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ICCE Consensus for Celiac Disease

Introduction

Celiac disease is a disorder in which the ingestion of cereals results in small-intestinal mucosal damage in genetically susceptible individuals. The mucosal lesion develops gradually from inflammation, to crypt hyperplasia and partial or subtotal villous atrophy. The prevalence of celiac disease is now estimated at almost 1% of the general population in Europe and the United States.

Abdominal symptoms, diarrhea, growth failure, and malabsorption of various nutrients are the most common clinical manifestations of the disease [1]. However, the symptoms are often vague or subclinical, or the patients may be totally asymptomatic. The disease can also appear outside the gut, dermatitis herpetiformis being the most well-known extraintestinal manifestation; the patients suffer from itching papulovesicular skin disease. The mucosal lesion, present in 80% of patients, is milder than in classic celiac disease. Ataxia, polyneuropathy, and osteoporosis are other disorders appearing outside the intestine in celiac disease. Patients with various autoimmune diseases, such as autoimmune thyroiditis or type 1 diabetes, carry an increased risk of celiac disease [2].

Recent advances, driven by serological assays, have led to the realization that clinically overt typical malabsorption syndrome (chronic diarrhea, weight loss, abdominal distension) represents only a small proportion of patients with celiac disease. Underdiagnosis in the community is due to lack of awareness of the heterogeneity of presentation as well as under use of serological tests, particularly in the primary-care setting. Studies in Europe and the United States suggest that the prevalence of celiac disease may be 1% of the general population [3,4], but the clinical prevalence is often 10 times lower.

The diagnosis is made by demonstration of duodenal villous atrophy on specimens usually obtained by esophagogastroduodenoscopy (EGD). It is now possible to assess the small-intestinal villous structure by video capsule endoscopy. This method is well tolerated and offers, at least theoretically, an alternative to EGD. The current position and future prospects of video capsule endoscopy are discussed in this article.

Criteria for Diagnosis of Celiac Disease

The currently accepted criteria for diagnosis of celiac disease require the histological demonstration of villous atrophy, usually accompanied by increased intraepithelial lymphocytosis, followed by objective clinical response or histological recovery on a gluten-free diet. Serology, especially for tissue transglutaminase or endomysial antibody, but not gliadin antibodies, provides helpful adjunctive evidence for detection and diagnosis [5,6]. In some relatively rare cases, the symptoms continue or

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deteriorate despite an adequate gluten-free diet; the demonstration of villous recovery is essential in these patients.

Treatment of Celiac Disease

The treatment of celiac disease is limited to strict adherence to a life-long gluten-free diet (excluding wheat, rye, and barley). Compliance with this diet is difficult in practice, particularly because of the ubiquity of food contamination with the offending proteins [7]. Currently there are no set guidelines for following patients with celiac disease, but it is expected that there should be complete resolution of symptoms and signs without recurrence for the life of the patient while adhering to a gluten-free diet. However, partly because of the difficulty of adhering to a gluten-free diet, as well as the potential for complications, a substantial proportion of patients with celiac disease either respond incompletely or have a relapse. In the usual circumstances, the first step is to ensure that the patient has been on a gluten-free diet by direct dietary inquiry. A persistently positive tissue transglutaminase or endomysial antibody result would indicate significant gluten contamination [7], suggesting the need for thorough dietary advice or a repeat biopsy. While recurrence of symptoms or new development of symptoms while receiving treatment for a gluten-free diet are related to gluten contamination in the majority of patients, a significant proportion may have other disorders or complications affecting the small intestine [8]. Most feared among these are those of refractory sprue, adenocarcinoma, or an enteropathy-associated T-cell lymphoma, with a very high mortality rate [9,10]. Usually, the lymphomas present at an advanced stage, while the few patients that present with an acute event such as perforation or obstruction appear to have a better medium-term survival than those who present with chronic malabsorption and extensive disease.

