ORIGINAL INVESTIGATION

Accuracy of Ultrasonography in Predicting Celiac Disease

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Background: Various ultrasonographic (US) signs have been reported in overt celiac disease (CD). The aim of this study was to investigate the diagnostic accuracy of 6 US parameters in predicting CD.

Methods: One hundred sixty-two consecutive patients with chronic diarrhea (n=105), iron deficiency anemia (n=25), or dyspepsia (n=32) underwent anti-endomysial IgA antibody determination and duodenal biopsy. Moreover, US evaluation of 6 parameters (ie, fasting gallbladder volume, transverse diameter of small bowel loops, thickness of the small bowel wall, pattern of peristalsis, presence of free abdominal fluid, and diameter of the mesenteric lymph nodes) was done by 2 operators blind to the serological and histological findings. The pretest probability of CD was estimated to be between 5% and 10%. The percentage of agreement between US and histologic findings, the sensitivity, specificity, positive and negative likelihood ratios, and the posttest probability for positive and negative results were calculated.

Results: Celiac disease was diagnosed in 12 patients (7.4%). An increased gallbladder volume, the presence of free fluid in the abdominal cavity, and enlarged mesenteric lymph nodes showed a specificity of 96%, 96%, and 97%, respectively (95% confidence intervals [CIs], 92%-99%, 93%-99%, and 95%-99%), whereas the presence of dilated small bowel loops with increased fluid content and increased peristalsis had a sensitivity of 92% and 83%, respectively (95% CIs, 76%-100% and 62%-100%). Eleven (92%) of the 12 patients with celiac disease and 35 (23%) of the 150 patients who did not have the disease had at least 1 US sign ($P=.001$); all of the US signs were concomitantly present in 4 patients with CD (33%) and 1 patient without CD (0.6%) ($P=.001$).

Conclusion: Ultrasonographic evaluation can accurately predict CD but its place in the diagnostic algorithm depends upon the probability of the disease in the considered population.

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THE PREVALENCE OF CELIAC disease (CD) in Western countries is between 1 in 200 and 1 in 300.[1-4] It occurs when the small bowel mucosa of susceptible individuals is damaged by dietary gluten, and its clinical forms—which include chronic diarrhea, iron deficiency anemia, and dyspepsia—range from mild to severe forms.[1-4] As recently reviewed, diagnosis is supported by the determination of anti-endomysial IgA (EMA) antibodies (whose sensitivity ranges from 71% to 100% and specificity from 64% to 100%),[5,6] and confirmed by consistent histological duodenal findings.[1]

The recent availability of high-frequency transducers (5-12 MHz) has made it possible to evaluate the morphology of the small bowel loops and abdominal cavity ultrasonographically. Various ultrasonographic (US) signs have been reported in association with CD.[7-9] These data came from series in which the pretest probability of CD was high. However, because they included patients with overt malabsorption[7] or who were already known to have the disease,[8,9] they led to an overestimate of the technique's diagnostic performance.

The aim of this prospective study was to evaluate the diagnostic accuracy of several US signs in predicting CD in patients with chronic diarrhea, iron deficiency anemia, and dyspepsia, for whom the pretest probability of CD ranges from 5% to 10%, as estimated from a previous series.[10]

METHODS

PATIENTS AND DIAGNOSIS

Between October 1999 and December 2000, 162 patients (67 men and 95 women; mean ± SD age, 46±18 years; range, 14-88 years) were referred to our US unit as part of

their clinical evaluation for chronic diarrhea (n=105), iron deficiency anemia (n=25), or dyspepsia (n=32), and consecutively enrolled in the study accordingly to their most relevant finding. Three patients, all in the group with iron deficiency anemia, also had chronic diarrhea, and there were concomitant dyspeptic symptoms in 30 of the 105 patients with chronic diarrhea and in 11 of the 25 patients with iron deficiency anemia.

