

Is This Really Celiac Disease? Pitfalls in Diagnosis

Carlo Catassi, MD, MPH, and Alessio Fasano, MD

Corresponding author

Alessio Fasano, MD

University of Maryland School of Medicine, Mucosal Biology
Research Center and Center for Celiac Research, Health Science
Facility II, Room S345, 20 Penn Street, Baltimore, MD 21201, USA.
E-mail: afasano@mbrc.umaryland.edu

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Celiac disease (CD) is an autoimmune enteropathy triggered in susceptible individuals by ingestion of gliadin-containing grains. Although the autoimmune process targets mainly the intestinal mucosa, CD can manifest itself with a variety of signs and symptoms affecting any organ or tissue. For many years, CD has been underdiagnosed because of poor awareness. However, studies showing a high prevalence of CD in North America, followed by a consensus conference on CD organized by the National Institutes of Health, have fueled a campaign to raise awareness among subspecialists and primary physicians. Nevertheless, guidelines for the diagnosis of CD remain poorly appreciated and many health care professionals remain confused about its proper management. This review is intended to clarify “facts and fantasies” about CD diagnosis.

Introduction

Celiac disease (CD) is an immune-mediated enteropathy triggered by the ingestion of gluten in genetically susceptible individuals. Gluten is the major protein component of wheat, rye, and barley. The major predisposing genes are the HLA-DQ2 and HLA-DQ8 genotypes found in at least 95% of patients. Worldwide, CD is one of the most common lifelong disorders, affecting 0.5% to 1% of the general population in the United States and other developed countries. The development of the celiac enteropathy is paralleled by the appearance of serum antibodies, especially the IgA class anti-tissue transglutaminase (anti-tTG), antiendomysial antibody (EMA), and antigliadin antibodies (AGA), and eventually clinical manifestations. The clinical spectrum of CD is wide. Patients may have typical intestinal features (eg, chronic diarrhea, weight loss) or “atypical” extra-

intestinal features (eg, anemia, osteoporosis, neurologic disturbances), and silent forms occasionally are discovered through serologic screening. CD prevalence is increased in at-risk conditions such as family history of CD, autoimmune diseases (especially type 1 diabetes and thyroiditis), IgA deficiency, and some genetic syndromes (Down, Turner, and William syndromes). Many CD cases with atypical features currently escape diagnosis, exposing patients to the risk of long-term complications such as infertility and lymphoma. The vast majority of experts consider CD to be a permanent condition that requires the complete exclusion of gluten-containing products from the diet. In Western countries, gluten-containing foods contribute substantially to daily energy intake and are enjoyable to eat. The changes needed to begin and maintain a gluten-free diet (GFD) have a major impact on the quality of daily life [1,2].

Biopsy of the small intestine is the cornerstone of diagnosis and should be undertaken in all patients with suspected CD [3]. The characteristic histologic changes include an increased number of intraepithelial lymphocytes (> 30 lymphocytes per 100 enterocytes), elongation of the crypts, partial to total atrophy of the villi, and a decreased ratio of villi to crypts [4]. Specific and sensitive serologic tests help to identify individuals for whom biopsy of the small intestine is indicated to confirm the diagnosis. Commercially available tests include IgA and IgG AGA, EMA, and anti-tTG antibodies. Based on currently available evidence, measurement of IgA antibodies to tTG is recommended for initial testing for CD. Individuals with CD who are also IgA deficient will not have abnormally elevated levels of IgA anti-tTG or IgA EMA. Routine measurement of total serum IgA helps to identify individuals with selective IgA deficiency, who need to be screened with an IgG-based test, such as IgG anti-tTG. Polymerase chain reaction sequence-specific oligonucleotide typing methods are now available to identify alleles encoding HLA-DQ2 and HLA-DQ8. Because the HLA predisposing genotype is a necessary (but not sufficient) factor for disease development, the negative predictive value of HLA typing is very high. That is, CD will almost never develop in patients who are DQ2- and DQ8-negative [5]. Finally, the diagnosis of CD is considered definitive when symptoms resolve completely after treatment with a strict GFD in a previously symptomatic individual with

characteristic histologic changes on biopsy of the small intestine. A positive serologic test that reverts to negative after treatment with a strict GFD in such patients provides further evidence for the diagnosis of CD.

