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TOPIC HIGHLIGHT

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Is enteroscopy necessary for diagnosis of celiac disease?

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Abstract

Celiac disease (CD) is an autoimmune inflammatory disease of the small intestine as a result of reaction to wheat protein, gluten. Exclusion of dietary gluten is the mainstay of the treatment that necessitates a precise diagnosis of the disease. Serological screening may aid in identifying patients with suspected CD, which should be confirmed by intestinal biopsy. It has been shown that duodenal biopsies are good for detection of the disease in most patients. However, there is a group of patients with positive serology and inconclusive pathology. As a result of the widespread use of serology, many patients with equivocal findings grow quickly. Unfortunately current endoscopic methods can only diagnose villous atrophy, which can be present in the later grades of disease (i.e., Marsh Ⅲ). To diagnose CD correctly, going deeper in the intestine may be necessary. Enteroscopy can reveal changes in CD in the intestinal mucosa in 10%-17% of cases that have negative histology at initial workup. Invasiveness of the method limits its use. Capsule endoscopy may be a good substitute for enteroscopy. However, both techniques should be reserved for patients with suspected diagnosis of complications. This paper reviews the current literature in terms of the value of enteroscopy for diagnosis of CD.

INTRODUCTION

Celiac disease (CD) is the most common inflammatory disease of the small bowel with a prevalence of 1%-2.1% in different countries[1]. CD was previously thought to be a pediatric malabsorption syndrome, but it is now primarily recognized as an adult disease that resembles a multisystem disorder with a range of clinical manifestations that vary according to age of presentation. The clinical presentation among adults has clearly changed over time. Typical presentation should not be expected in the adult population; fewer patients present with diarrhea or a malabsorption syndrome. Instead, silent symptoms such as anemia, osteoporosis or dyspepsia are the most common manifestations, and interestingly, patients are frequently overweight or even obese at presentation. Patients may also present with vague dyspeptic symptoms or esophageal reflux, irritable bowel syndrome, iron deficiency, or neurological disorders. In fact, over time there has been a substantial increase in prevalence of the disease, and serological testing for CD has affected the rate of diagnosis[1-4].

Widespread use and availability of serology and awareness of the disease have led to a surge in the diagnosis of CD from a very rare disease to a common one.

In fact, screening of asymptomatic and at-risk individuals has contributed to this high prevalence[3]. The majority of CD patients detected by screening (> 80%) are clinically silent or so called "oligosymptomatic"[4]. Mainstay vehicles for screening are autoantibodies to tissue transglutaminase and endomysial antibody (EMA), which are highly sensitive and specific[4-7].

Despite these effective tools, small bowel biopsy should be performed in suspected patients, and histopathological examination of the small intestine must show any of the following: villous atrophy, crypt hyperplasia and elevated intraepithelial lymphocytes (IELs). Although small bowel mucosal changes are not specific for CD, abnormal biopsy findings can confirm the diagnosis in the context of the clinical setting that includes symptoms, serology and exclusion of other disorders. The only current and effective treatment is dietary restriction of the gluten in affected individuals, which necessitates the correct diagnosis.

CD AT A GLANCE

Characteristic pathological changes of the small bowel found in CD have been classified by Marsh and further modified by Oberhuber[8,9]. It is believed that small-bowel mucosal damage has three phases. In phase 1, the infiltrative phase, there are increased numbers of IELs. In phase 2, the hyperplastic phase, there is crypt hypertrophy. The destructive phase 3 of the disease is associated with varying degrees of villous atrophy that can be assessed during endoscopy[8,9]. The mucosal changes associated with CD can be patchy with parts of the mucosa appearing normal and nearby parts severely affected in children and adults. This patchy villous atrophy or disease poses a significant sampling error that leads to the possibility of missing the diagnosis, which can be detrimental for a young patient with long life expectancy, because the course of untreated CD is not always benign. Delay in diagnosis in patients with severe presentation is associated with increased mortality, primarily because of malignancy. A major question is the ultimate outcome of undiagnosed, presumed silent CD? It has been suggested that there is a significantly increased risk of mortality in patients with undiagnosed CD. However, the association with increased mortality is not universal nor is the association with increased malignancy[10-12]. Early diagnosis and treatment of CD has the potential to decrease risks of lymphoma, gastrointestinal cancer, bone disease, endocrine abnormalities, infertility and other autoimmune diseases[13].

