Chapter 9
Diagnosis of Celiac Disease

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Introduction

Celiac disease (CD), often described as the "clinical chameleon," is an autoimmune disorder with a range of clinical symptoms and presentations. This chapter will review which patients should get tested for CD, the serological markers available to diagnose CD, and the role of genetic testing and small bowel endoscopy in the diagnosis of this disease.

Patients and Populations to Consider

CD is a complex and often difficult disorder to diagnose considering its wide range of clinical presentations that have been observed. While the overall diagnosis rate of CD is increasing in the United States and worldwide, the vast majority of patients in the United States remain undiagnosed [3–5]. Therefore, determining which patients to test for CD outside of those who present with classical CD symptoms has been difficult to characterize. Testing for CD should be considered in the following group of individuals.

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Gastrointestinal Symptoms

The classical presentation of CD includes bulky, foul-smelling diarrhea that often occurs in parallel with malabsorptive symptoms including weight loss, vitamin deficiencies, and anemia [1, 2, 6]. Although there has been a shift in recent years from the classical presentation of CD to atypical or asymptomatic presentations [7], the diagnosis of CD should be pursued in patients with chronic or recurrent diarrhea, malabsorption, and unexplained weight loss. In addition, patients with CD can often present with symptoms that are initially misdiagnosed as irritable bowel syndrome (IBS), including abdominal pain and bloating associated with a change in bowel habit. A meta-analysis of patients with established CD discovered that IBS-like symptoms can occur in upwards of 40 % of established CD patients and occur more often in CD patients than controls [8]. Considering the overlap between symptoms among patients with IBS and CD, patients who meet ROME III criteria should additionally be evaluated for CD prior to the diagnosis of IBS. This approach is supported by a meta-analysis that found a fourfold in increase in the prevalence of CD among patients with IBS [9].

Nonclassical Presentations

Clinicians often recognize the classical presentation of CD; however, diarrhea has been the presenting symptom in fewer than 50 % of patients diagnosed with CD in recent past decades [7]. Increasingly, patients are presenting with nonclassical symptoms that have been linked to CD, including elevated transaminases, osteoporosis, neurological symptoms (ataxia, peripheral neuropathy), migraine headache, depression, and a variety of metabolic derangements (Table 9.1) [10, 11]. Since the majority of these symptoms resolve upon adoption of a gluten-free diet, there is a clear benefit in diagnosing these patients with CD [11]. While the presentations can vary extensively, it is especially important for clinicians to be familiar with these nonclassical presentations to diagnose and treat patients with CD.

Higher Prevalence Populations

While screening the general population for CD is not recommended at this time, there are several populations that have an increased prevalence of CD. First-degree relatives of patients with CD have a higher risk than the general population for developing CD, with an overall prevalence of approximately 10 % [2, 12, 13]. In addition, patients with type 1 diabetes mellitus, autoimmune thyroid disease, autoimmune liver disease, genetic disorders (Down syndrome and Turner's syndrome), and IgA deficiency have a higher prevalence of CD as well (Table 9.2) [2, 14–18].

Table 9.1 Nonclassical presentations and metabolic abnormalities associated with celiac disease[a]

Neurological–psychiatric manifestations
Cerebellar ataxia
Peripheral neuropathy
Headache (tension and migraine)
Depression/anxiety
Epilepsy
Intracranial calcifications
Hematological manifestations
Anemia
Vitamin B_{12} deficiency
Dermatological manifestations
Dermatitis herpetiformis
Metabolic derangements
Hypercalcemia
Hypophosphatemia
Hypoalbuminemia
Folate deficiency
Hyperamylasemia
Hypocholesterolemia (low HDL and LDL)
Bone disease
Osteoporosis
Osteopenia

[a]Adapted from [11]

While there has been debate for and against screening these high-risk populations, most guidelines currently recommend testing for CD only if patients in these groups develop classical or nonclassical symptoms of CD [2, 19].

