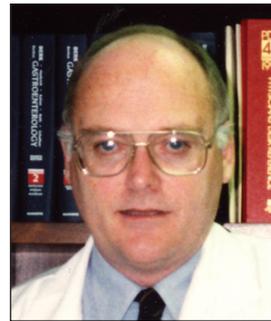


Kevin W. Olden, M.D., Series Editor

Celiac Disease versus Irritable Bowel Syndrome: A Diagnostic Dilemma



D. Shane Pendley



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When to suspect celiac disease (CD) in a patient who meets Rome II criteria for irritable bowel syndrome (IBS) can be a diagnostic challenge. Both IBS and CD have overlapping symptoms, and can be confused for each other. This can make the diagnosis of these disorders challenging for the clinician. Our purpose was to suggest a possible diagnostic approach to patients suspected to have one or both of these disorders. Ultimately, we recommended no further diagnostic testing in patients who present with symptoms meeting Rome II Criteria for IBS with no alarm symptoms for CD, with further diagnostic testing for CD, specifically TTG and AEA testing and potentially small bowel biopsy, recommended in patients with a first order relative with CD, alarm symptoms for CD, or who fail to respond to treatment for IBS after a 1 to 2 month period. We further describe “alarm symptoms” for CD and explain our rationale in our suggested diagnostic algorithm, citing relevant current literature on the topics of IBS and CD.

INTRODUCTION

Irritable bowel syndrome is a gastrointestinal disorder characterized by an alteration in bowel habit with abdominal pain in the absence of detectable

structural disease (1). It is characterized by abdominal pain or discomfort in association with diarrhea, constipation, alternating diarrhea and constipation, or a mixture of these symptoms. It occurs in approximately 10%–20% of the U.S. population (2). The cause of IBS is unknown but a variety of mechanisms have been proposed (3,4).

Celiac disease (CD), also known as non-tropical sprue or gluten-sensitive enteropathy, is an autoimmune disorder characterized by intestinal malabsorption that occurs after an inflammatory T-cell mediated response occurs in susceptible individuals after inges-

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Table 1
Comparison of Symptoms of CD and IBS

Symptoms of CD

- Diarrhea—watery/greasy/loose stools
- Abdominal pain/cramping/bloating
- Abnormal stool frequency

Symptoms of IBS

- Abnormal stool form (which may include loose or hard stools)
- Abdominal pain/cramping/bloating
- Abnormal stool frequency
- Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation)
- Passage of rectal mucus

tion of dietary grains containing gluten, a protein found in wheat, rye, and barley (5). Evidence suggests a prevalence of CD of roughly 0.75% in the general U.S. population, with a higher prevalence seen in first and second-degree relatives of patients with diagnosed CD and in patients with gastrointestinal symptoms (6). The pathologic mechanism of CD involves activation of T-cells against host tissue in the small bowel, causing chronic inflammation and villous atrophy. This in turn leads to malabsorption of most dietary nutrients due to a significant reduction in the absorptive area available within the small intestine. The mechanism for the small bowel mucosal damage seen in CD requires deamidation of dietary gluten peptides by intestinal tissue transglutaminase (TTG), which causes a HLA-DQ2 mediated autoimmune response (7,8). The targets of this T-cell response include gliadin (after the modification of ingested gluten by TTG as mentioned above), intestinal endomysium (a structural portion of intestinal smooth muscle), and TTG (an enzyme found within the small bowel, of which gluten is one of its substrates). Thus, the pathophysiologic cascade in CD requires TTG to occur, as it is necessary both to deamidate gluten making it an antigenic target for the autoimmune T-cell response, and it is also a target of that response itself after it begins.

Both IBS and CD have overlapping symptoms, and can be confused for each other (Table 1) (9–11).

This can make the differential diagnosis of these two disorders challenging for the clinician. The purpose of this article is to discuss this challenge and to suggest a possible diagnostic approach to patients suspected to have one or both of these disorders.