All of the patients gave written informed consent to participate in the study, which was approved by the ethics committee of the Istituto di Ricovero e Cura a Carattere Scientifico, Ospedale Maggiore, Milan, Italy.

Anti-endomysial IgA antibodies (using Biognost Endomysiale IgA AK; Bios GmbH Labordiagnostik, Gräfelfing, Germany) and total immunoglobulin levels were evaluated for all patients, who also underwent upper gastrointestinal tract endoscopy with multiple distal duodenal biopsies. The histological findings were classified according to the Marsh criteria[11] and represented the diagnostic reference standard.

After an overnight fast and without any specific preparation (ie, without oral antiflatulents or water enemas), the patients underwent a US abdominal scan performed using commercially available equipment (ATL HDI 5000; Advanced Technology Laboratories, Bothell, Wash) with 3.5 and 5-12 MHz transducers; US exploration of small bowel loops was performed by slowly scanning the entire abdomen along a spiral line starting in the right upper quadrant. The following parameters were assessed:

- Fasting gallbladder volume, which was calculated with the ellipsoid method[12]; according to previous data,[9] it was considered increased if found to be greater than 20 mL.
- Transverse diameter of the small bowel loops and intraluminal fluid content; the concomitant presence of dilated small bowel loops (outer diameter >2.5 cm, including the bowel wall) and increased intraluminal fluid content[8] were considered abnormal.
- Thickness of the small bowel wall. In healthy individuals, it ranges from 1 to 2 mm when noncontracted. In accordance with Rettembacher et al[8] we considered abnormal a small bowel wall thickness greater than 3 mm, independently of its distension or collapse; only bowel segments longer than 4 cm were considered to ensure that this sign was not incidental or artifactual.
- Pattern of peristalsis, which was defined according to previously reported criteria.[8] In fasting healthy subjects, small bowel peristalsis is slow, only occasionally detectable, and limited to a single part of the bowel. Intense and frequent peristalsis along the entire small bowel was considered abnormal, as was the presence of free fluid between the bowel loops.[8]
- Diameter of mesenteric lymph nodes; mesenteric lymph nodes were considered enlarged when the long axis was greater than 5 mm.[8]

To evaluate the interobserver agreement, the US parameters were independently and sequentially evaluated by 2 gastroenterologists (M.F. and A.C.) who were blind to the clinical, serological, and histological findings. They had undergone long US training and performed more than 500 US scans of small bowel loops before the start of this study.

A final diagnosis was reached in all cases according to the current guidelines for each of the presenting conditions.[13-15]

The pretest probability of CD was estimated at about 5% to 10%, as derived from the series in primary care by Hin et al[10] and confirmed in our own group of 1875 consecutive patients similar for sex (37% men and 63% women), age (mean, 49±11 years; range, 16-81 years) and presenting features (58% had chronic diarrhea, 16% had iron deficiency anemia, and 26% had dyspepsia) who underwent a complete clinical evaluation including clinical examination, total serum IgA and EMA determination, and distal duodenal biopsy if their test result for EMA was positive. In this group a total of 181 patients (9.6%) received a final diagnosis of CD.

STATISTICAL ANALYSIS

The percentage agreement between US signs and duodenal histological findings was assessed by calculating the κ values[16] and their 95% confidence intervals (CIs). The proportion of potential agreement beyond chance when comparing 2 or more clinical findings or the results of different techniques was considered as "slight" (κ=0.0-0.20), "fair" (κ=0.21-0.40), "moderate" (κ=0.41-0.60), "substantial" (κ=0.61-0.80), or "almost perfect" (κ=0.81-1.00). The sensitivity and specificity, the positive and negative likelihood ratios, and the posttest probability value for positive and negative results (positive and negative predictive values [PPV and NPV]), together with the corresponding 95% CIs, were evaluated to assess the diagnostic performance of each US parameter in predicting CD.[17,18]

The χ^2 test was used when appropriate. The interobserver agreement for the 6 US parameters was calculated in terms of κ values (κ statistics >0.4).[16]

The diagnostic performance of each US parameter was evaluated in terms of both screening and confirmatory strategies. In the case of signs with a high degree of sensitivity, a negative result excluded the diagnosis (SnNout: negative result, diagnosis out); in the case of signs with a high degree of specificity, a positive result effectively ruled in the diagnosis (SpPin: positive result, diagnosis in).[19]

All patients with CD were given a gluten-free diet, with reevaluation of IgA EMA and US parameters at 1 year.