Screening for Celiac Disease

CD meets the World Health Organization (WHO) criteria for diseases that warrant mass screening: early clinical detection is difficult; the condition is common; screening tests are highly sensitive and specific; effective treatment is available; and untreated disease can lead to complications [20]. In addition, initiation of a gluten-free diet reduces mortality risk, and screening for CD has been found to be cost-effective under certain circumstances [21]. However, as will be discussed below, serological testing is not 100 % sensitive or specific, and due to the CD prevalence of 0.7–1.0 % in the general population, mass screening will cause a high number of false-positive test results, leading to unnecessary procedures and complications [20]. While a case-finding approach has also been proposed, in which health-care providers would order serologic tests for patients who exhibit signs or symptoms or have a disease associated with CD, this approach may be difficult to implement in clinical

Table 9.2 Clinical and genetic conditions associated with celiac disease[a]

Endocrine
Type 1 diabetes mellitus
Autoimmune thyroid disease
Addison's disease
Secondary hyperparathyroidism
Immunological-rheumatologic
Sjögren syndrome
Arthritis
Systemic lupus erythematosus
Rheumatoid arthritis
IgA deficiency
Immune thrombocytopenic purpura
Myasthenia gravis
Dermatological
Vitiligo
Alopecia areata
Psoriasis
Malnutrition-related changes (petechiae; vitamin K, edema; hypoproteinemia, follicular hyperkeratosis; vitamin A, dermatitis; B vitamins)
Cardiopulmonary
Idiopathic dilated cardiomyopathy
Autoimmune myocarditis
Cystic fibrosis
Fibrosing alveolitis
Sarcoidosis
Idiopathic pulmonary hemosiderosis
Extrinsic allergic alveolitis (bird fancier's lung)
Recurrent pericarditis
Gastrointestinal
Crohn's disease
Microscopic colitis
Pancreatic insufficiency
Ulcerative colitis
Eosinophilic esophagitis
Hematological
Anemia
Autoimmune hemolytic anemia
Hemorrhage
Howell–Jolly bodies
Thrombocytosis
Hyposplenism
Hepatic
Elevated liver biochemical tests
Primary biliary cirrhosis
Primary sclerosing cholangitis
Autoimmune hepatitis
Autoimmune cholangitis

(continued)

Table 9.2 (continued)

Neurologic and Psychiatric
Ataxia
Behavioral abnormalities
Demyelinating central nervous system lesions
Peripheral neuropathy
Reproductive disorders
Delayed menarche
Recurrent miscarriage
Infertility
Impotence
Renal
IgA nephropathy
Musculoskeletal
Muscular atrophy and weakness
Osteoarthropathy
Polymyositis
Pathological fractures
Genetic disorders
Down syndrome
Turner syndrome
Williams syndrome
IgA deficiency

[a]Adapted from [11] and [77]

practice. At this time, there is no universally accepted threshold at which to test patients for CD, and as such, it is incumbent upon health-care providers to recognize both classical and nonclassical signs and symptoms of CD in addition to understanding the steps necessary to diagnose CD.

Serological Evaluation

Serological evaluation is the initial step in diagnosing CD and may be helpful in monitoring adherence to a gluten-free diet [2, 20]. Antibody testing is the first step in diagnosing patients with CD. Characteristics of commonly used serologies are listed below and summarized in Table 9.3.

Antigliadin Antibody

The antigliadin antibody was the first serological test developed for the diagnosis of CD in the early 1980s [22, 23]. The assay measures both IgG and circulating IgA antigliadin antibodies. While the IgA antigliadin antibodies were found to have a

Table 9.3 Sensitivity, specificity, and positive and negative predictive values of serologic tests for untreated celiac disease[a]

Test	Sensitivity (reported range) (%)	Specificity (reported range) (%)	Positive predictive value (%), pretest probability of 5 %	Negative predictive value (%), pretest probability of 5 %
IgA AGA	85 (57–100)	90 (47–94)	18	99
IgG AGA	85 (42–100)	80 (50–94)	31	99
EMA	95 (86–100)	99 (97–100)	83	99
IgA anti-TTG[b]	98 (78–100)	98 (90–100)	72	99
IgG anti-TTG[c]	70 (45–95)	95 (94–100)	42	99
IgA anti-DGP	88 (74–100)	95 (90–99)	44	99
IgG anti-DGP	80 (63–95)	98 (90–99)	68	99
IgA/IgG anti-DGP	97 (75–99)	95 (87–100)	51	99