CLINICAL FEATURES OF IRRITABLE BOWEL SYNDROME

Irritable Bowel Syndrome (IBS) is a functional bowel disorder that is characterized by diarrhea, constipation, abdominal pain, alternating diarrhea and constipation, or a mixture of these symptoms in the absence of identifiable organic disease. IBS is diagnosed using the Rome II Criteria, which was developed to aid in the identification of IBS using symptom based criteria. This in turn would, ideally, obviate the need for an extensive, and costly medical work-up (Table 2). The problem that the clinician faces when evaluating a patient with symptoms of diarrhea or alternating constipation and diarrhea, is that IBS-D (diarrhea predom-

(continued on page 47)

Table 2
Rome II Criteria, republished from Rome II: The Functional Gastrointestinal Disorders (1) with permission

“at least 12 weeks or more, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two out of three features: relieved with defecation *and/or* onset associated with change in frequency of stool *and/or* onset associated with a change in form (appearance) of stool.

Symptoms that cumulatively support the diagnosis of irritable bowel syndrome

- abnormal stool frequency (for research purposes “abnormal” may be defined as greater than 3 bowel movements per day and less than 3 bowel movements per week);
- abnormal stool form (lumpy/hard or loose/watery stool);
- abnormal stool passage (straining, urgency, or feeling of incomplete evacuation);
- passage of mucus;
- bloating or feeling of abdominal distension (1)”

(continued from page 44)

Table 3
Sensitivity and Specificity of Serologic Tests for Untreated Celiac Disease
 (Data and table adapted from Farrell and Kelly (5), republished with permission)

<i>Serologic test</i>	<i>Sensitivity* %</i>	<i>Specificity* %</i>	<i>Positive Predictive Value %</i>	<i>Negative Predictive Value %</i>
Test for IgA antiendomysial antibody Indirect immunofluorescence assay	85–98	97–100	98–100	80–95
ELISA using guinea pig tissue transglutaminase	95–98	94–95	91–95	96–98
Dot blot test that uses human tissue transglutaminase	93	99	99	93
Test for IgA antigliadin antibodies	75–90	82–95	28–100	65–100
Test for IgG antigliadin antibodies	69–85	73–90	20–95	41–88

*As noted in the original publication of this table by Farrell and Kelly (5), “there are wide variations in the sensitivity and specificity of these tests among different laboratories.” Furthermore, as discussed in this article, there is clinical evidence that there appears to be further variability in the sensitivity and specificity in AGA, EMA, and TTG testing dependent upon how much villous atrophy is present in the patient (24,25,26).

inant IBS) and, to some extent, IBS-A (IBS with alternating diarrhea/constipation), have symptoms that closely resemble and may be indistinguishable from symptoms found in individuals with CD.

CLINICAL FEATURES OF CELIAC DISEASE

Common symptoms of CD include diarrhea, abdominal cramping, and bloating. Other more insidious signs and symptoms may also mark the presence of CD, including anemia (either microcytic from poor iron absorption, macrocytic from poor B vitamin and folate absorption, or normocytic from a combination of the above factors), osteopenia, IgA deficiency, hypertransaminasemia (12), hepatoma (13), infertility, ataxia (14), peripheral neuropathy (15), seizures or hematuria (16). Comorbidities that may occur with CD include type 1 diabetes mellitus, autoimmune thyroid dysfunction, and Addison’s Disease. CD may also be present with no overt clinical symptoms at all.

There is no known cure for CD. Treatment involves strict lifelong adherence to a gluten-free diet, which prevents antigenic stimulation of the inflammatory cascade by the offending gliadin protein, and often abolishes all symptoms associated with the disorder.

DIAGNOSTIC TESTING FOR IBS

IBS traditionally was diagnosed only after other “organic” causes of IBS-like symptoms were ruled out, and was considered a “diagnosis of exclusion.” Multiple diagnostic modalities have been studied in efforts to identify diagnostic testing that might aid in the correct diagnosis of IBS, but none have been shown to be consistently useful (17, 18, 19). Currently, the Rome criteria for diagnosis of IBS has been shown to be 65 percent sensitive and 100 percent specific in identifying IBS without the need for extensive laboratory and clinical testing (20,21,22,23). However, it is not clear how well the Rome criteria for IBS perform in the presence of chronic diarrheal illnesses such as microscopic colitis or celiac disease (23).

