Evidence Report

Chapter 1. Introduction

Overview

Celiac disease (CD) is a disorder of small bowel malabsorption. It is characterized by mucosal inflammation, villous atrophy and crypt hyperplasia, which occur upon exposure to gluten, and clinical and histological improvement with withdrawal of gluten from the diet.[1-4] CD—also referred to as celiac sprue, gluten-sensitive enteropathy, non-tropical sprue, in addition to a host of other names—is thought to result from the activation of both a cell-mediated (T-cell) and humoral (B-cell) immune response upon exposure to the glutens (prolamins and glutenins) of wheat, barley, rye, and oats, in a genetically susceptible person.[5,6] Genetic susceptibility is suggested by a high concordance among monozygotic twins of close to 70 percent,[7] and an association with certain type II human leukocyte antigens (HLA).[8,9] HLA DQ2 is found in up to 95 percent of CD patients, while most of the remaining patients have HLA DQ8.[8-10] However, there is only a 30 percent HLA concordance among siblings, suggesting that other genetic factors are also at play.[11] More recent evidence suggests that the presence of auto-antibodies to a connective tissue element surrounding smooth muscle called endomysium is highly specific for CD. The target of this autoantibody is now known to be an enzyme called tissue transglutaminase (tTG). This enzyme may play a prominent role in the pathogenesis of CD by modifying gliadin, resulting in a greater proliferative response of gliadin specific T-cells, which contributes to mucosal inflammation and further B-cell activation.[5,6,12,13]

CD appears to represent a spectrum of clinical features and presentations. Although "classical" CD (i.e., fully developed gluten-induced villous atrophy and classical features of intestinal malabsorption) is most commonly described, it appears that most patients have atypical CD (i.e., fully developed gluten-induced villous atrophy found in the setting of another presentation such as iron deficiency, osteoporosis, short stature, or infertility) or silent CD (i.e., fully developed gluten-induced villous atrophy discovered in an asymptomatic patient by serologic screening or perhaps an endoscopy for another reason). Other authors describe a latent form of CD that is characterized by a previous diagnosis that responded to a gluten-free diet (GFD) and retained a normal mucosal histology upon later introduction of gluten. Latent CD can also represent patients with currently normal intestinal mucosa who will subsequently develop gluten-sensitive enteropathy.[13,14]

The true prevalence of CD is difficult to estimate because of the variable presentation of the disease, particularly since many patients can have little or no symptoms. With this limitation in mind, the prevalence of the disease is highest in Celtic populations where estimates of 1:300 to 1:122 have been described. The prevalence of CD in North America has been estimated to be 1:3000, but a recent American study found the prevalence among the general not-at-risk population to be 1:105, while the prevalence in at-risk groups such as first-degree relatives of CD patients was 1:22, suggesting that CD is greatly under-diagnosed. CD can affect persons of many ethnic backgrounds, but appears to rarely affect persons of purely Chinese, Japanese, or Afro-Caribbean decent.[13]

Note: Appendixes and Evidence Tables are provided electronically at http://www.ahrq.gov/clinic/tp/celiactp.htm

The diagnosis of CD in adults is classically made on the basis of clinical suspicion—that is, recognizing atypical presentations such as isolated iron deficiency, combined iron and folate deficiency, and osteoporosis—compatible with a duodenal biopsy while taking a gluten-containing diet, followed by clinical and histological improvement following commencement of a GFD.[2,4] However, several serologic markers have become available which have altered the classic diagnostic pathway. The sensitivity of IgA anti-gliadin antibodies (AGA) is reported to range from 70 to 85 percent, whereas the specificity ranges from 70 to 90 percent. IgA anti-endomysial (EMA) and anti-tissue transglutaminase (tTG) antibodies have sensitivities in excess of 90 percent and specificities of over 95 percent.[14] Significant variability seems to exist in the reported values among the different studies, and these IgA-based tests can be negative in IgA-deficient patients, accounting for about 3 percent of CD cases.

The sensitivity and specificity of the anti-EMA and anti-tTG antibodies, along with the perceived under diagnosis of CD, has led to suggestions of using these tests for population screening. Aside from the recognized influence of CD prevalence on the predictive value of a serologic test result, little consensus exists regarding the value of population screening. Furthermore, specific questions regarding clinically important outcomes resulting from screening remain unclear. In particular, little data is available on adherence to a GFD in asymptomatic CD patients detected by screening.

