for seronegative first-degree relatives of an individual with celiac disease to determine the usefulness of ongoing serologic screening,[50,65] as well as for those with a mismatch between serologic and histologic findings.[50] Although the absence of a risk gene effectively rules out a diagnosis of celiac disease, it is important to recognize the capability of the performing laboratory to identify HLA DQ2 heterodimers as individual carriage of one-half of the DQ2 molecule, particularly of DQB1*02, still confers risk of celiac disease.

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