Serology and endoscopy in coeliac disease: applications and limitations
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Correlation of endoscopic markers of villous atrophy with histology

PREVALENCE OF COELIAC DISEASE AND ITS ENDOSCOPIC MARKERS AMONG PATIENTS HAVING ROUTINE UPPER GASTROINTESTINAL ENDOSCOPY

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Abstract

Objective: To determine the prevalence of duodenal villous atrophy among patients undergoing routine upper gastrointestinal endoscopy and the value of endoscopic markers for VA in selecting patients for duodenal biopsy.

Methods: One hundred and fifty adult patients with upper gastrointestinal symptoms or iron deficiency anaemia had inspection and biopsy of the distal duodenum during endoscopy. Endoscopic markers for villous atrophy sought were mosaic or nodular mucosa, scalloping of duodenal folds, and reduction in number or absence of duodenal folds.

Results: Endoscopic markers were seen in 7 patients (5%): scalloped folds with mosaic pattern mucosa in (3 patients), scalloped folds, reduced in number with mosaic pattern mucosa (3 patients), and nodular mucosa with reduction in fold numbers in one patient. All seven had partial, subtotal or total villous atrophy. One of 143 patients with no endoscopic abnormality had patchy villous atrophy. The prevalence of villous atrophy was thus 1:19 (8 of 150). Endoscopic markers had a sensitivity of 87.5% (7/8), specificity of 100% (142/142), positive predictive value of 100% (7/7) and negative predictive value of 99% (142/143). Of the 8 patients with villous atrophy, the indications for endoscopy were upper gastrointestinal symptoms in 7 patients (two with anaemia) and anaemia without gastrointestinal symptoms in one. After six months of dietary gluten exclusion, improvement by at least one criterion was documented in all 8 patients.

Conclusions: Coeliac disease should be considered as a cause of dyspeptic and reflux symptoms, as well as of iron deficiency anaemia. Careful inspection of the duodenum during routine upper gastrointestinal endoscopy allows accurate selection of patients for biopsy but may not detect patchy villous atrophy or milder enteropathy.
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Introduction

Coeliac disease may present with non-specific upper gastrointestinal (GI) symptoms of dyspepsia, abdominal pain and nausea [1], and also with iron deficiency anaemia in the absence of GI symptoms [2]. Many patients will therefore have upper GI endoscopy as an initial investigation, which provides an opportunity to biopsy the distal duodenum. While routine biopsies in all patients undergoing endoscopy would have significant resource implications, endoscopic abnormalities of the distal duodenum associated with villous atrophy (VA) have been described [3] and these may be used to select patients for biopsy. We prospectively sought these markers and obtained duodenal biopsies in a series of patients undergoing routine endoscopy for upper GI symptoms and for anaemia. We wished to determine firstly how common VA was in this group of patients, and secondly whether endoscopic markers could be used reliably to select patients for duodenal biopsy.

Methods

We studied consecutive patients undergoing first-time endoscopy for upper GI symptoms or for iron deficiency anaemia by one gastroenterologist in a district general hospital in Northern Ireland. Patients undergoing endoscopy specifically for duodenal biopsy, i.e. with diarrhea, macrocytic anaemia, positive family history of coeliac disease, or known positive coeliac serology (antigliadin or endomysial antibody), were excluded. All examinations were performed with Olympus GIF-XQ230 or XQ200 videoscopes. The distal duodenum was examined after maximum insufflation for mosaic pattern or nodularity of the mucosa, reduction in number of duodenal folds, and scalloping of duodenal folds. Three biopsies were taken from the distal duodenum with standard forceps. They were orientated and mounted on filter paper before submission in formalin for examination by a consultant histopathologist who was unaware of clinical details or endoscopic findings. Histologic abnormalities sought included partial, subtotal and total villous atrophy (PVA, STVA, TVA), crypt hyperplasia, and increased intraepithelial lymphocytes (IELs). We reviewed patients with any of these to enquire about symptoms associated with coeliac disease, associated conditions, and whether there was a family history. Patient height (meters) and weight (kilograms) were measured for calculation of body mass index (weight/height$^2$) with ranges
for underweight, normal and overweight as defined by Garrow [4] applied. If not already done, blood was taken for hemoglobin concentration and serum ferritin, as well as for IgA class endomysial antibody (EmA) testing by indirect immunofluorescence. An explanation of the coeliac condition was given and referral made to hospital dietitians for advice regarding dietary gluten exclusion. The response to gluten-free diet was assessed at outpatient follow-up after 6 months.