Though strict guidelines for CD diagnosis and follow-up have been published by internationally recognized institutions [4,6], long delay in diagnosis and misdiagnosis of CD remain common problems. On the other hand, the clinician is often faced with borderline situations, such as so-called potential CD, that can be difficult to manage. This article reviews pitfalls contributing to the underdiagnosis and overdiagnosis of CD.

Celiac Disease: The Clinical Chameleon

In the 2nd century AD, Aretaeus from Cappadocia described what is believed to be the first report of a gastrointestinal condition resembling CD [7]. The connection between the ingestion of certain cereals and the onset of gastrointestinal symptoms typical of CD was established 1700 years later [8]. Through history, CD has been perceived as a disease with a uniform clinical presentation. Case identification was based entirely on the search for symptoms such as chronic diarrhea, abdominal distention, and weight loss (or poor weight gain) occurring in young children a few weeks or months after the introduction of solid food into their diet. It is now appreciated that the symptoms of CD are more protean and vary markedly with the age of the patient, the duration and extent of disease, and the presence of extraintestinal pathology [1]. This variability is probably related to the multifactorial nature of the disease, whose clinical expression depends on both genetic and environmental factors. Though CD was once thought to be primarily a disease of the gastrointestinal tract, we now know that it may present with signs and symptoms in many other organ systems [9]. These include the musculoskeletal system, the skin and mucous membranes, the reproductive system, the hematologic system, the hepatobiliary system, and the central nervous system (CNS). The challenges of correct diagnosis are associated with both lack of awareness of the multifaceted clinical presentations of CD and the vague nature of some of the symptoms, which can be caused by many other clinical conditions. Atypical presentations associated with CD include short stature, osteoporosis, infertility, and neurologic syndromes.

Short stature

It is well established that short stature can be the only presenting clinical feature of CD, with no gastrointestinal symptoms [10]. In unselected patients admitted for short stature, the prevalence of CD varies from 2.9% to 8.3% [11,12], and CD is by far more common than growth hormone (GH) deficiency or any other organic disorder. The pathogenesis of CD-associated short stature is still unclear. Younger children with CD show significant changes in serum insulinlike growth factor-I (IGF-I), and older children

and adolescents have changes in IGF binding protein; both correlate with clinical course and response to dietary treatments. The alteration in the circulating IGF system could be implicated in the pathogenesis of growth retardation occurring in CD [13]. Zinc deficiency is the basic nutritional deficit that impairs the production of IGF-I. Zinc deficiency, together with other deficiencies characteristically found in patients with CD, is deleterious for bone metabolism, growth, and immune function. Likewise, a low response of GH secretion after stimulation, which reverts to normal after starting a GFD, has been reported [14]. It is not known whether the impaired pituitary release of GH is related to malnutrition, the action of circulating gluten peptides in the CNS, or abnormal metabolism of brain monoamines. After starting the GFD, a significant increase in height velocity is often noticed, especially within 1 year of gluten restriction. The target height is usually reached within 2 to 3 years, but the catch-up growth is not always complete, probably because of the marked acceleration in bone maturation that parallels the rapid increase in growth velocity.

Osteoporosis

CD predisposes to metabolic osteopathy. Calcium malabsorption, hypocalcemia, and skeletal demineralization are well-recognized features of untreated CD. These are common in patients with malabsorption at diagnosis but are also present in asymptomatic patients. The prevalence of CD among osteoporotic individuals (3.4%) is much higher than among nonosteoporotic individuals (0.2%) [15•]. The prevalence of CD in osteoporosis is high enough to justify a recommendation for serologic screening of all patients with osteoporosis for CD. The effect of dietary treatment is quite rapid and remarkable. Children consuming a GFD show normal bone marrow content or bone mineral density measurements even after only 1 year of treatment [16]. However, the mechanisms that underlie such changes are still poorly understood.