AGA, antigliadin antibody; *DGP*, deamidated gliadin peptide; *EMA*, endomysial antibody; *TTG*, tissue transglutaminase

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[b]Antihuman TTG-based assays only; older tests based on guinea pig antibodies have lower sensitivity and specificity

[c]Sensitivity is significantly higher, about 90–95 %, in IgA-deficient populations but lower in the overall celiac population

higher sensitivity and specificity as compared to its IgG subclass, the assay's overall sensitivity and specificity are dependent on manufactured-based arbitrary cutoff values [2, 22, 24–26]. Despite the variability seen among different commercial assays, it has generally been thought that the sensitivity and specificity of both the IgG and IgA antigliadin antibodies lie between 80 and 90 % with a positive predictive value of less than 30 % in most populations [20, 24, 25]. Considering the low positive predictive value and the development of superior antibody testing for CD, both IgG and IgA antigliadin antibody testing are no longer recommended to diagnose CD.

Deamidated Gliadin Peptide Antibody

Deamidated gliadin peptide (DGP) represents the conversion of certain gluten peptides to deamidated peptides via intestinal transglutaminase (TTG). The deamidated peptides then activate the inflammatory T-cell response by binding to antigen-presenting cells in patients with CD [27]. This results in an antibody response that has a higher specificity for CD than antibodies to native gluten [28]. The combined sensitivity and specificity for IgA and IgG anti-deamidated gliadin peptide are above 80 % and above 95 %, respectively [22]. However, studies have shown that IgA anti-TTG performs better and is less costly than the IgA-DGP [29]. Currently, DGP antibody testing is recommended for use in IgA-deficient patients to diagnose CD and in the pediatric population.

IgA Anti-endomysial Antibody

Endomysial antibody (EMA) testing was developed in the mid-1980s after the development of antigliadin antibody testing. EMA testing is based on indirect immunofluorescence, requires either monkey esophagus or human umbilical cord tissue as a substrate, and uses TTG as the target antigen [2, 22]. This test introduces interobserver and inter-site variability since one individual reads each sample under the microscope and reports the test as either positive or negative at a given titer [22]. Despite these factors, the sensitivity of IgA anti-EMA can vary, i.e., on the level of villous atrophy present, but is generally >90 % with a specificity of 97–100 % [2, 22, 30, 31].

IgA anti-EMA antibody testing is not currently recommended as the first-line therapy due to the high cost, variability, and subsequent development of IgA anti-TTG. In addition, studies have not shown a benefit to concurrently testing both anti-TTG and IgA anti-EMA simultaneously, but the test can be used as a confirmatory test in patients with borderline positive or possibly false-positive anti-TTG antibodies [31, 32].

Anti-tissue Transglutaminase Antibody

TTG was identified as a CD autoantigen in the late 1990s, [33] which allowed the development of an enzyme-linked immunosorbent assay (ELISA) test using guinea pig liver (first-generation assays), human red-cell derived, and human recombinant TTG [20, 22, 23]. Not only did the development of an ELISA-based assay avoid the time-consuming, expensive, and operator-dependent indirect immunofluorescence testing done with anti-EMA testing, but the high sensitivity and specificity found with the study are comparable to the anti-EMA testing currently available [22, 31, 34]. For these reasons, IgA anti-TTG is recommended as the initial test of choice for CD. IgG anti-TTG is also available for commercial use; however, the sensitivity and specificity of this test are wildly variable and are reserved for use in patients with IgA deficiency [31].

A new anti-TTG point-of-care test using a drop of whole blood has recently been developed. The test does bring ease to diagnosing CD but lacks the sensitivity and specificity of the ELISA-based test and lacks a titer that can be followed throughout patients' clinical illness. At this time, the test is not recommended for diagnosis due to possible false-negative results [35–37].