As a consequence of an intensified screening policy, individuals with positive antibodies but without diagnostic small-bowel mucosal villous atrophy frequently are found. The condition often is considered false-positive, but there also is evidence to suggest that such a finding is indicative of early stage CD. Randomized clinical trials on the natural history and treatment of CD patients with mild mucosal changes and positive antibodies are lacking, and there is no consensus whether these patients should be treated at all with a gluten-free diet before villous atrophy has developed[2,10,13-15].

Despite recent advances in endoscopic imaging and serological tests, the accurate diagnosis of CD remains challenging. The site and number of biopsies to diagnose CD correctly have been the focus of recent research. Newly introduced technologies may carry a high yield but availability may limit their widespread use.

The gold standard of diagnosis relies on duodenal biopsy[16]; however, the reliability of duodenal biopsy is not straightforward. Patients come to biopsy because of the result of positive serological tests, a high index of suspicion for a mucosal disease process, or because of routine duodenal biopsy at endoscopy[17]. Biopsies from different sites of the duodenum in patients with positive celiac serology undergoing biopsy showed that none of the biopsies were considered normal. Moreover, in only 50% of patients was the degree of villous atrophy present in all sites the same; consistent with the patchy nature of the degree of villous atrophy. An interesting observation is that total villous atrophy significantly increased in a distal direction. Although more severe degrees of villous atrophy have been found distally, the diagnosis has mostly been confirmed in any location in the duodenum or jejunum[2,9,10,15].

INTESTINAL INVOLVEMENT

CD involves the proximal small intestine including duodenum and upper jejunum and extends distally for a variable length into the ileum. Damaged small bowel mucosa heals in a distal to proximal direction. Mucosal atrophy is continuous in most patients as a diffuse proximal enteropathy, which can be seen by any means of endoscopy. Autopsy studies on CD patients have also confirmed the involvement of the duodenum and jejunum in most cases and occasional extension into the ileum. However, distribution and extent of the CD are variable[13,18].

Dickey *et al*[19] have evaluated terminal ileal biopsies of 30 patients with CD and control patients and found that IEL counts were significantly higher in the CD group. They concluded that increased IELs in the terminal ileum correlated with duodenal atrophy, and that this finding should alert physicians to consider CD.

Although evaluation of the extent of the bowel involvement is not possible by conventional methods, capsule endoscopy (CE) can give an estimation about whether the whole of the small bowel is affected. It has been reported that 66.6% of patients with CD had an extension of the mucosal changes beyond the proximal small intestine and 11.1% had entire small bowel involvement[20]. According to Murray *et al*[21], in the majority of patients, the abnormal findings seen in the CE started in the proximal duodenum and extended into the jejunum. Findings of atrophy were seen in a continuous pattern in the duodenum, but features of atrophy were seen less obviously and were patchy in the jejunum. Extensive enteropathy was seen in 59% of the patients, denoting that CD affected the small bowel more than we think.

Mucosal specimens can be obtained using radiographically guided suction capsule (Crosby capsule) biopsy, which has disadvantages such as long procedure time, high failure rate, discomfort and radiation exposure during the procedure, although it is possible to take large biopsy specimens. Perforation, intramural hematoma of the small bowel and pancreatitis are reported complications[22]. Nowadays, Crosby capsule biopsy is not performed due to comparable efficacy of the duodenal biopsy to detect villous atrophy. Another important fact to take into account is the patchy nature of CD, which necessitates multiple biopsy approach to minimize sampling errors[23].

There are no clear-cut recommendations for the exact number of biopsy specimens to confirm or exclude diagnosis of CD, although the American Gastroenterological Association technical review recommends 4-6 biopsies[24]. Unfortunately, there is a gap between evidence-based data and real-life practice. A survey has shown that 63% of patients had fewer than four duodenum biopsies, which may indicate the reluctance of the endoscopists to take an adequate number of biopsies[25].