RESULTS

A final diagnosis of CD was reached in 12 patients (7.4%), 6 men and 6 women aged between 16 and 77 years (mean ± SD, 49±17 years) referred for chronic diarrhea (n=7/105 [6.7%]), iron deficiency anemia (n=4/25 [16%]), or dyspepsia (n=1/32 [3.1%]). All had positive EMA test results and normal total IgA serum levels, and their duodenal lesions were consistent grade III (11 cases) or grade IV (1 case) of the Marsh classification. The results of the duodenal histological evaluation of the 150 patients whose test results for IgA EMA were negative were not consistent with CD. Of the 150 patients without CD, 72 had a functional disorder, 70 had an organic disease (involving the small bowel in 11 cases), and 8 had a non–GI-related disorder (**Table 1**). Regarding US signs, mean±SD values for gallbladder volume, transverse diameter of small bowel loops, bowel wall thickening, and diameter of mesenteric lymph nodes in patients with and without CD were 25±5.3 mL vs 11±4 mL ($P<.001$); 2.8 ± 1.0 cm vs 1.1 ± 0.6 cm ($P<.001$); 3.5 ± 1.1 mm vs 1.6 ± 0.4 mm ($P<.001$), and 4.6 ± 2.9 mm vs 2.3 ± 1.4 mm ($P<.001$), respectively. In patients with CD, even in the case of small bowel wall thickening, the layer stratification was normal and the mesenteric lymph nodes, even if enlarged, maintained both a normal echotexture and a normal echogenic hilum. The main US characteristics observed in patients with CD are exemplified in **Figure 1** for a single case. No differences were observed regarding the US signs between patients with chronic diarrhea (n=7) and those with iron deficiency anemia (n=4) or dyspepsia (n=1).

Table 1. Final Diagnosis of the 150 Patients Without Celiac Disease Referred for Chronic Diarrhea, Iron Deficiency Anemia, or Dyspepsia

Type of Disorder	Patients, No. (%)
Functional	
Non–ulcer-related dyspepsia	15 (10)
Irritable bowel syndrome	57 (38)
Organic	
Helicobacter pylori–related disease	19 (13)
Gastric cancer	3 (2)
Giardiasis and common variable immunodeficiency	1 (0.6)
Primary lymphangiectasia	1 (0.6)
Ileal carcinoid	1 (0.6)
Crohn disease	9* (6)
Ulcerative colitis	9 (6)
Diverticular disease	4 (3)
Colon cancer	7 (5)
Ischemic colitis	2 (1)
Radiation enteritis	2 (1)
Antibiotic-associated diarrhea with or without *Clostridium difficile*	4 (3)
Previous abdominal surgery	2 (1)
Cholelithiasis	6 (4)
Nongastrointestinal disorders	
Endocrinologic diseases	3 (2)
Medication-related disorders	5 (4)

*Six of theses 9 patients had ileal involvement.