IgA Deficiency

Selective IgA deficiency is more prevalent among patients with CD versus non-CD control patients (2 % vs. 0.2–0.5 %) [38–41]. With an increased prevalence, IgA-based serological tests are more likely to be falsely negative in untreated CD among

this patient population. Therefore, it is recommended to measure total serum IgA levels along with IgA-based serologic tests [22]. Among patients who are IgA deficient, a number of IgG-based serologic tests have been developed for CD diagnosis, including IgG antigliadin antibody, IgG anti-TTG antibody, and IgG anti-DGP [2, 22]. Traditionally, the IgG antigliadin assay has been used for these patients but frequently yields false-positive results. Therefore, using serum IgG anti-TTG assays or IgG anti-DGP tests is preferable [2, 22, 42].

There are subsets of patients who have detectable but low levels of IgA, and it is important to note that the accuracy of IgA-based tests is not thought to be significantly compromised in this group of patients [22, 43].

Genetic Testing

Approximately, 40 % of all individuals in the USA are positive for either the HLA class II heterodimer HLA-DQ2 (DQA1*05/DQB1*02) or HLA-DQ8 (DQA1*03/DQB1*0302) [2], but nearly all patients with CD are either DQ2 (95 %) or DQ8 (5 %) positive [20, 44]. Due to the fact that nearly all patients with CD will either be DQ2 or DQ8 positive, the absence of these loci provides an almost 100 % negative predictive value for the diagnosis of CD [2]. Since the routine addition of genetic testing to the standard serological evaluation described above does not increase diagnostic performance [45], genetic testing is not indicated in most initial evaluations of CD. However, due to the high negative predictive value, genetic testing is useful in excluding CD in cases where the diagnosis is unclear or among patients who are already on a gluten-free diet, as the test is not affected by gluten exclusion.

Small Intestinal Biopsy

Although serological testing has high sensitivity and specificity for the diagnosis of CD, is routinely available, and is noninvasive with minimal risks, small intestinal biopsy remains the gold standard for diagnosis of CD [2, 20]. Duodenal biopsy is routinely performed and recommended in patients after testing positive with a serological marker for CD. In addition, patients with normal serological markers but with signs and symptoms that are highly suspicious for CD should undergo endoscopic evaluation since approximately 10 % of patients with CD may be seronegative [22].

The histologic findings of CD are described using the Marsh–Oberhuber classification (Table 9.4) [46]. The hallmarks of CD include increased intraepithelial lymphocytes (IELs), crypt hyperplasia, and villous atrophy [47–50]. Endoscopic markers of villous atrophy have also been described, including a reduction in the number of duodenal folds, scalloping, mucosal grooves, and a mosaic appearance of the mucosa. However, the endoscopic appearance of small bowel has not been

Table 9.4 Marsh–Oberhuber classification of celiac disease[a]

Marsh class	Type of lesion	Villous architecture	Crypts	IELs
Marsh I	Infiltrative	Normal	Normal	>30/100 enterocytes
Marsh II	Infiltrative–hyperplastic	Normal	Hyperplasia	>30/100 enterocytes
Marsh III				
3A	Flat destructive	Mild villous atrophy	Hyperplasia	>30/100 enterocytes
3B	Flat destructive	Moderate villous atrophy	Hyperplasia	>30/100 enterocytes
3C	Flat destructive	Total villous atrophy	Hyperplasia	>30/100 enterocytes
Marsh 4	Atrophic–hypoplastic	Total villous atrophy	Hyperplasia	>30/100 enterocytes

IELs intraepithelial lymphocytes
[a]Adapted from [46]

shown to be sensitive or specific for the diagnosis of CD [2]. These findings have also been noted to occur in patients with tropical sprue, HIV enteropathy, and HIV-associated opportunistic infections, such as cytomegalovirus and *Cryptosporidium* [51]. Furthermore, studies have shown that a normal endoscopic appearance does not rule out CD. In one study of 129 patients with newly diagnosed CD, researchers found that about one-third of patients had a completely normal endoscopic appearance despite histological evidence of CD [52]. Therefore, diagnosing or excluding CD on the basis of the appearance of a patient's small bowel is not recommended.