The major complications of CD include intestinal and extraintestinal malignancies, ulcerative jejunoileitis, and collagenous sprue. Unlike most gastrointestinal (GI) lymphomas that are typically of B-cell origin, lymphomas associated with CD appear to be most commonly of T-cell origin. Unfortunately, the prognoses for patients with CD-associated T-cell lymphomas, ulcerative jejunoileitis and collagenous sprue, appear grim. It is widely believed that strict adherence to a GFD reduces the risk of these complications. It is suggested that by 5 years of dietary adherence the risk of lymphoma in CD patients approaches that of the general population.[14]

The challenge of CD remains to determine which patient populations should be screened, the best means of screening, and whether early detection of patients with CD leads to improved patient outcomes. For patient outcomes to improve as a result of screening, the degree to which "positively" screened individuals, particularly those who were asymptomatic, adhere to the stringent GFD, needs to be determined.

Definition of CD

As briefly described in the Overview, CD can take on a variety of forms. Paramount to the conduct of this review and subsequent interpretation of the literature is the identification of clear definitions of the many faces of CD. Implicit to a definition of CD (with a few exceptions that are detailed below) is the concept that the clinical and the small intestinal pathological features are present in patients who consume a gluten-containing diet, normalize with the introduction of a GFD, and recur with the re-introduction of dietary gluten.[2,4] The historical tendency to rely on biopsy features as part of the definition of CD, creates difficulties (as discussed below) in accurately addressing the sensitivity and specificity of biopsy for the diagnosis of CD, and in assessing the sensitivity and specificity of the serologic

markers, if different studies use different criteria to define CD. For the purpose of this review, the following definitions have been used.

General Definitions

1) **Classical CD**. The most commonly described form. It describes patients with the classical features of intestinal malabsorption who have fully developed gluten-induced villous atrophy and the other classic histological features. These patients present because of GI symptoms, and are identified as CD sufferers through the investigation of these symptoms. This group can also be said to have symptomatic CD.

2) **Atypical CD**. Appears to be one of the most common forms. These patients generally have little to no GI symptoms, but seek medical attention because of another reason such as iron deficiency, osteoporosis, short stature, or infertility. These patients generally have fully developed gluten-induced villous atrophy. Because these patients are "asymptomatic" from the GI perspective, if their atypical CD feature is not recognized, they may be difficult or impossible to distinguish from "true" silent (asymptomatic) CD patients.

3) **Silent CD**. A very common form of CD. Refers to patients who are asymptomatic but are discovered to have fully developed gluten-induced villous atrophy after having undergone serologic screening or perhaps an endoscopy and biopsy for another reason. These patients are clinically silent, in that they do not manifest any clear GI symptoms or associated atypical features of CD such as iron deficiency or osteoporosis. These patients can be confused with atypical CD if their atypical features are not recognized in an early stage. As well, Fasano et al.[15] have shown that many of these patients do not manifest fully developed villous atrophy.

4) **Latent CD**. Represents patients with a previous diagnosis of CD that responded to a GFD and who retain a normal mucosal histology upon later re-introduction of gluten. Latent CD can also represent patients with currently normal intestinal mucosa who will subsequently develop gluten-sensitive enteropathy.

5) **Refractory CD.** For the purpose of this review, patients with refractory CD are patients with true CD and villous atrophy (i.e., not a misdiagnosis) who do not, or no longer, respond to a GFD. Although the most common reason for failure to respond to a GFD is dietary indiscretion or unknown exposure to gluten, refractory CD also occurs in patients on a GFD who have developed a complication such as ulcerative-jejunoileitis, or enteropathy-associated lymphoma. Patients with refractory CD do not necessarily have positive serology for CD. Refractory CD was reviewed in the context of the requested objectives.

In order to utilize the above definitions, there needs to be clear and valid histological criteria for the diagnosis of CD. The histological patterns, particularly the more mild lesions, are not specific for CD and can be seen in a variety of other disorders (Table 1, Appendix A).

To help standardize the histological criteria for the diagnosis of CD, several scoring systems have been developed. The classic Marsh criteria,[1] and its modification by Rostami,[16] are presented in Table 2 (Appendix A). The revised ESPGAN criteria[4] use histological, serological and clinical criteria (Table 3, Appendix A).

Report Purpose and Target Population

The purpose of this report is to systematically review the available CD literature in order to provide organized evidence relating to a number of objectives put forth by the AHRQ. The findings of the report are intended to assist an assembled group of American and world experts in the field of CD in the development of a National Institute of Health (NIH) Consensus Development Conference Guidelines sponsored by AHRQ and OMAR.

Methodological Considerations

At first glance, the determination of the sensitivity and specificity of the various diagnostic modalities for CD seems straightforward. There are a multitude of studies that have assessed the diagnostic characteristics of each of the serological markers using a variety of different laboratory methods. However, these studies are remarkably heterogeneous on a number of levels.