Results

Patients
One hundred and fifty patients were studied over 16 weeks. Their mean age was 57 years (standard deviation 15, range 12-90). Eighty-nine (59%) were women. One hundred and twenty-six patients had outpatient endoscopy; these were referred by primary care practitioners for open access endoscopy (OAE) (64 patients), from gastroenterology clinics (51) or from other hospital physicians (11). Twenty-four patients had inpatient endoscopy. Indications were one or more of reflux symptoms (62 patients), ulcer-type symptoms—epigastric pain, dyspepsia (48), iron deficiency anaemia (43), dysphagia (19), nausea and/or vomiting (17), weight loss (8), and hematemesis and/or melena (3). Thirty-one patients had iron deficiency anaemia with no GI symptoms.

Endoscopic findings
Apart from gastritis and hiatus hernia, endoscopic abnormalities proximal to the distal duodenum were present in 46 patients (31%) and included esophagitis (17, 11%), peptic esophageal stricture (8, 5%), Barrett’s esophagus (3, 2%), esophageal candida (2, 1%), gastric erosions or benign ulcer (4, 3%), gastric cancer (2, 1%), congestive gastropathy (1, 1%) and duodenal erosions or ulcer (9, 6%). Seven patients (5%) had suspicious mucosal abnormalities in the distal duodenum. Six had mosaic pattern mucosa and scalloping of duodenal folds, of whom three also had reduction in fold numbers (Chapter 10). The seventh had loss of folds and nodular mucosa.

Histology
The seven patients with endoscopic markers had PVA (one patient), STVA (3), or TVA (3),
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with crypt hyperplasia and increased IELs. Of the 143 patients without endoscopic distal duodenal abnormality, one had patchy VA, with villous pattern ranging from normal to STVA though all three biopsy samples had increased IELs. None of the remaining 142 patients without endoscopic markers had VA, crypt hyperplasia or increased IELs. Thus the prevalence of enteropathy was 1:19 (8 of 150), manifest as VA. Endoscopic markers had sensitivity for VA of 87.5% (7 of 8), positive predictive value of 100% (7 of 7), specificity of 100% (142 of 142) and negative predictive value of 99% (142 of 143).

Clinical details
Features of presentation in the 8 patients with VA are listed in the Table. No patient reported diarrhea or a family history of coeliac disease. Two had had osteoporosis confirmed by bone densitometry. BMI was in the underweight range (<20) for one patient, normal (20-24.9) for three, and in the overweight range (≥25) for four patients. Hemoglobin concentration was <12 g/dl in five patients, though had been identified as low before endoscopy in only three. Three patients, with TVA or STVA, were EmA negative.