Although progress has been made with serological markers for CD and the varying presentations of CD have been described, patients with signs and symptoms consistent with CD do not always undergo duodenal biopsy during EGD. In a study of the Clinical Outcomes Research Initiative (CORI), which is a national endoscopic database, almost 4,000 patients underwent EGD for diarrhea, iron deficiency, anemia, and weight loss from 2000 to 2003 [53]. All of the patients had normal-appearing duodenums, but a biopsy was performed in only 11 % of patients. When the CORI database was revisited recently, the rate of duodenal biopsy from 2004 to 2009 for the same symptoms increased to 43 %, which is improved but still low [54]. In the same study, they found that male patients and elderly individuals were less likely to receive a duodenal biopsy [54]. The improved but still low rate of duodenal biopsy argues that a potential cause for the underdiagnosis of CD is related to a lack of recognition of both the typical and atypical presentations of CD, the equal seroprevalence rates among men and women, the fact that CD can present at any age, and the important role that duodenal biopsies play in its diagnosis [55, 56].

The location and number of biopsies taken during EGD plays an important role in the accurate diagnosis of CD. Due to the patchy nature of villous atrophy and the predilection to affect areas of the duodenum with varying degrees of severity, multiple biopsies of both the duodenal bulb and the distal duodenum maximize the diagnostic yield [57, 58]. Traditionally, duodenal bulb biopsies had been avoided by gastroenterologists due to the acid-induced damage, gastric metaplasia, Brunner

gland hyperplasia, or the presence of lymphoid follicles that may serve as a potential confounding element in the histopathological assessment of the small bowel [59]. However, a number of studies have shown that duodenal bulb biopsies can sometimes be the only evidence of villous atrophy [2, 58, 59]. When biopsying the duodenal bulb, the 9 or 12 o'clock position appears to have the highest diagnostic yield [57].

The number of distal duodenal biopsies obtained during EGD affects its sensitivity for the diagnosis of CD. The sensitivity of biopsy for the diagnosis of CD increases when four duodenal specimens are taken [60, 61]. Therefore, AGA recommendations state that four to six specimens should be submitted during duodenal biopsy for optimal detection of CD [2]. However, despite the improved sensitivity of diagnosing CD with at least four duodenal biopsies, clinical practice seems to be lagging behind. In one study analyzing a national pathology database, 132,352 patients underwent duodenal biopsy from 2006 to 2009 [62]. Among these patients, four or more specimens were submitted during duodenal biopsy in only 35 % of patients. Older patients were less likely than younger patients to have an adequate number of duodenal biopsies submitted. Even when the clinical indication was labeled as suspected CD, adherence to the recommended number of duodenal biopsies occurred in only 38.5 % of submissions. Furthermore, this study found that when fewer than four specimens were submitted for histological evaluation, the proportion of patients diagnosed with CD was only 0.7 % as compared to 1.8 % when four or more specimens were submitted. As a result of the number of studies showing that the submission of four or more duodenal biopsies and biopsies of the duodenal bulb improves the diagnosis of CD, we recommend that for adequate diagnosis of CD, at least four specimens be submitted, including a specimen from the duodenal bulb.

Duodenal biopsy may be subject to misinterpretation by pathologists, which may lead to false negatives and false positives. Review by a pathologist expert in the diagnosis of CD is advised, especially in the case of subtle findings or discrepancy between serologic and histologic results [63].

The Impact of Gluten-Free Diet on the Diagnosis of CD

The popularity of the gluten-free diet (GFD) has been increasing in the USA [64]. While previously difficult to find outside of specialty stores, gluten-free ingredients, snacks, and meals have become more available in grocery stores and restaurants. As a result, patients may present to a medical provider already on a GFD but still seeking a diagnosis for their symptoms.