Site of the biopsy is another object of the debate. Pais *et al*[26] have found that duodenal biopsy specimens show some variability in terms of histological changes, and a minority of patients may have a discrepancy of more than two Marsh grades between biopsy sites. Ravelli *et al*[15] have found no cases of normal histology and coexisting villous atrophy in the same patient. This observation was supported by another study by Thijs *et al*[22] in which no discrepancy between jejunal and duodenal biopsies was found. Biopsies from the duodenum have been demonstrated to be useful for the diagnosis of CD and almost replaced the need for the jejunal biopsy.

Unfortunately, biopsy specimens from the duodenum harbor some problems and may not be a good place for the diagnosis of CD, given the nature of the disease and necessity of a strict diet. Not only is there more natural irregularity of the proximal duodenal mucosa, but specifically, the influence of nutrients mixed with gastric acid from the stomach and digestive fluids released into the duodenum in reaction to a meal may induce a chronic mild inflammatory response[27,28]. This may alter the appearance of mucosal inflammation and villous architectural changes, and therefore, disqualify duodenal biopsies for diagnostic use, especially when minor architectural changes and intraepithelial lymphocytosis must be considered[29].

All of the current endoscopic imaging techniques rely on the morphological changes of the mucosa associated with CD, which may direct the endoscopist for sampling. The value of endoscopy in the diagnosis of CD is limited to villous atrophy (Marsh grade 3). Celiac patients with villous atrophy are easily diagnosed, and most of them have positive serology, thus making this group of patients non-challenging. Histological changes in this group are so characteristic that they cannot be mistaken for other diseases. In contrast, patients with milder enteropathy, which is the most prevalent form of the disease at present, may show increased IELs that cannot be identified under white light or even with narrow band imaging or magnification endoscopy.

Diagnostic accuracy of biopsy specimens can be improved with advanced endoscopic technologies. Magnification endoscopy with narrow band imaging is a useful tool for obtaining biopsies at diseased sites[30]. These white light or blue-green light endoscopies are not capable of detecting increased IELs, which in turn limits us to the advanced stage of the disease with apparent atrophy and changes, but the problem is to detect the patients with subtle changes (i.e., Marsh grades 1 and 2). Confocal endomicroscopy (CEM) may aid in diagnosis in theory. However, fact is a little different from theory; CEM is good at detecting atrophy, although it cannot differentiate subgrades, and increased IELs, but falls short at detecting crypt hyperplasia, topical acriflavine use is helpful for quantification of IELs but fluorescein is not helpful. Very limited availability and safety issues on acriflavine use are the major drawbacks of CEM, and some imaging improvements should be done before its prime time use in CD[31].

ENDOSCOPIC FEATURES OF CD

The opportunity to make a correct diagnosis of CD might, therefore, also depend on the endoscopic appearance of the small bowel mucosa. Several endoscopic markers related but not specific to CD have been identified. These endoscopic markers are useful to determine whether duodenal biopsies are indicated and possibly to target from where biopsies should be taken. Endoscopic markers of CD are as follows: a reduction or absence of duodenal folds; scalloping, which is a notched appearance of the duodenal folds; visible submucosal vasculature; a mosaic pattern, which is the micronodular or cobblestone appearance of the mucosal surface; and mucosal fissures, crevices or grooves[17] (Figure 1). These indirect signs of villous atrophy have been helpful for predicting the presence or absence of duodenal villi and for targeting duodenal biopsies during upper endoscopy for diagnosing CD. Nevertheless, the sensitivity of these signs has been demonstrated to be variable in the different studies, and therefore, multiple endoscopic biopsies from descending duodenum and bulbar mucosa are recommended to ameliorate the diagnostic accuracy and to avoid underdiagnosis of patchy forms of CD[32,33].