For example, there appears to be notable heterogeneity in the actual definition of CD, an issue that has important consequences on all of the task order objectives. Central to the classic definition of CD is the recognition that biopsy is the gold standard for diagnosis. However, it has become clear over the years that the majority of patients with CD do not have the classically described features of intestinal malabsorption, and that a large proportion of patients do not have the classic flat mucosa (sub-total or total villous atrophy). To further aid in the diagnosis of CD, multiple authors have devised and modified histological criteria to grade the mucosal lesions of patients with CD. But still at issue is the broad differential of disorders that can cause villous atrophy, particularly the milder histological grades. To help address this issue, others have attempted to address specific features of the biopsy, such as the number of intraepithelial lymphocytes (IELs), the number of gamma delta positive ($\gamma\delta$+) IELs and other lymphocyte subtypes, as well as the localization of IELs towards the villous tip, just to name a few.

The serological screening studies, together with the recognition that a low-grade histological lesion can be consistent with CD, have helped bring to light the concept of a spectrum of CD and the so-called “celiac iceberg.” In brief, it is recognized that classic CD with the typical symptoms of malabsorption and a fully developed mucosal lesion represents a small proportion of patients. The majority of patients are asymptomatic and are classified as having either atypical CD, silent CD, or less commonly latent CD. Some authors question whether most, if not all cases of silent CD, are in fact atypical CD, although the associated consequence of this has not been recognized. To further complicate the issue, Fasano[15] has clearly characterized patients with silent CD without fully developed mucosal lesions, and found that only 34 percent of the patients had subtotal or total villous atrophy.

It should be recognized that the majority of studies assessing the diagnostic characteristics of the serological markers have defined CD by a biopsy with Marsh III or modified IIIa

lesions or greater. These studies have reported a high sensitivity and specificity for these tests, particularly for the anti-EMA and anti-tTG antibody tests. However, some studies have looked at the characteristics of these tests in lower-grade lesions, and have found that while 100 percent of patients with Marsh IIIc histology show antibodies to endomysium, only 60 percent of patients with Marsh IIIa histology have anti-EMA antibodies.[17,18] Furthermore, it is apparent that serological markers can be used to monitor adherence to a GFD; for example, EMA and tTG antibodies fall to normal or non-diagnostic levels on a GFD, but the correlation with improvement of villous height is not as clear-cut. Finally, with the discovery by Sollid et al.[8] and others, that over 95 percent of patients with CD have HLA DQ2 and most of the remainder having HLA DQ8, it became hopeful that a reliable confirmatory test based on HLA typing would be available. Unfortunately, up to 40 percent of the general population and a much higher proportion of those with autoimmune disorders such as type I diabetes also have HLA DQ2 and/or HLA DQ8. Therefore, the specificity of this test can be quite low, making its positive predictive value relatively low. It is also becoming apparent that HLA DQ2/8 may not be the true risk-genes, and researchers are actively studying other candidate genes that may be associated with DQ2/8, or in patients without DQ2/8, other genes altogether.

The preceding overview was presented to simply illustrate the complexity involved in separately assessing the sensitivity and specificity of the serological markers, HLA typing, and biopsy itself, in the diagnosis of CD. Over time, the status of the biopsy as the gold standard for the diagnosis of CD has been eroded. Yet at the same time, most of what we know about the sensitivity and specificity of serological markers and HLA typing rely on biopsy as the gold standard. Therefore, one is locked in a circular argument of how best to choose the gold standard test(s), when each has important shortcomings and is dependent on another to define its own diagnostic characteristics. The major problem in accurately evaluating the diagnostic characteristics of these tests, is the issue of identifying all possible CD patients in a general screened population to use as a benchmark. Serology would be the most convenient strategy, but appears to loose sensitivity in patients with low-grade lesions. Screening a general population with biopsy has significant practical/cost issues, as well as potential ethical problems; however, if such a study was performed along with measuring the serological and HLA status of patients, this would allow for identification of Marsh I or II lesions that would need to be characterized further. HLA DQ2/8-negative patients could likely be excluded from having CD. But those patients with Marsh I-II lesions would have to be followed, whether or not they were serology positive or HLA DQ2/8 positive, to see if CD develops; alternatively, they could be tested with a GFD and subsequently rechallenged to see whether they truly have CD. Only in this way can the true sensitivity of biopsy be determined. Using this multi-test gold standard with follow-up of equivocal cases, would also be the best way of assessing the sensitivity and specificity of serology markers and HLA DQ2/DQ8 typing.

Finally, a question which needs to be addressed is: “What are the implications of identifying a truly asymptomatic individual, for example with serological screening, who has no other obvious complications such as iron deficiency or osteoporosis, and is then found to have a Marsh I or II lesion?” This returns the circular argument back to “What is truly CD?”—a question that is beyond the scope of this review.