During the study period we confirmed VA in a further 7 patients, who underwent duodenal biopsy because of positive EmA, a history of diarrhea, or a family history of coeliac disease: thus 47% (7 of 15) of patients were diagnosed coeliac because of duodenal abnormalities seen during endoscopy.
<table>
<thead>
<tr>
<th>Age/sex Source</th>
<th>Reason for endoscopy</th>
<th>Endoscopic abnormality</th>
<th>Histology EmA status</th>
<th>Hb status, BMI</th>
<th>Response to diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>55/F OAE</td>
<td>Reflux Abdominal pain</td>
<td>None seen</td>
<td>Patchy VA EmA +ve</td>
<td>Hb 14.3, Ferritin 10.1 BMI 25</td>
<td>Symptoms improved EmA +ve</td>
</tr>
<tr>
<td>60/F OAE</td>
<td>Reflux</td>
<td>Mosaic; Reduced fold nos. Scalloped folds</td>
<td>TVA EmA +ve</td>
<td>Hb 10.8, Ferritin 10.2 BMI 23</td>
<td>Symptoms improved Weight gain 6kg EmA -ve</td>
</tr>
<tr>
<td>57/F OAE</td>
<td>Reflux</td>
<td>Mosaic Scalloped folds</td>
<td>TVA EmA +ve</td>
<td>Hb 11.3 Ferritin 14.3 BMI 21</td>
<td>Symptoms improved EmA -ve</td>
</tr>
<tr>
<td>60/M OAE</td>
<td>Abdominal pain</td>
<td>Mosaic Scalloped folds</td>
<td>STVA EmA +ve</td>
<td>Hb 15.3, Ferritin 20.6 BMI 30</td>
<td>Symptoms improved EmA -ve</td>
</tr>
<tr>
<td>63/M OAE</td>
<td>Nausea, vomiting</td>
<td>Reduced fold nos. Nodular</td>
<td>PVA EmA +ve</td>
<td>Hb 14.8, Ferritin 65 BMI 26</td>
<td>Symptoms improved Weight gain 3kg EmA -ve</td>
</tr>
<tr>
<td>58/F GE</td>
<td>Anaemia</td>
<td>Mosaic Reduced fold nos Scalloped folds</td>
<td>TVA EmA -ve</td>
<td>Hb 9.1, Ferritin 6.2 BMI 24</td>
<td>Weight gain 2kg</td>
</tr>
<tr>
<td>34/M GE</td>
<td>Reflux Anaemia</td>
<td>Mosaic Scalloped folds</td>
<td>STVA EmA -ve</td>
<td>Hb 11.9, Ferritin 4.7 BMI 26</td>
<td>Symptoms improved Weight gain 4kg</td>
</tr>
<tr>
<td>52/F OAE</td>
<td>Abdominal pain Anaemia</td>
<td>Mosaic Reduced fold nos. Scalloped folds</td>
<td>STVA EmA -ve</td>
<td>Hb 10.3 Ferritin 7.9 BMI 19</td>
<td>Symptoms improved Weight gain 5kg</td>
</tr>
</tbody>
</table>

M, male; F, female; GE, gastroenterology clinic; OAE, open access endoscopy; BMI, body mass index; STVA, subtotal villous atrophy; PVA, partial villous atrophy; EmA, endomysial antibody; Hb, hemoglobin concentration (g/dl); ferritin normal range 10-130 ng/ml (females), 27-399 ng/ml (males).
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Response to treatment
All symptomatic patients reported improvement at six month review. Weight gain was recorded in five patients (range 2-6kg) and EmA had disappeared in four of the five initially EmA positive patients.

Discussion
Presentation of coeliac disease (i.e. VA due to gluten sensitivity) with mild or non-specific symptoms is well recognised. None of seven patients identified from Swedish blood donor screening had symptoms apart from slight bloating [5]. Fewer than half of new patients in our own clinical practice report diarrhea [6,7], and upper GI symptoms are common. A minority of patients is underweight, and many, particularly men, are overweight [8]. Over 20% of men and 40% of women had dyspepsia in one series [1]. Of 36 adult patients surveyed by Usai et al [9], 76% reported abdominal pain, 50% dysphagia, 50% nausea, 30% vomiting, and 14% noncardiac chest pain. While some of these symptoms are common in the general population, there is objective evidence of gut dysmotility in coeliac disease. Duodenal and jejunal manometry showed an increased frequency of migrating motor complexes in adult patients compared with controls, while abnormal discrete clustered contractions, giant jejunal contractions, and bursts of nonpropagated contractions were common [10]. Esophageal manometry in 18 adult patients showed motor abnormalities, including nutcracker esophagus, repetitive contractions and a hypotonic lower esophageal sphincter, in two-thirds [9]. Iovino et al [11] reported esophageal symptoms in 45% of 22 adult patients, which after dietary gluten exclusion fell to 9% with a significant rise in lower esophageal sphincter pressures. Endoscopic forceps biopsy of the distal duodenum has largely replaced x-ray guided capsule biopsy and allows demonstration of endoscopic abnormalities associated with VA. Brocchi et al [12] looked for fold loss (reduction in number or absent folds) in 65 patients undergoing endoscopy specifically for duodenal biopsy. Although their analysis categorised PVA (in most cases due to treated coeliac disease) along with normal duodenal histology, fold loss was in fact present in 88% of STVA and 54% of PVA cases, with 97% of 35 patients with normal histology having no fold loss. McIntyre et al [13] studied 75 patients suspected of having coeliac disease and found fold loss to have a sensitivity of 73%, specificity of 97% and positive predictive value of 85% for TVA which was present in 15 patients.