Contradictory results concerning the value of these endoscopic markers of villous atrophy have been reported. Among several studies, the overall sensitivity and specificity of endoscopic markers of CD vary from 6% to 94% and from 83% to 100%, respectively. Several possible explanations exist for the absence of endoscopic markers in patients with CD. For example, such markers might actually be absent for degrees of enteropathy milder than subtotal or total villous atrophy (e.g., partial villous atrophy) and absent in cases in which the histo-

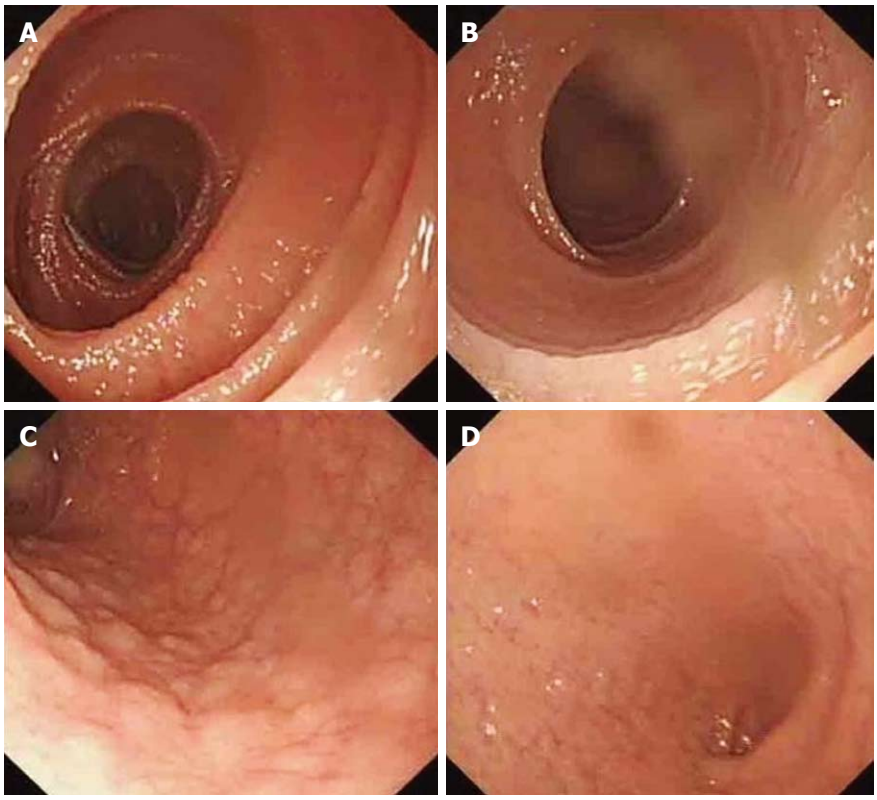

Figure 1 Proximal jejunum mucosa showing scalloping (A), reduced loss of mucosal folds (B), nodularity and mosaic appearance (C) and total mucosal atrophy (D), seen in patients with celiac disease during enteroscopy.

pathological involvement of the duodenum is patchy. In contrast, scalloping of duodenal folds has been reported in some patients who have moderate-to-severe enteropathy that is unrelated to CD; scalloping has a positive predictive value of 69% for CD and 96% for any duodenal mucosal pathology[34]. Scalloping is not specific for CD but rather a predictor of mucosal disease as evidenced by villous atrophy, widening, and edema[35].

It is possible to augment the villous changes by a simple procedure of underwater examination of the mucosa, which is called the water-immersion technique (WIT), which consists of the instillation of water into the duodenum after removal of air and adds only a few seconds to the examination time. WIT-assisted duodenoscopy has been demonstrated as reliable in distinguishing accurately the presence or absence of villi in the duodenal bulb and the descending duodenum[32,33]. However, no study has specifically addressed the value of WIT during enteroscopy. We usually perform WIT to assess the villi structure in the jejunum during the enteroscopy examination of patients with diarrhea and malabsorption and find it useful for diagnosis of CD.