Refractory sprue, also known as unclassified sprue, is defined as symptomatic villous atrophy mimicking celiac disease, but not responding primarily or secondarily to gluten withdrawal. In a patient with celiac disease refractory to a gluten-free diet, the first step requires reassessing the initial diagnosis of celiac disease, in order to exclude other disorder such as tropical sprue, common variable immunodeficiency, and autoimmune enteropathy. The second point that warrants assessment is observance of the gluten-free diet, since it is probably the first cause of failure of the diet. Other causes responsible for symptoms mainly include collagenous or lymphocytic colitis and more rarely pancreatic insufficiency, secondary lactase deficiency, bacterial overgrowth, coexisting inflammatory bowel disease, irritable bowel syndrome or anal incontinence [11].

Refractory sprue can be defined as circumstances in which patients who have been adhering to a strict gluten-free diet for at least 6 months develop alarm symptoms such as weight loss, recurrence of malabsorption, abdominal pain and anemia. These patients are found to have continued villous atrophy with inflammation. They may appear to be indistinguishable from patients with untreated celiac disease. These patients may be very ill, with severe consequences of malnutrition. Patients who have refractory sprue can be classed into two separate categories: firstly, those who have developed a clonal expansion of their intraepithelial lymphocytes (IELs); and secondly, those who have not. The importance of identification of a clone is primarily prognostic, in that those with this complication appear to have a very high likelihood of developing an enteropathy-associated T-cell lymphoma, described as a cryptic enteropathic T-cell lymphoma [10,12,13]. Investigations of these patients are largely dependent on contrast radiology or computed-tomographic enteroclysis, positron-emission tomography (PET) and extended upper endoscopy, as well as push or push-and-pull enteroscopy [10].

Video Capsule Endoscopy and Celiac Disease

Video capsule endoscopy is a recently developed technology that has also been termed physiologic endoscopy. It provides high-resolution magnified views of the small intestinal mucosa in a non-invasive manner. This provides an unparalleled definition of the small-intestinal villi, which have the appearance on capsule endoscopy of a deep-pile carpet. Specific terms that describe the mucosal abnormalities detected at EGD in patients with villous atrophy due to celiac disease include scalloping of folds, fissures or grooves, a mosaic pattern, and absence or reduced duodenal folds. Data have suggested that there is a variable degree of sensitivity for atrophic changes in people undergoing EGD. These signs are, however, relatively specific for celiac disease. Patients with lesser degrees of villous atrophy are expected to have a normal endoscopic appearance on EGD. Thus, even in an endoscopically normal-appearing small bowel, biopsies should be taken if there is a possibility of celiac disease. The diagnostic accuracy of the mucosal changes described above, as detected by capsule endoscopy in celiac disease, remains uncertain.

Aims of the Consensus

The consensus addressed four specific areas:

- The initial diagnosis of celiac disease
- The follow-up of treated celiac disease:
  - In patients with an appropriate symptomatic response to a gluten-free diet
  - In symptomatic patients on a gluten-free diet, including both those who do not respond primarily despite a relatively certain diagnosis and also previously treated patients continuing on a gluten-free diet who have a relapse or a new occurrence of symptoms
- Surveillance for malignant scomplications of celiac disease
- Educational need for recognizing villous atrophy

The Initial Diagnosis of Celiac Disease

Capsule endoscopy, as mentioned above, provides high-resolution magnification views of the intestinal mucosa. The indications for imaging the small bowel using capsule endoscopy are not limited to a suspicion of celiac disease, and include iron-deficiency anemia, chronic diarrhea, and abdominal pain due to suspected Crohn's disease. All video capsule endoscopists therefore need to be familiar with the changes characteristic of celiac disease. However, no standard terminology or accepted interpretation of findings has yet been published. The characteristic find-

ings related to villous atrophy include scalloping, fissuring, a mosaic pattern, flat mucosa (absence of visible villi), loss of the circular folds, and nodularity, among other terms. Data on the accuracy of video capsule endoscopy in untreated celiac disease have not been subjected to rigorous testing. However, data from a number of pilot studies have been published or were presented at the Congress, as follows:

- The Toronto group carried out a pilot study on capsule endoscopy in 10 patients with untreated celiac disease. The characteristic changes of villous atrophy were apparent in all of the patients [14].
- A study by Murray et al. [15] included 38 patients ultimately shown to have celiac disease, of whom approximately 90% had changes suggestive of atrophy. This was substantially higher than the rate of description of atrophic changes on prior EGD. There was good interobserver agreement.
- Krauss et al. [16] reported preliminary results from a multicenter study on symptomatic treated celiac disease. This study includes a comparison of patients with newly diagnosed celiac disease. In the 16 patients with newly diagnosed celiac disease, the capsule detection of atrophy was highly predictive of the presence of atrophy on biopsy.
- The study by de Franchis and colleagues [17] reported on 25 patients, including 17 with biopsy-proven celiac disease. They found a very high concordance between video capsule endoscopy results and celiac disease diagnosis, with a sensitivity of 95%.

These data, although preliminary and in most cases not yet subjected to peer-reviewed publication, certainly suggest that the images obtained with the video capsule are superior to those obtained with EGD. It appears that capsule endoscopy has a reasonably high sensitivity for untreated celiac disease. Very few data on specificity are available. Unfortunately, no well-designed trial has tested for noninferiority or equivalence between video capsule endoscopy and EGD with biopsy. It is the view of this Consensus Panel that such a study should now be pursued. A comparison of video capsule endoscopy and biopsy in celiac patients in whom the mucosal atrophy is partial or the histology borderline should also be carried out. There are additional important issues of economics, some of which could be addressed by modeling and some analyzed by actual study. In terms of patient or parent preference, it is probable on the basis of anecdotal reports, that anyone who can swallow the capsule spontaneously is highly likely to prefer this test over EGD. Video capsule endoscopy can be performed using endoscopic placement in young children or those with swallowing disorders or dysphagia [18,19].

On the basis of these preliminary data, the Consensus Panel also considered that video capsule endoscopy may be a reasonable alternative to upper endoscopy in patients who are positive for tissue transglutaminase or endomysial antibodies and who subsequently undergo video capsule endoscopy for confirmation of atrophy. Positive findings could be regarded as definitive, although negative findings could be associated with partial villous atrophy. Those patients would then likely require EGD with biopsy. For this reason, it was considered that video capsule endoscopy at this time may be limited to those patients with a strongly suggestive serologic profile who are unwilling or unable to undergo EGD. Gliadin antibodies alone could not be regarded as specific antibodies in this context [20,21].

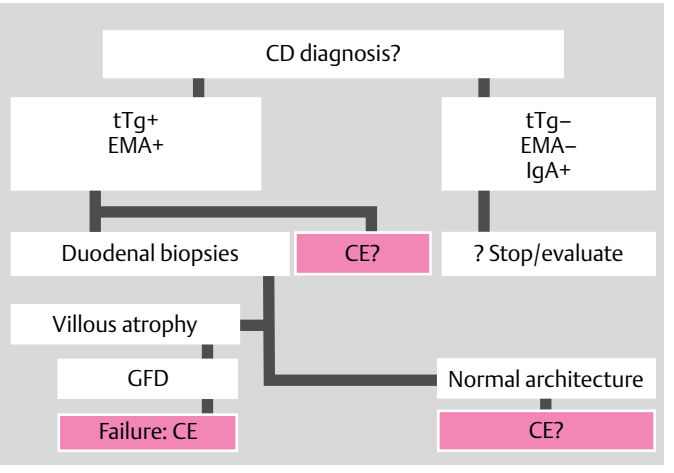

Figure **1** Proposed algorithm for the role of video capsule endoscopy (VCE) for the diagnosis of celiac disease. There are two potential roles for VCE in the initial diagnosis of celiac disease. It may be an alternative means of identifying villous atrophy in patients with serological evidence of celiac disease. In patients with positive serology but only subtle histological signs of celiac disease, such as increased intraepithelial lymphocytes, VCE may allow the detection of patchy atrophy changes. CD: celiac disease; CE: capsule endoscopy; EMA: endomysial antibody; IgA: immunoglobulin A; tTG: tissue transglutaminase.