Serological markers for CD normalize after 6–12 months of adherence to a GFD, though this rate is variable. Histological changes that characterize CD can persist despite normalization of serological markers. One study of 381 patients with biopsy-proven CD found that the median time to mucosal healing was 3.8 years [65]. Furthermore, many patients with confirmed mucosal healing have IELs that persisted despite normal crypt-to-villous ratio [66, 67]. While it is not recommended to

begin a GFD prior to diagnostic evaluation, a patient with CD who is compliant with a GFD might still have persistent histopathology consistent with CD. Despite this, the AGA recommends that patients on a GFD at the time of biopsy undergo a gluten challenge to prevent any impact the diet might have on the pathological interpretation [2]. While an 8-week challenge had previously been recommended, a shorter challenge period may be adequate as illustrated in Appendix 8 [68]. Genetic testing for DQ2 and DQ8, as described above, is another option in patients who are on a GFD at the time of biopsy. Because of the almost 100 % negative predictive value, a negative test, even on a GFD, completely rules out CD.

Diagnosis in Children

Once thought to be a disease of infants and young children, presenting after the introduction of gluten, CD has been shown to now present at any age. Children with CD often present with gastrointestinal symptoms including diarrhea, abdominal pain, vomiting, constipation, abdominal distention, and failure to thrive [69]. Non-gastrointestinal manifestations of CD in the pediatric population are quite extensive but include idiopathic short stature, neurological and behavioral symptoms, dental enamel defects, unexplained elevation in serum transaminases, and unexplained iron deficiency. Furthermore, high-risk populations for CD among children are similar to those in the adult population, including type 1 diabetes, Turner syndrome, Williams syndrome, Down syndrome, and first-degree relatives of CD patients. Of note, patients with Down syndrome appear to have a high risk of CD, since up to 16 % of these patients are affected [70].

Recommendations on whom to test and screen for CD differ in the pediatric population as compared to adults, mostly in that screening for CD is recommended in asymptomatic patients that belong to a high-risk pediatric population. The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) recommends that testing be done in patients with gastrointestinal symptoms, non-gastrointestinal symptoms (including dermatitis herpetiformis, short stature, and delayed puberty), and asymptomatic patients who reside in a high-risk population. Testing of these asymptomatic patients is recommended to begin around 3 years of age as long as the child has been on a gluten-containing diet for at least 1 year prior to testing [69].

Serological Markers for Diagnosis of CD in Pediatric Patients

The initial test of choice for the diagnosis of CD in pediatric patients is IgA anti-TTG and total serum IgA level [69]. In those patients with IgA deficiency, IgG anti-TTG or IgG anti-DGP can be used [69]. However, even among patients with normal total IgA levels, IgA anti-TTG and EMA antibodies are often negative in children with CD who are younger than 2 years of age [20]. A series of studies have shown

that anti-DGP antibodies will test positive despite normal TTG and EMA values (and correlate to histological findings confirming CD on endoscopy) and that IgA and IgG anti-DGP had a sensitivity of almost 100 % in pediatric patients less than 3 years old [71, 72]. As a result, DGP appears to be a reliable alternative to testing for CD in very young children who might present with symptoms concerning for CD.

Intestinal Biopsy

Intestinal biopsy, which includes multiple distal duodenal biopsies and sampling of the duodenal bulb, has been the gold standard for definitive diagnosis of CD in both adults and children. Several recent studies have suggested that symptomatic patients with TTG about ten times the upper limit of normal could be reliably diagnosed with CD without EGD and histological confirmation [73–75]. As a result, The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) released a new set of recommendations for the diagnosis of CD delineating two groups of patients with different diagnostic formulas. These recommendations indicate that among children with symptoms suggestive of CD, an IgA anti-TTG antibody level greater than ten times the upper limit of normal and a positive HLA haplotype can be sufficient to diagnose CD without a duodenal biopsy [76]. However, asymptomatic patients at high risk of CD still need both positive serology and histological findings on duodenal biopsy in order to diagnose CD [76]. While these are general guidelines to follow, they may reduce the amount of invasive testing pediatric patients undergo during the diagnosis of CD. It is unclear whether this practice will be widely adopted in Europe or North America.

Conclusion

The diagnosis of CD in both adults and children can be straightforward, as in the cases of those who present with classical gastrointestinal symptoms, or protracted due to the nonclassical or silent presentations that can often occur. The groundwork for diagnosing CD lies in serological markers, followed by characteristic histological changes on duodenal biopsy. Genetic testing can sometimes be useful due to its high negative predictive value.

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