Infertility

There is now substantial evidence that CD is associated with infertility in both men and women. In women, it can also lead to delayed menarche, amenorrhea, early menopause, recurrent abortions, and a reduced pregnancy rate [17]. In men, it can cause hypogonadism, immature secondary sex characteristics, and reduced semen quality. The real mechanism by which CD produces these changes is unclear, but factors such as malnutrition and deficiencies of iron, folate, and zinc have all been implicated. Gluten withdrawal and correction of deficient dietary elements can lead to a return of fertility in both men and women. CD must always be borne in mind among patients who develop diarrhea and weight loss during pregnancy or the puerperium.

Neurologic syndromes

A number of neurologic syndromes may be associated with CD disease, but it is unclear whether these are directly or

indirectly caused by gluten ingestion. It has been proposed that idiopathic cerebellar ataxia [18], peripheral neuropathy [19], epilepsy [20], dementia and depression [21], and CNS white-matter disease are gluten-sensitive syndromes. Studies of GFD in patients with gluten sensitivity and neurologic syndromes have shown variable results. Further studies clearly are needed to assess the efficacy of GFD and to address the underlying mechanisms of nervous system pathology in gluten sensitivity.

Underdiagnosis and Diagnostic Delay

Despite growing awareness of its clinical polymorphism, CD remains largely underdiagnosed. In developed countries, an average of 5 to 10 CD cases remain undiagnosed for each diagnosed case, usually because of atypical, minimal, or even absent complaints. A recent screening study in the United Kingdom indicates that more than 90% of CD in schoolchildren is being missed [22]. In the United States, the projected number of patients with CD is approximately 3 million, yet fewer than 100,000 have been correctly diagnosed [23]. Green and coworkers [3] recently reviewed the clinical histories of all CD patients presenting at the Celiac Center in New York City between 1981 and 2004. The delay between the onset of symptoms and diagnosis had decreased from 11 years before 1981 to 4.6 years after 2000 but was still unacceptably long. The lack of reduction in duration of symptoms for those presenting with diarrhea suggested that physicians who see patients with diarrhea do not initially consider celiac disease even when the classic presentation is present [24]. The Canadian Celiac Health Survey of 2681 patients with biopsy-proven CD diagnosed between 1998 and 2002 disclosed a mean delay in diagnosis after onset of symptoms of 11.7 years [25]. Diagnoses given to respondents before confirmation of CD included anemia (40%), stress, irritable bowel syndrome, vitamin deficiency, peptic ulcer, food allergies, and chronic fatigue syndrome. In 2004, a survey performed in Southern California revealed that only about one third of primary care physicians had ever diagnosed CD in a patient, and only 44% were aware that EMA testing can be used for diagnosis [26].

With respect to diagnosis, CD resembles an iceberg, with by far the largest part hidden from view. How to deal with underdiagnosis is currently a matter of debate in the scientific community. There are many valid arguments in favor of mass screening:

- CD is a common disorder causing significant morbidity in the general population.
- Early detection is often difficult on a clinical basis.
- If not recognized, the disease can manifest itself with severe complications that are difficult to manage (eg, infertility, osteoporosis, lymphoma).

- There is an effective treatment, the GFD.
- Sensitive and simple screening tests (eg, the anti-tTG test) are available.

From a societal perspective, the economic analysis of CD mass screening using a serologic test (tTG or EMA) followed by intestinal biopsy for positive results showed that the screening strategy costs \$44,491 per life-year gained for screening compared with no screening [27]. However the cost-effectiveness of CD screening requires further investigation. Although it is well established that patients with untreated CD may develop complications, the natural history of undiagnosed and untreated CD—particularly the “silent” form—remains unclear. This limitation is strong, as treatment with GFD is likely to interfere greatly with the quality of life, especially for adults. Despite the high sensitivity of the serologic CD markers, their positive predictive value decreases when applied in the general population. Furthermore, the appropriate age for CD screening remains to be elucidated. For all these reasons, the best approach to the iceberg of undiagnosed CD seems to be serologic testing of at-risk groups, a procedure defined as “case-finding,” which minimizes costs and is ethically appropriate.