DIAGNOSTIC TESTING FOR CELIAC DISEASE

The “gold standard” traditionally used in establishing a definitive diagnosis of CD has been endoscopic duodenal biopsy (5). Histologic findings consistent with a CD diagnosis are intestinal villous atrophy and/or blunting. Serologic tests are often obtained in evaluating a patient with suspected CD and include testing for anti-endomysial IgA antibodies (AEA), tissue transglutaminase (TTG) antibodies, and antigliadin IgG and IgA

antibodies (AGA). Although the presence of these serologic markers may point to a diagnosis of CD, they have a disappointing level of sensitivity and specificity when compared with small intestinal / duodenal biopsy (24). However, there is growing evidence to support serologic testing as reasonable in patients suspected to have CD, even if it may not be of clear benefit in screening the general population (sensitivity and specificity of serologic tests available for CD, Table 3) (5).

In one study done by Rostami, et al, serologic screening using AGA and AEA on 101 patients (69 untreated celiac patients and 16 first-degree relatives of CD patients, with 16 patients excluded from the study due to failure to satisfy diagnostic criteria for CD and 3 patients excluded due to IgA deficiency) was shown to have poor sensitivity for the detection of untreated CD in patients found to have villous atrophy on endoscopy, while retaining 100% sensitivity and specificity for CD in patients with total villous atrophy on endoscopy (25). Combined screening utilizing both AGA and AEA testing showed a sensitivity for CD of 76% (53/69) in the study population (25). Similarly, Novogradsky, et al (24) reviewed results of TTG antibody testing and duodenal biopsy results of 145 U.S. patients at the time of diagnosis of CD between 2000 and 2003 and found a variability in the sensitivity and specificity of TTG antibody testing depending on the degree of villous atrophy noted on duodenal biopsy. Per their findings, “a strong association was noted between a positive TTG [antibody] and degree of villous atrophy sensitivity: 92% in patients with total villous atrophy versus 35% in patients with partial villous atrophy).

In a comparison between AGA and TTG antibody testing, Gomez, et al studied 1000 patients and found an increased sensitivity and reduced cost when using TTG antibody testing as an initial serum screening test for untreated CD versus IgA and IgG AGA testing as an initial serum screening test for undiagnosed CD (26).

To further complicate the diagnostic evaluation of CD, the clinical entity known as CD is evolving, with “atypical” presentations becoming more evident. Histologic evidence of CD is being found in a wider spectrum of patients than previously suspected at risk for the disorder (27,28). A small portion of CD sufferers with diagnostically-proven CD are “clinically silent” or latent, and have no overt clinical symptoms from

their disease (29). Increasingly since the 1950’s, more patients with CD are being diagnosed at later ages yet, at times, with a shorter duration of symptoms than in times past (29). This poses a problem for the clinician, as the variable presentations of CD may mimic other illnesses including IBS. Added to this is the fact that CD occurs in a wide spectrum of patients with presentation at variable ages and in ethnic groups previously thought not to be at risk for CD. It therefore becomes evident that CD can be a difficult disease to recognize clinically, making it unclear as to when clinical suspicion should be raised for its presence.

Matteoni, et al (30) demonstrated a higher prevalence of CD identified in patients found to have microscopic colitis (which includes both lymphocytic colitis and collagenous colitis) than in the general population. Recently, Tursi, et al (31) identified a possible correlation between Crohn’s Disease and CD, although this study was small. Further studies are needed to further determine if there is a relationship between CD and Crohn’s Disease.

Given the clinical evidence demonstrating a potential relationship between the prevalence of CD and certain other disorders, a diagnostic algorithm for the presence of CD can be helpful. In particular, in patients who do not initially respond to conventional treatment for functional bowel disorder. So, the question remains: what should that evaluation entail?