Maurino et al [3] studied 100 patients undergoing duodenal biopsy and found that of 36
with STVA or TVA, 27 had loss of folds, 12 scalloped folds, 14 mosaic pattern and 5 visible underlying blood vessels: the presence of any marker had a sensitivity of 94%, specificity of 92%, positive predictive value of 87% and negative predictive value of 97%. No patient in the study had PVA.

However, these figures are based on patient groups with a high prevalence of VA, where the predictive value of any screening test is likely to be high and may not be applicable to less selected populations. Assessment of endoscopic markers in unselected dyspeptic populations is required. Brocchi et al [12] found four patients with fold loss among 873 undergoing upper GI endoscopy who had STVA, giving a prevalence of 1:218. Of 146 patients undergoing endoscopy for dyspepsia [3] only one had a marker (mosaic mucosa) which was falsely positive. We obtained biopsies if markers were present among 500 OAE patients and found a prevalence of marker positive VA of 1:63 [14]. These studies did not obtain biopsies from patients without markers, so may have underestimated the true prevalence of VA. To our knowledge, the present study is the first to assess the performance of endoscopic markers by obtaining biopsies from all patients having routine endoscopy. The prevalence of VA with endoscopic abnormality (7 of 150, 1:21) was much higher that in our earlier OAE study. This may reflect a higher proportion of patients with anaemia, though most patients with VA had normal hemoglobin concentrations or had not had hemoglobin concentration checked before endoscopy. It is also possible that the endoscopist’s ability to identify endoscopic markers has improved.

While earlier studies focussed on endoscopic markers as predictors of STVA or TVA, two of our patients had PVA. We routinely treat such patients as coeliac as they have other histologic indicators of gluten-sensitive enteropathy, most notably IELs as described by Marsh [15], and respond symptomatically to dietary gluten exclusion. Both patients also had EmA. Three of the five patients with TVA or STVA were EmA negative and would have been unlikely to have been diagnosed without endoscopic detection. While the markers had satisfactory sensitivity and specificity for PVA as well as STVA, they are unlikely to be of value for milder degrees of enteropathy (IELs without villous abnormality: Marsh type 1) and were not seen in one patient where the villous abnormality was patchy.

Our study was performed in a population where coeliac disease is very common, with a prevalence of 1:150 on population screening [16], so the prevalence of 1:19 among our patients may not be reproducible elsewhere. However, the prevalence of coeliac disease in
Northern Ireland estimated by screening is less than twice that of other western European countries (1:300 Italian schoolchildren [17]; 1:250 Swedish blood donors [5]), and a recent study of serum EmA in 2000 American blood donors suggests that the true prevalence of coeliac disease in the United States is also of the order of 1:250 [18]. It is therefore likely that a significant number of patients elsewhere undergoing endoscopy for dyspeptic symptoms, as well as for anaemia, will have coeliac disease which is responsible for their symptoms. Endoscopic markers appear to perform sufficiently well in this situation to be able to select patients for duodenal biopsy, although they will not identify patients with non-VA enteropathy and may miss VA if it is patchy.
References