A primary care practice provides the best opportunity to first identify individuals who are at risk for CD and need referral for definitive diagnosis. We recently undertook a multicenter, prospective, case-finding study using serologic testing (IgA class anti-tTG antibody determination) of adults who were seeking medical attention from their primary care physician in the United States and Canada [28]. By applying simple and well-established criteria for CD case-finding on a sample of adults (Table 1), we achieved a 32-fold to 43-fold increase in the diagnostic rate. The most frequent risk factors for undiagnosed CD were thyroid disease, family history of CD, persistent gastrointestinal complaints, and iron deficiency (with or without anemia). Many patients with newly diagnosed CD reported a longstanding history of symptoms (usually covering years) that should have raised the suspicion of CD much earlier. This study demonstrated that an active case-finding strategy in the primary care setting is an effective means of improving the diagnostic rate for CD in North America.

Misinterpretation of Diagnostic Tests

Although the number and the accuracy of diagnostic tests have been increasing in recent years, CD overdiagnosis is still a problem, sometimes related to confusion about the definition of CD. Furthermore the shift from a three-biopsy diagnostic algorithm to a “single-shot” algorithm that rarely includes a gluten challenge increases the possibility that the patient may be left on a lifelong GFD without conclusive evidence of the diagnosis.

Table 1. Case-finding of celiac disease*

Gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal pain, bloating, constipation)
Iron deficiency
Osteoporosis/osteopenia (premenopausal women, men of all ages)
Short stature (prepubertal children)
Idiopathic infertility, miscarriages
Chronic fatigue
Family history of celiac disease
Autoimmune diseases with high comorbidity with celiac disease (eg, type 1 diabetes, Hashimoto thyroiditis)
Genetic diseases with high comorbidity with celiac disease (eg, Down syndrome)

*A serologic screening (eg, IgA anti-tissue transglutaminase and total IgA) is indicated in all the conditions listed.

Serologic tests

A common reason for CD overdiagnosis is misinterpretation of diagnostic tests. Specificity of serologic CD markers is not 100%. Although the specificity of IgA anti-tTG and EMA is very high (close to 100%), other CD serologic markers have a lower diagnostic accuracy, which may be the source of diagnostic errors. The specificity of IgG class AGA is only 80% in adults and 80% to 90% in children, suggesting that testing for CD with AGA has a limited role in the era of EMA and tTG [29]. False positivity of both IgG and IgA AGA can be found in patients with inflammatory bowel disorders or Down syndrome [30]. The reason for the false positivity in these clinical conditions is not known, but it is possible that increased absorption of gluten or of its peptide fragments can be followed by a humoral immune response to the non-self antigen. The diagnostic accuracy of serum antibodies directed against deamidated gliadin seems to be higher [31], a recent finding that requires further confirmation. The determination of IgG anti-tTG is useful in patients with selective IgA deficiency (serum IgA < 5 mg/dL), but this condition should be kept separate from transient IgA deficiency, a developmental and transient condition that is typical of infants and does not affect the possibility of an IgA-based antibody response. Prospective studies on children who are at genetic risk of CD have recently shown that even the best serologic marker of CD that is currently available, IgA anti-tTG, may fluctuate over time from a borderline positive to a normal value and vice versa. The quantitative assessment of the IgA anti-tTG level is useful to help determine who should have intestinal biopsy during the screening process [32].