In rare patients with positive serology for celiac disease and negative histology, video capsule endoscopy might be of interest. However, no robust data are available. A proposed algorithm for the use of video capsule endoscopy at diagnosis is shown in Figure **1**.

Symptomatic Treated Celiac Disease

There are several ongoing studies and anecdotal experiences describing the findings of video capsule endoscopy in patients with celiac disease who are symptomatic despite being on a gluten-free diet. Approximately 60% of such cases have villous atrophy, ulcers, or small mucosal erosions. The significance of the latter finding is not known. There is a small, but significant, proportion of such patients in whom lymphoma or adenocarcinoma has been discovered.

In a study of 47 patients with "complicated" celiac disease, Culliford et al. [22] detected a high rate of abnormalities at video capsule endoscopy. These patients had undergone extensive prior evaluations due to either abdominal pain, evidence of gastrointestinal bleeding or refractory iron deficiency or a high risk of cancer based on a previous history of small intestinal adenoma or adenocarcinoma. Unexpected findings including ulcerations were seen in 45% (n = 21). Other capsule findings included small-bowel cancer (n = 1), polyps (n = 1), stricture (n = 1), submucosal mass (n = 1), ulcerated nodular mucosa suspicious for lymphoma (n = 2) and intussusception (n = 1). This study suggests that video capsule endoscopy is of value in the investigation of patients who are symptomatic on a gluten-free diet. It also highlights the need

to have confirmatory studies to fully define the abnormalities that are detected by video capsule endoscopy.

The studies required to define and compare with the abnormalities detected by capsule endoscopy include sensitive radiographic studies such as computed-tomographic enteroclysis and PET scanning, or a direct endoscopic or histologic examination by push enteroscopy, double-balloon enteroscopy, or laparoscopy. Only significant abnormalities found by capsule (large ulcers, stenosis or tumors) should be investigated by invasive endoscopic or surgical means. Indeed, small ulcers may be found by video capsule in untreated celiac patients in up to 10% of cases [16]. An algorithm for celiac disease patients with alarm symptoms despite a gluten-free diet is shown in Figure **2**.

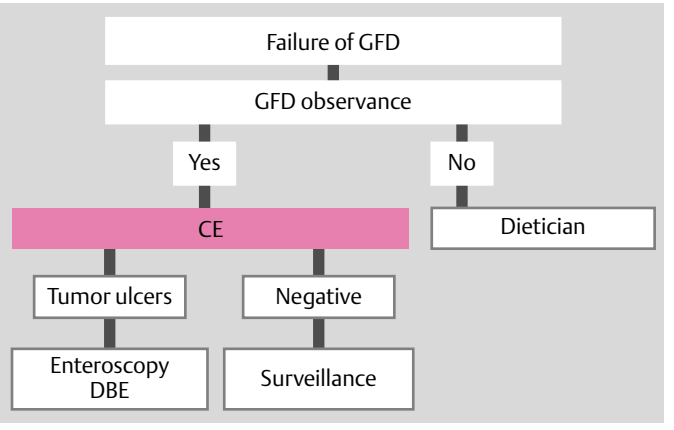

Figure **2** Proposed algorithm for the role of video capsule endoscopy (VCE) in patients with well-confirmed celiac disease with alarm symptoms who are observing a gluten-free diet (GFD). VCE may be useful for identifying persistent atrophy and its extent in the intestine, the presence of tumors that may be approached by a more invasive test like double-balloon enteroscopy (DBE), and nonspecific findings such as small-bowel ulceration. The lack of any abnormality does not preclude refractory sprue that requires close follow-up. CE: capsule endoscopy.