The percentage agreement beyond chance between the US signs and duodenal histological findings in patients with CD is shown in **Table 2**. The agreement was "moderate" for increased gallbladder volume, thickened small bowel wall, increased peristalsis, free abdominal fluid, enlarged mesenteric lymph nodes, and the concomitant presence of all 6 US signs (κ=0.62, 0.45, 0.43, 0.43, 0.46, and 0.46, respectively); and "fair" for dilated small bowel loops and increased intraluminal content, and the presence of at least 1 sign (κ=0.31 for both). The positive likelihood ratio values of increased gallbladder volume, free abdominal fluid, and enlarged mesenteric lymph nodes were greater than 10 (17.0, 12.5, and 15.6, respectively), thus allowing a confirmatory strategy. The negative likelihood ratio values of dilated small bowel loops and increased peristalsis were 0.1, thus supporting a screening strategy (Table 2). **Figure 2** shows the relationship between the sensitivity and (1–specificity) of each of the US parameters—for at least 1 of these parameters and for the combination of all 6. The presence of at least 1 parameter was the most sensitive and the presence of all 6 parameters the most specific. Eleven (92%) of the 12 patients with CD and 35 (23%) of the 150 patients without CD had at least 1 positive US sign (χ^2 = 25.52; P = .001); 4 patients with CD (33%) and 1 patient without CD (0.6%) showed the concomitant presence of all 6 (χ^2 = 39.64, P = .001).

The κ values of the interobserver agreement in evaluating the US signs were 0.81, 0.95, 0.82, 0.76, 0.82, and 0.79 for increased galbladder volume, dilated small bowel loops, thickened small bowel wall, increased peristalsis, presence of abdominal free fluid, and enlarged mesenteric lymph nodes, respectively. Overall, US scan of small bowel was accomplished within 30 minutes.

The 12 patients with CD were prescribed a gluten-free diet as their only therapeutic regimen. At 1 year, all had negative test results for EMA and a complete reversal of the US abnormalities was recorded.

COMMENT

The data from this US study indicate that increased gallbladder volume, the presence of free abdominal fluid, and enlarged mesenteric lymph nodes reliably and accurately predict CD, and that the absence of intestinal dilatation and increased peristalsis make it possible to exclude the diagnosis.

Celiac disease is the most common enteropathy in Western countries, with a prevalence between 1 in 200 and 1 in 300.[1-4] The clinical spectrum of the disease varies from overt to asymptomatic forms, and a definite diagnosis is based on serological tests[1-6] and duodenal histological findings.[1] There has been a recent increase in the use of real-time abdominal US as a means of examining inpatients and outpatients with various bowel diseases including Crohn disease, abdominal tuberculosis, and small bowel obstruction.[20-26] Several US parameters have been associated with CD[7-9] but we believe that their accuracy was overestimated because of selection bias.[27] For example, the 94% sensitivity and 88% specificity reported in 1 of these studies[7] were due to the fact that it only included children with overt malabsorption, a population not representative of the disease spectrum, and the recent study by Rettembacher et al[8] included 11 adult patients in whom different signs were considered consistent with CD on the basis of their absence in the control group of healthy subjects.

We prospectively evaluated 6 US parameters previously reported as being associated with CD[7-9] in 162 consecutive patients referred to our tertiary-referral gastrointestinal unit because of chronic diarrhea, iron deficiency anemia, or dyspepsia. On the basis of a previous series in primary care[10] and of our own data about 1875 similar patients previously referred to us (unpublished data); we estimated a pretest probability of CD ranging from 5% to 10%.

Our results indicate that US can reliably predict a diagnosis of CD: the κ value of concordance beyond chance between each US sign and duodenal histology, which is still the gold standard for a CD diagnosis,[1-3] ranged from 0.31 for dilated small bowel loops to 0.62 for enlarged gallbladder volume.

The sensitivity of US findings of dilated small bowel loops (92%) and of increased peristalsis (83%) indicate that CD can be confidently ruled out in their absence (NPV, 99% and 98%, respectively), whereas the specificity of increased gallbladder volume (96%), of the presence of free fluid between loops (96%), and of enlarged mesenteric lymph nodes (97%) support their confirmatory role. Interestingly, no difference was observed regarding the US findings between pauci-asymptomatic celiac patients (ie, those with iron deficiency, anemia, or dyspepsia) and those with chronic diarrhea.