HLA typing

The HLA-DQ2 and HLA-DQ8 determination has a low positive predictive value. The role of HLA-DQ2 and HLA-DQ8 is well known, as almost all patients carry the

genes encoding these heterodimers. About 95% of CD patients express HLA-DQ2, and the remaining patients are usually HLA-DQ8 positive. However, the HLA-DQ2 allele is common in the general population and is carried by about 30% of whites. Only about 3% of individuals in the general population who carry HLA-DQ2 will develop CD. Thus, HLA-DQ2 or HLA-DQ8 is necessary for disease development but is not sufficient, as its estimated risk effect is only 36% to 53% [5]. HLA genotyping is increasingly used for diagnostic purposes in doubtful cases or at-risk groups. The negative predictive value obtained from HLA-DQ testing is impressive and the proportion of false negatives is small. Therefore, HLA testing is useful to rule out CD. By contrast, the positive predictive value of HLA testing is poor: HLA genotyping is almost worthless in predicting CD because of the high frequencies of the DQ risk alleles among unaffected individuals. Even when the a priori chance of diagnosing celiac disease is 50%, positive HLA tests will not increase the likelihood of disease very much [33]. The value of a positive HLA determination is frequently overestimated in clinical practice.

Biopsy of the small intestine

Specificity

Is the small-intestine biopsy really the gold standard for CD diagnosis? Although its role in the diagnosis of CD is undisputable, a number of interpretative issues can be the source of diagnostic errors. The histologic changes that occur in CD follow a sequential course of architectural changes (classified by Marsh and modified by Oberhuber et al. [34] into five stages: types 1, 2, 3a, 3b, and 3c). The Marsh-Oberhuber 3 lesion is characterized by crypt hyperplasia, increased intraepithelial lymphocytes (IELs) (> 30 per 100 enterocytes), and injury to villi that may range from mild villous blunting to total villous atrophy. These histologic changes are not specific for CD, however. They may be caused by several other enteropathies, such as infectious diarrhea, autoimmune enteropathy, and food allergy [2,3]. The specificity of the histologic picture decreases in parallel to the degree of the enteropathy, so a type 1 lesion (often defined as an infiltrative lesion with isolated increase of IEL count) should be accepted as signifying CD only with other, very strong diagnostic evidence, such as HLA compatibility and clearcut and persistent positivity of IgA anti-tTG [35]. The poor specificity of mild enteropathy is an even bigger problem in developing countries that have a high prevalence of "environmental enteropathy" secondary to infection and malnutrition [36,37].

Technical aspects

Furthermore, the evaluation of small-intestine biopsy specimens is influenced by a number of technical aspects. In one study, CD-associated villous atrophy was occasionally detected only in the duodenal bulb [38], a site of sampling that is generally avoided because of possible

difficulties in proper histologic interpretation, whereas Ravelli et al. [39] detected greater severity of duodenal damage with increasing distance from the mouth.

Another concern is patchiness of the mucosal lesion. The distribution of villous atrophy in the duodenum of both children and adults with CD may be patchy. For diagnostic purposes, a minimum of three biopsies, including a duodenal bulb biopsy, is needed to ensure that villous atrophy is detected. However, a five-biopsy regimen is required for recognition of the most severe lesion [40].

Poor orientation of biopsy samples is another technical problem. Correct handling and processing of biopsy specimens are required for a proper evaluation of the intestinal architecture, especially when the damage is less severe. If the villi are not sectioned along their longitudinal axis, the tangential cut may be responsible for an artifact that simulates shortness of the villi and increased round-cell contents within the epithelium and lamina propria, leading to an incorrect diagnosis of CD.

Poor reproducibility is also a problem. The histologic evaluation is strongly dependent on the observer's judgment and experience. The Marsh-Oberhuber scoring system for intestinal damage is an efficient diagnostic tool, but it has been criticized for having too many diagnostic categories, which may lead to reduced intraobserver and interobserver agreement and eventually to misdiagnosis [41].

Reaching a conclusive diagnosis

It is clear that no single tool (serologic tests, HLA typing, or intestinal biopsy) can lead with certainty to CD diagnosis. Rather, a combined analysis of symptoms, positive CD serology (with or without HLA testing), an intestinal biopsy showing mucosal damage typical of CD, and a clinical and serologic response to the implementation of a GFD should guide the clinician to a conclusive diagnosis.