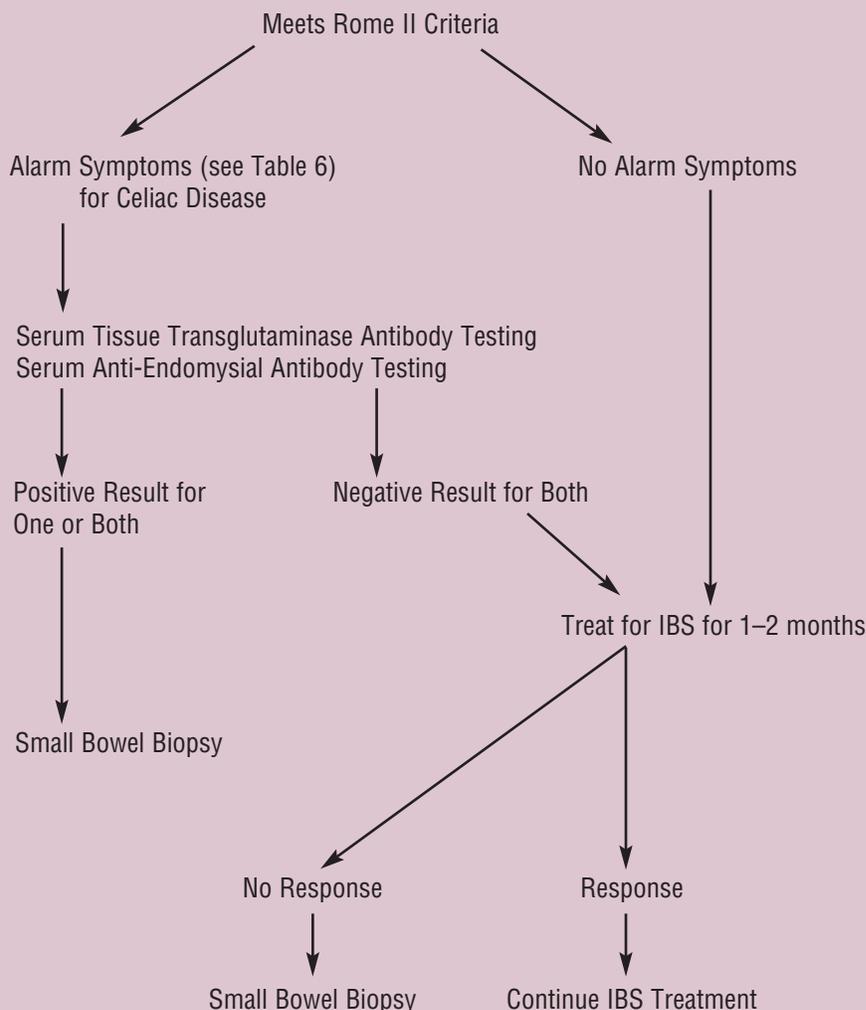
THE DIAGNOSTIC DILEMMA

One potential approach in the diagnostic evaluation for patients who present with symptoms suggestive of both CD and IBS includes routine serologic testing for markers that are found in patients with CD. In a case-control study done by Sanders, et al (32) with 300 patients who met Rome II criteria for IBS and 300 age and sex matched healthy controls who were all screened for the presence of CD using serum IgA and IgG AGA, and EMA testing. In those patients found to have positive antibodies, duodenal biopsy was performed to determine histologic evidence of CD. Sixty-six of the IBS patients were found to have a positive serum screening test for CD (22%), and 9 of them refused biopsy, 43 had normal duodenal mucosa, and 14 had histologic evidence of CD (5%). Eleven of the 14 patients with histo-

(continued on page 50)

(continued from page 48)

Table 4
Diagnostic Approach to Evaluation of Patient with Potential IBS and/or Celiac Disease



logic evidence of CD were EMA positive on serum screening for CD, while 3 were EMA negative. In the control group, only two patients were found to be EMA positive on screening, and both were found to have CD on biopsy. These results suggest an increased prevalence of CD in patients who fulfill Rome II diagnostic criteria for IBS. This study also suggests the usefulness of serum antibody screening for CD in patients who fulfill Rome II Criteria for the diagnosis of IBS.

In support of the findings of Sanders, et al, an evidence-based literature review done by Cash and colleagues evaluated six published manuscripts found

that in patients fulfilling Rome II criteria for IBS there is a 10 times greater pretest probability of CD than in the general population. They further went on to say that “routine performance of serologic tests for CD may be useful in this [patients who meet symptom-based criteria for IBS] patient population, although further study is needed in this area (33).”