Follow-Up of Patients Responsive to a Gluten-Free Diet

The current European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) criteria [23] require a histological or clinical remission on a gluten-free diet. In cases in which the clinical recovery is not evident, video capsule endoscopy might provide an alternative to follow-up using EGD and biopsy. Preliminary data suggest that when patients have atrophy apparent on video capsule endoscopy before treatment, there is a greatly reduced frequency of abnormal findings after at least 6 months of a gluten-free diet. In those in whom atrophy persists, the extent is dramatically reduced.

Future Studies

We suggest that future studies should address interobserver and intraobserver variability, as well as establishing a standard terminology (Figure **3**) for the features of celiac disease found by capsule endoscopy. Preliminary data from Murray et al. [15] suggest that the extent of the disease does not predict the clinical features; however, a larger study or meta-analysis is needed to address this issue.

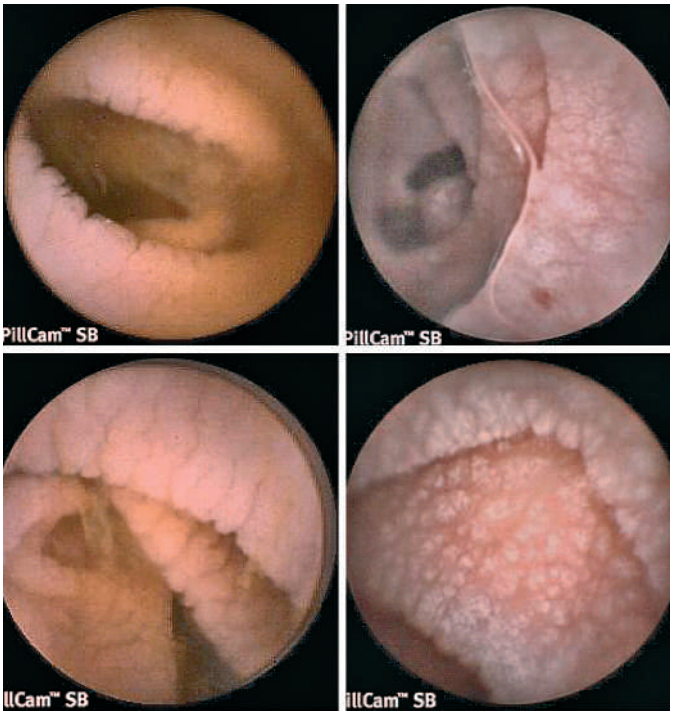

Figure **3** Range of endoscopic features of celiac disease on video capsule endoscopy.

We suggest there is an urgent need to incorporate the video capsule endoscopic features of celiac disease into training courses on video capsule endoscopy for gastroenterology trainees, with specific capsule courses directed at practitioners. In addition, training should include both specific disease entities such as celiac disease and possibly also a guideline for the number of cases needed to be formulated for gastroenterology trainees in order to be regarded as proficient in the technique. Lastly, studies regarding the screening or surveillance for malignancies in patients thought to be at high risk for developing disease need to be conducted. Patients over the age of 50 at diagnosis may be worthwhile candidates, as it appears they are at a greater risk of subsequent malignancy.

Summary

The Celiac Disease Consensus Group considered that there was adequate evidence to support the use of capsule endoscopy as a prognostic test in patients who have treated and previously confirmed celiac disease who develop alarm symptoms. We also consider that capsule endoscopy may have a future role as an initial diagnostic test for confirming atrophy in patients who are positive for tissue transglutaminase or endomysial antibodies. Capsule endoscopy could at present be used as an alternative to biopsy in selected patients who are unwilling or unable to undergo EGD for confirmation of villous atrophy.

Disclaimer

This statement is based on discussions held at the Fourth International Congress of Capsule Endoscopy, Miami Beach, Florida, March 2005. This work represents the views of the authors and the participants in a consensus-building exercise held at the above meeting. Its content is solely the responsibility of the authors.

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