Potential and Latent CD

The diagnosis of CD is easy in cases with symptoms, typical CD serology, and unequivocal villous atrophy in the small intestine. However, the decision to begin the demanding and lifelong treatment of CD, the GFD, occasionally may be difficult. Patients often suffer from only subtle symptoms, if any. Borderline shortening of villi is common, making the histologic diagnosis questionable. An increase in IELs, which is typical even in early-stage untreated CD, is not specific.

A subset of CD patients show an apparent discrepancy between serologic and histologic findings. CD is defined as "potential" in a patient showing positive serologic CD markers and a CD-predisposing HLA genotype but normal (or nearly normal) small-bowel mucosal structure while on a gluten-containing diet. CD is "latent" in a patient having positive serology and some degree of villous atrophy but no symptoms [42]. The diagnosis of latent CD is usually retrospective, and it is difficult to interpret whether minor

Table 2. Diagnostic criteria for celiac disease (CD)*

Typical symptoms (weight loss, chronic diarrhea, iron deficiency)
Positivity of CD autoimmune markers (eg, IgA or IgG anti-tissue transglutaminase in IgA-deficient subjects)
HLA compatible genotype (DQ2 and/or DQ8)
Celiac enteropathy on biopsy of small intestine (Marsh-Oberhuber grade 1–grade 3c)
Response to treatment with the gluten-free diet

*At least 4 of 5 required. In doubtful cases, the diagnosis should be confirmed by a gluten challenge performed after ≥ 2 y of a gluten-free diet.

mucosal changes in the small intestine are due to early developing CD or whether the inflammatory infiltration is an unspecific finding [43]. The value of $\gamma\delta$ T-cell counts in discovering patients with early developing CD has been shown to be superior to the detection of mucosal Marsh-1-type lymphocytosis, which may also be seen in other conditions. Nevertheless, the increase of $\gamma\delta$ T-cell counts in the mucosa of the small intestine is a sensitive (though nonspecific) marker of untreated celiac disease. In patients with normal morphology of the villi of the small intestine, positive serum EMA or tTG antibodies have predicted forthcoming CD [44]. These autoantibodies are produced in the small-bowel mucosa and can be deposited on extracellular tTG in the intestinal mucosa even when not yet measurable in serum. Recently, the detection of such tTG-targeted intestinal autoantibody deposits proved to be a powerful tool in diagnosing mild enteropathy CD without villous atrophy, showing a sensitivity and specificity of 93% [45,46].

There is no general agreement on the treatment of potential CD. A GFD should not be started in a patient with suspected CD and a normal small-bowel biopsy who has no symptoms, but careful monitoring is indicated, including a repeated biopsy after 6 to 12 months.

Conclusions

CD misdiagnosis remains an unresolved problem. CD is undiagnosed in most patients, who therefore are exposed to the risks of long diagnostic delay and disease complications. Increased awareness of CD's clinical polymorphism and a wider application of serologic tools in clinical practice are key factors for improving the detection rate of this common disorder, which affects about 1% of the general population in both developed and developing countries. On the other hand, overdiagnosis of a condition that requires lifelong treatment with the GFD should be carefully avoided. By using standardized criteria, the diagnostic process is usually straightforward. Sometimes the picture is less clear, but the judicious application of clinical, serologic, genetic, and histologic data will help in deciding whether treatment should be started (Table 2). With a few exceptions (eg, during pregnancy) a GFD should never be started before all the

diagnostic evidence, including a biopsy of the small intestine, is available. In doubtful cases, it is always better to confirm the initial diagnosis by a gluten challenge, to be performed after at least 2 years of treatment with the GFD.

Disclosures

Dr. Fasano holds stock in Alba Therapeutics. No other potential conflicts of interest relevant to this article were reported.

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The prevalence of CD is much higher among osteoporotic individuals than among nonosteoporotic individuals. This study justifies a recommendation for CD serologic screening of all patients with osteoporosis.

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