MAKING THE CASE FOR ENTEROSCOPY

CD is a gluten-dependent enteropathy characterized by chronic small intestinal inflammation and villous atrophy. However, CD is not the only cause of an inflammatory cell infiltrate with or without villous atrophy in duodenal mucosa. Other causes include postviral enteritis, cow or soy milk enteritis, Crohn's disease, common variable immunodeficiency, autoimmune enteropathy, nonsteroidal anti-inflammatory drugs, giardiasis, tropical sprue, and tuberculosis. It is more likely that the normal state of the bulb mucosa is not as free of inflammation as is mucosa of the second or third part of the duodenum, nor does it have a villous/crypt ratio the same as these zones. It has been proposed that the anatomical location of the bulb makes it more vulnerable than the more distal duodenum to injury by gluten. However, similar reasoning applies also to potential injury of the bulbar mucosa by aforementioned causes and gastric acid. In addition, Brunner's glands and lymphoid nodules can give a common endoscopic finding of nodularity in the duodenal bulb, which can also distort the overlying architecture. On biopsy, lymphoid aggregates are also commonly found in the duodenal bulb of younger children. That is why some findings in the bulb may be a part of life rather than disease. Biopsy samples from the duodenal bulb may be difficult to interpret, in fact, the duodenal bulb is not considered a useful site for the diagnosis of CD, even though this site has rarely been reported to be the only one showing reliable histological changes in adults and children with CD. Taking biopsy samples more distally may decrease the likelihood of confusing histological findings[34].

CD has many atypical manifestations, and endoscopic findings alone are not considered sensitive or specific for the diagnosis of CD. Pais *et al*[26] examined 247 patients

to determine how many duodenal biopsy specimens were needed to diagnose CD. They concluded that only two specimens led to confirmation of CD in 90% of cases and that four descending duodenal biopsy specimens led to 100% confidence in the diagnosis. Comparison of biopsy specimens from the second, third, and fourth parts of the duodenum, the ligament of Treitz, and the proximal jejunum has shown that each site is suitable for diagnosing CD[7]. Mucosal specimens taken from the distal duodenal or jejunal mucosa are strongly correlated, therefore, biopsy samples from the second or third part of the duodenum are considered adequate to obtain material for histological interpretation[29]. Thus, biopsy of the other parts of the small intestine may be needed for precise diagnosis of CD, which is an indication for enteroscopy.

ENTEROSCOPY

We have long been aware that complete examination of the small bowel is crucial for evaluation of refractory disease or its complications. However, conventional endoscopy has limited value for evaluation of complications like ulcerative jejunoileitis and lymphoma that may be located deep in the small bowel, which necessitates deep enteroscopy techniques such as push enteroscopy (PE), balloon-assisted enteroscopy (BAE) and CE. Invasiveness of the enteroscopy technique limits its use. Two studies have explored the value of PE for the diagnosis of complicated CD.

Höroldt *et al*[36] have searched the possible role of PE with jejunal biopsies. They prospectively recruited 31 patients who had symptoms suggestive of CD and positive serology, but non-diagnostic duodenal biopsies that were either normal or showed increased IELs. Enteroscopy with duodenal and additional jejunal biopsies was performed in all of the patients, who continued a normal gluten containing diet, 6-12 wk after index endoscopy. Repeat biopsies confirmed CD in five of the eight patients who were positive for EMA. Moreover, in 60% of cases, these changes were diagnostic in the jejunal biopsies only. De Vitis *et al*[37] also studied a similar group of 23 patients, and in their group, only four patients were diagnosed with CD according to jejunal biopsies alone. According to these enteroscopy studies, CD can be further diagnosed in 10%-17% of patients with equivocal findings in the previous studies of patients who were presumed to have CD. A limitation of PE is that it evaluates a fraction of the small bowel, leaving the majority of the small bowel uninvestigated.