Eight (73%) of 11 patients with CD had a gallbladder volume greater than 20 mL (the 12th patient had un-

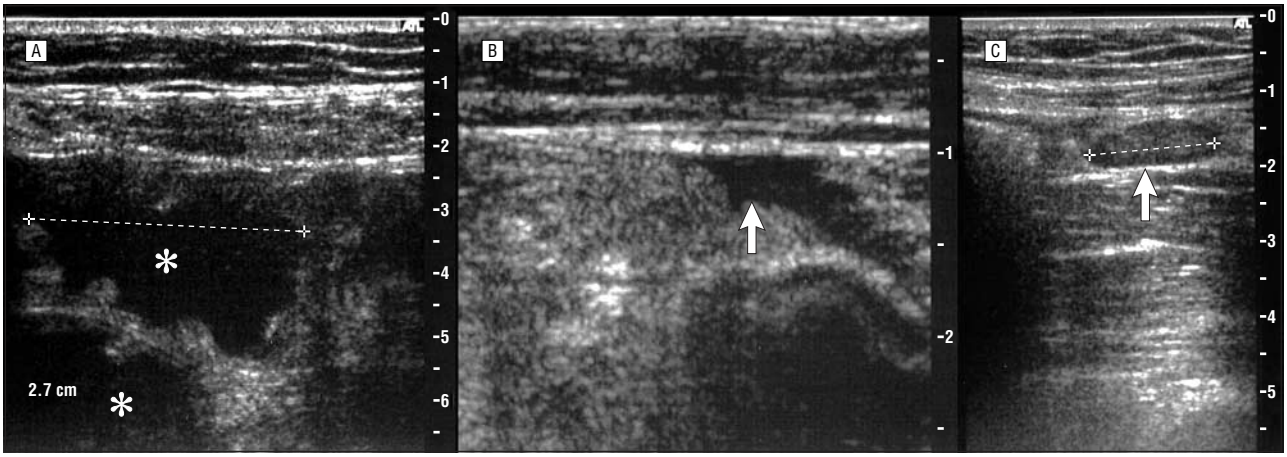

Figure 1. Ultrasound pictures obtained from a patient with celiac disease showing (asterisks and arrows) dilated small bowel loops with increased fluid content (A), free abdominal fluid (B), and enlarged mesenteric lymph node (C).

Table 2. Diagnostic Performances of 6 Ultrasonographic Parameters in Predicting Celiac Disease*

US Parameters (Normal Value)	Celiac Disease, No.		κ Value	Sensitivity, %	Specificity, %	LR+	LR–	PPV, %	NPV, %
	Yes (n = 12)	No (n = 150)							
Increased gallbladder volume† (≤2.5 mL)	8	6	0.62 (0.50-0.69)	73 (46-99)	96 (92-99)	17.0 (7.3-41.0)	0.28 (0.1-0.7)	57 (31-83)	98 (95-100)
Dilated small bowel loops + increased fluid content (≤2.5 cm)	11	35	0.31 (0.19-0.41)	92 (76-100)	77 (70-84)	4.0 (2.8-5.5)	0.10 (0.1-0.7)	24 (11-36)	99 (97-100)
Thickened small bowel wall (≤3 mm)	9	14	0.45 (0.34-0.55)	75 (50-99)	91 (86-95)	8.0 (4.4-14.5)	0.27 (0.1-0.7)	39 (19-59)	98 (95-100)
Increased peristalsis	10	19	0.43 (0.31-0.52)	83 (62-100)	87 (82-92)	6.6 (4.0-10.7)	0.10 (0.05-0.7)	34 (17-51)	98 (96-100)
Free abdominal fluid	6	6	0.43 (0.31-0.52)	50 (22-78)	96 (93-99)	12.5 (4.7-33)	0.52 (0.3-0.9)	50 (22-78)	96 (92-99)
Enlarged mesenteric lymph nodes (≤5 mm)	5	4	0.46 (0.35-0.56)	42 (14-69)	97 (95-99)	15.6 (6.8-50.6)	0.59 (0.4-0.9)	55 (23-88)	95 (92-99)
At least 1 parameter	11	35	0.31 (0.20-0.42)	92 (76-100)	77 (70-83)	4.0 (2.8-5.5)	0.10 (0.01-0.7)	24 (11-36)	99 (97-100)
All 6 parameters	4	1	0.46 (0.34-0.55)	33 (7-60)	99 (98-100)	50 (6-412)	0.67 (0.4-1.0)	80 (44-100)	95 (91-98)