Although some question remains as to the value of serologic testing in screening the general population for CD, it seems prudent that some evidence-based suggestions be established for further diagnostic evaluation in

(continued on page 52)

(continued from page 50)

those patients who meet symptom criteria for IBS but who fail to have a clinical response after an appropriate period of treatment. The aim of this article is to suggest a method for evaluation of patients with symptoms of both CD and IBS, based upon initial presentation and also upon symptom response to treatment of IBS, if the patient fulfills Rome II criteria for the diagnosis of IBS.

SUGGESTIONS ON EVALUATING THE PATIENT WITH SYMPTOMS CONSISTENT WITH BOTH CELIAC DISEASE AND IBS

A potentially beneficial diagnostic testing approach that could reasonably be suggested includes no further diagnostic testing in those patients who present with symptoms that fulfill Rome II Criteria for IBS and who have no alarm symptoms for CD (Table 4). Further diagnostic testing for CD, specifically TTG and AEA testing is indicated in those patients who are found to have a first order relative with CD, to have alarm symptoms for CD (Table 4) at any time during the course of their medical care, or in those patients who fail to respond to appropriate treatment for IBS after a 1 to 2 month period (Table 4).

Serologic testing such as serum thyroid-stimulating hormone to assess thyroid function, serum complete blood count to screen for anemia, erythrocyte sedimentation rate to assess for inflammation, serum chemistry or fasting glucose to assess for the presence of diabetes mellitus, and liver-associated transaminases to screen for autoimmune liver dysfunction is not indicated for initial screening of patients who present with symptoms which could be indicative of CD or IBS (19), as symptom criteria alone for IBS have been shown to be sensi-

Table 5
“Red Flags” in the diagnosis of IBS
 (republished from Olden (34) with permission)

- weight loss, anemia, occult blood in stool
- travel history to locations with endemic parasites
- nighttime symptoms
- new onset after age 50
- family history of colon cancer or IBD
- arthritis or dermatitis on physical exam
- signs of malabsorption
- signs of thyroid dysfunction

Table 6
Alarm Symptoms Suggestive of Celiac Disease

1. Presence of comorbid autoimmune disorders: autoimmune thyroid disease (35), Addison’s Disease, multiple endocrine disorders, diabetes mellitus type 1 (36). (one exception is autoimmune hepatitis)
2. Presence of abnormal serum TSH, AST, GGT, ESR (37), ALT
3. Diagnostic evidence of osteopenia/osteoporosis/osteomalacia in a pediatric patient or a patient without reasonable risk factors for the development of bone disease (i.e. advanced age, post-menopausal women), who has symptoms of diarrhea, constipation, both (alternating), and/or abdominal pain.
4. Infertility / subfertility (38, 39)
5. Ataxia (14, 40)
6. Dermatitis Herpetiformis
7. Symptom exacerbation (specifically, abdominal pain and / or diarrhea) after treatment of presumed IBS with gluten-containing fiber products.
8. Selective IgA deficiency
9. Anemia

tive, specific, and durable in patients without “red flag” symptoms (Table 5) (21,22,23,34). However, the low cost and ease of administration of these tests may justify their use in patients with IBS-D (who have an increased probability for CD, given the diarrhea which characterizes both CD and IBS-D). A review done by Cash, et al found that “routine performance of serologic tests for celiac disease may be useful in this [patients who meet symptom-based criteria for IBS] patient population, although further study is needed in this area (33).

SUMMARY

When to suspect CD in a patient who meets Rome II criteria for IBS can be a diagnostic challenge. However, through judicious use of the Rome II criteria and simultaneously being mindful of the risk of missing a CD diagnosis as well as potential diagnostic strategies as outlined in this article when evaluating symptoms of diarrhea, constipation, or abdominal pain (or any combination of these), the clinician can safely diagnose CD, IBS, or both conditions comorbidly while sparing

(continued on page 58)

(continued from page 52)

the patient unnecessary inconvenience, expense, and suffering. The key elements in deciding which diagnostic strategy is most appropriate include: eliciting a thorough clinical history (including an extensive family history) and identification of “alarm symptoms” suggestive of CD (Table 6). ■

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