Cellier *et al*[38] demonstrated that PE detected jejunal ulcerations in 62.5% of CD patients, in whom no duodenal lesions were observed. They found that PE with jejunal biopsies has diagnostic value only in patients with refractory CD but not in those with uncomplicated CD. However PE requires expertise and takes longer than standard esophagogastroduodenoscopy (EGD). Nowadays, it has mostly been replaced by BAE, which enables concise investigation of the small bowel. However, is it worth digging deeper? BAE makes it possible to evaluate the entire small bowel with biopsy capability. After the introduction of BAE into clinical practice, it has been used to evaluate the small bowel in various diseases, with a high success rate for complete bowel examination[39]. Unfortunately, there is no study specially addressing the value of BAE in the diagnosis of uncomplicated CD. According to a report by Hadithi *et al*[40], who performed double balloon enteroscopy (DBE) in refractory CD, DBE had a significant diagnostic yield and revealed complications such as ulcerative jejunoileitis and lymphoma in 30% of patients. A further important result of the study was that DBE successfully ruled out T cell lymphoma in 25% of patients. Potential risks of BAE limit its use in every patient, which makes it difficult to recommend the procedure to every single CD patient, and it should be reserved for those patients with unequivocal findings or abnormal imaging results. Enteroscopy should be considered in patients with refractory CD and in those with a high clinical or serological suspicion of CD but inconclusive duodenal biopsies. Although this group of patients will always remain small, it is important to bear in mind that enteroscopy can sometimes be of value to diagnose CD[41]. It should be emphasized that BAE is an effective way for the evaluation of the complications of CD and should be utilized early in the diagnostic algorithm.

Another way of examining the small intestine is CE, which may be a possible substitute for EGD because of its minimal invasiveness, however, its cost and limited availability make it insufficient to replace EGD. CE has an eightfold magnification capacity and therefore is able to assess the small bowel mucosa. For this reason, CE could offer an alternative in patients who are unable or unwilling to undergo endoscopic examination. CE is done without air inflation, with the round dome-shaped edge housing the optical system close to the mucosa. It allows examination of the entire small bowel and facilitates diagnosis of complications[42]. CE studies have failed to demonstrate any correlation between clinical presentation and the length of involvement. Diagnostic yield of CE increases significantly when a CD patient is under the risk of having a complication or malignancy, such as patients with iron deficiency anemia or refractory disease. In these high probability patients, ulcerations or other positive findings can be revealed in up to half the patients[43]. CE is not superior to the conventional EGD in the case of new diagnosis of CD patients[44]. Another point to remember is that CE is a poor modality for examination of the duodenum due to rapid transfer of the capsule in this area. That is why, if there is limited proximal enteropathy, CE may miss the mucosal changes; even Marsh grade 3c changes can be missed. Addition of Fuji Intelligent Color Enhancement - capability or post-processing of the acquired images may aid discrimination of villous atrophy[45]. When should we use CE for the diagnosis of uncomplicated CD? Patients who have less than four duodenal biopsies should be directed for repeat endoscopy with at least four biopsies and CE should be performed in those patients

who still have normal duodenal histology and are positive for celiac serology and HLA-DQ2 or HLA-DQ8[46]. Similar reasoning may also apply to BAE with biopsy of the jejunum or deep intestine, and in this case, BAE with biopsy could be superior to CE in terms of biopsy and histological confirmation of the disease. Otherwise, both methods rely on white light visible morphological changes. Therefore, it should be stressed that CE is not a substitute for histological examination, however, CE can detect complications missed by routine EGD[44]. That is why the use of both BAEs and CE to evaluate the entire small bowel at the time of initial diagnosis does not seem to be justified[47].

CONCLUSION

Is enteroscopy needed for the diagnosis of the CD? We can answer "yes" to this question, with reserve. Based on these findings, enteroscopy examination for CD should be reserved for patients with positive serology and negative histopathology at initial EGD, and in the search for complications during follow-up. Enteroscopy cannot be recommended at the initial work-up of CD patients. CE may find a place for the diagnosis of complications of CD because of its noninvasiveness and ease of use. The main problem is to diagnose the early forms of the disease by simple examination, for which the current endoscopy methods have failed in terms of detection, because these methods successfully detect atrophy, which is the only visible sign of the disease. We believe that addition of water immersion, even during enteroscopy, is helpful, easy and incurs no cost, and should be performed in every suspected patient to minimize unnecessary biopsies.

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