Abbreviations: LR+, positive likelihood ratio; LR–, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.
*Values in parentheses are 95% confidence intervals.
†One patient with celiac disease and 7 patients without celiac disease had previously undergone cholecystectomy.

dergone cholecystectomy) vs 6 (4%) of 143 of the patients without CD who had their gallbladder intact. The 96% specificity of this sign, together with its highest positive likelihood ratio (17), increased the pretest probability of CD from 8% to 57%, whereas its absence decreased its probability to only 2%. In relation to the possible underlying pathogenic mechanism, we have previously reported that gallbladder enlargement parallels the increase in somatostatin levels in untreated CD patients.[9]

Unlike Rettembacher et al,[8] we considered dilated small bowel loops and increased fluid content together because an increase in the latter significantly improves the visualization of the former. This finding, which was observed in 11 of the patients with CD, was the most sensitive (92%).

The small bowel wall thickening and hyperperistalsis in patients with CD described by Rettembacher et al[8] confirmed previous radiological data obtained by means of a small bowel enema.[28] Finally, despite being poorly sensitive, the presence of free fluid between the small bowel loops and enlarged mesenteric lymph nodes showed a high specificity (>95%), making these signs relevant for ruling in CD diagnosis.

The concomitance of all of the considered US signs maximized the specificity of the procedure to 99%, at the expense of sensitivity (33%); nevertheless, the positive likelihood ratio value of 50 allowed a confirmatory strategy with a PPV of 80%. On the contrary, in the presence of at least 1 US sign, the sensitivity was 92% with a negative likelihood ratio value of 0.10 and a NPV of 99%—a diagnostic performance that was similar to that of dilated small bowel loops.

The reliability of our results is further supported by the strength of the intraobserver and interobserver agreement, although specific training was necessary.

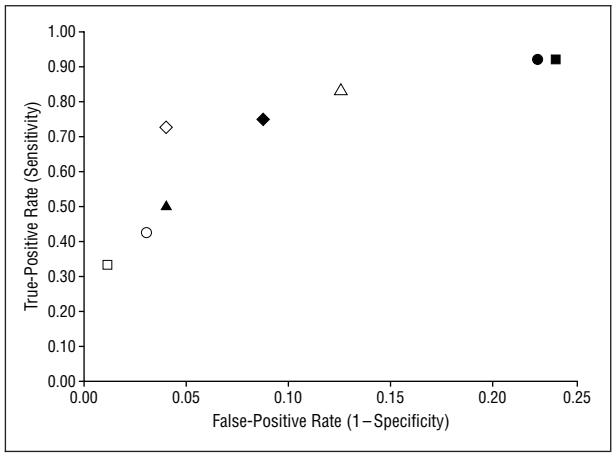

Figure 2. Relationship between sensitivity and (1–specificity) for 6 ultrasound parameters used to predict celiac disease (CD): enlarged mesenteric lymph nodes (open circle), free abdominal fluid (black triangle), increased gallbladder volume (open diamond), thickened small bowel wall (black diamond), increased peristalsis (open triangle), and dilated small bowel loops (black circle). The same relationship is also given for the combination of all 6 parameters (open square) and the presence of at least 1 parameter (black square).

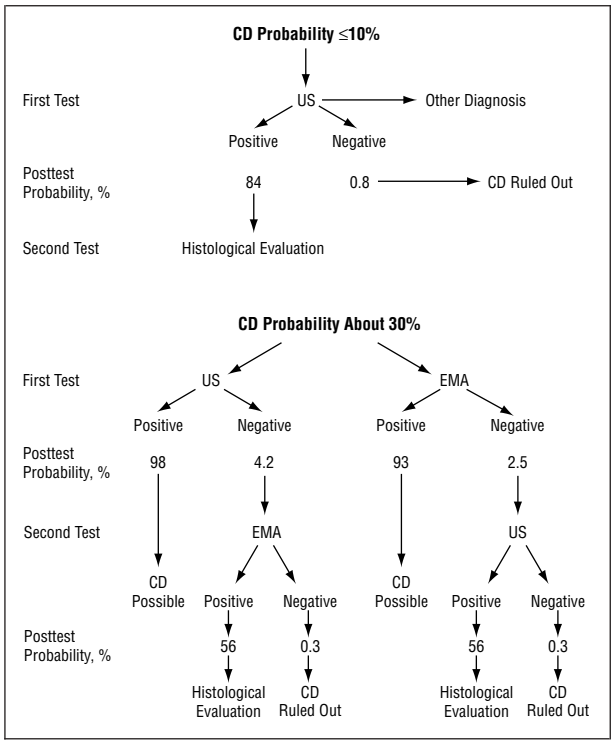

Figure 3. Diagnostic algorithm for celiac disease (CD) according to pretest probability of the disease. In the posttest calculation of probability using ultrasound (US) examination, the absence of dilated small bowel loops with increased fluid content was considered a negative finding because it had the highest sensitivity (92%) and the lowest negative likelihood ratio (LR–) (0.10). A positive finding was the presence of all 6 US signs because it had the highest specificity (99%) and the highest positive likelihood ratio (LR+) (50). The posttest probability for anti-endomysial IgA (EMA) was calculated considering an LR+ of 31 and an LR– of 0.06.[6]

Our study population may not be representative of the general population because it was restricted to patients attending a tertiary referral gastrointestinal unit. However, we believe that selection bias was reduced because we examined consecutive patients with nonspecific symptoms and, therefore, a relatively low prevalence of CD (<10%), and that evaluation biases were avoided because both the positive and negative US findings were compared with the same gold standard of duodenal histological results. Finally, the use of Bayesian inference makes it possible to transfer our results to a population with a different prevalence of CD because the estimated positive and negative likelihood ratios are, at least in theory, independent of the pretest probability of the disease. However, further studies are necessary to confirm the operative characteristics of US findings in other setting, particularly to assess their reproducibility and transferability.

In our opinion, the choice of the initial test should depend on the estimated level of suspicion, as shown in **Figure 3**. When, as in our series, the CD probability is low (eg, ≤10%), negative US findings, mainly the lack of dilated small bowel loops with increased fluid content, can more effectively rule out the diagnosis; negative findings can also be very useful in discriminating between functional and organic disease. Interestingly, in our own 6 cases with ileal Crohn disease and 2 cases with radiation enteritis, the US findings differed completely from those found in patients with CD and were determinant for the final diagnosis. On the other hand, the presence of all 6 US signs increases CD probability from 10% to 84%, thus making confirmation by intestinal biopsy necessary. When we are facing a moderate probability of CD (eg, of about 30%), both IgA EMA and US testing can confirm the diagnosis, based on a PPV greater than 90%, a level at which the diagnostic role of histology could be challenged. Finally, independent of the test sequence, when both US and EMA results are negative, CD diagnosis can be confidently excluded as the posttest probability drops to less than 1% (NPV = 99%), whereas, in case of discordance, duodenal histological evaluation becomes mandatory.

Overall, US can accurately predict CD but its place in the diagnostic algorithm depends upon the probability of the disease in the considered population.

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