Serology and endoscopy in coeliac disease: applications and limitations
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Endoscopic recognition of coeliac disease during open access endoscopy

DIAGNOSIS OF COELIAC DISEASE AT OPEN ACCESS ENDOSCOPY

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Abstract

**Background:** Coeliac disease may present with dyspepsia or reflux. There are characteristic duodenal appearances associated with villous atrophy (mosaic pattern mucosa and loss, reduction in number or scalloping of duodenal folds) which may prompt small bowel biopsy during routine upper gastrointestinal endoscopy. These appearances were sought in patients referred by their general practitioners for open access endoscopy (OAE), to determine the prevalence and significance of coeliac disease as a cause of symptoms.

**Methods:** Five hundred consecutive patients undergoing OAE by one consultant gastroenterologist were studied. Forceps biopsies from the distal duodenum were taken if appearances were suggestive. If villous atrophy was confirmed, the response of symptoms to dietary gluten exclusion was assessed.

**Results:** Ten patients had suspicious endoscopic appearances of whom 8 had villous atrophy, giving a prevalence of coeliac disease of 1.6% (1:63). All 8 had mosaic pattern mucosa with three also having reduction of duodenal folds, and four having scalloped folds. All had serum endomysial antibodies (EmA). Apart from diarrhoea, described by one patient, there were no symptoms of “typical” coeliac disease at diagnosis: three patients were overweight. After dietary gluten exclusion, all reported symptomatic improvement with disappearance of EmA in 5 patients to date.

**Conclusions:** There is a high prevalence of coeliac disease among patients undergoing OAE, which is relevant to their clinical symptoms and which can be identified by careful endoscopic inspection of the duodenum.
Introduction

Coeliac disease can present with non-specific upper gastrointestinal symptoms of dyspepsia, abdominal pain and nausea [1]. Some coeliac patients may, after attending their general practitioners, have open access endoscopy (OAE) as their initial investigation. As screening studies have shown that the prevalence of coeliac disease in the normal western European population is at least 1:300 [2-4], a significant number of patients undergoing OAE may have this diagnosis. There are characteristic appearances associated with villous atrophy which may be visible endoscopically [5], and these were prospectively sought in patients undergoing OAE.

Methods

An OAE service for general practitioners began at Altnagelvin Hospital in January 1996. Referral guidelines over the study period were similar to protocols devised elsewhere in the United Kingdom. We advised referral, irrespective of the nature of the symptoms, if patients were aged 45 or over. Patients under 45 were referred (1) if they had sinister features (anaemia, vomiting, weight loss); (2) if they had recurrence of symptoms after a trial of empirical antiulcer therapy and had positive Helicobacter pylori serology; or (3) if their symptoms were refractory to empirical therapy even if they had negative H pylori serology. General practitioners were advised to refer patients with anaemia (without gastrointestinal symptoms) or with dysphagia to the outpatient gastroenterology clinic rather than for OAE. Five hundred consecutive patients undergoing OAE by a consultant gastroenterologist, using Olympus GIF-XQ230 and XQ200 videoscopes, had examination of the duodenum for mosaic pattern mucosa, reduction in number of duodenal folds, and scalloping of duodenal folds (Chapter 10). If any of these were present, biopsies were taken from the distal duodenum using standard forceps and submitted in formalin after orientation for histological examination. Blood was sent at the same attendance for serum IgA class endomysial antibody (EmA) testing by indirect immunofluorescence with a titre of 1:5 or greater taken as positive. Patients with histologically confirmed villous atrophy were reviewed so that a full current and past history could be taken. Enquiry was made not only about "classical" coeliac symptoms but also about conditions known to be associated with coeliac disease (including thyroid disease.
and obstetric problems [6,7] and whether there was a family history. An explanation of the condition given before referral for dietetic advice. Height (m) and weight (kg) were measured for calculation of body mass index (BMI; weight/height²). Further tests at review comprised full blood count and serum ferritin, B12, folic acid, calcium and albumin. The response of patients to gluten exclusion was assessed by history and repeat EmA at outpatient follow-up.

Results

Five hundred patients were studied over a 14 month period: 260 (52%) were female, and mean age was 50 years (range 14-89, SD 15.2); 178 (36%) were under the age of 45. Indications for OAE were one or more of ulcer type symptoms (dyspepsia, epigastric pain) in 316 patients (63%), reflux symptoms in 256 (51%), nausea and/or vomiting in 139 (28%) and weight loss in 37 (7%). The duodenum could not be entered because of antral gastric cancer in three patients and gastric volvulus in one. Apart from gastritis, which was present in 273 patients (55%), endoscopic abnormalities included one or more of hiatus hernia (178 patients, 36%), endoscopically visible oesophagitis (58, 12%), gastric erosions or benign ulcer (28, 6%), gastric cancer (4, 1%), and duodenal erosions or ulcer (74, 15%). A total of ten patients had suspicious mucosal abnormalities in the duodenum, of whom eight (1.6% of 500, or 1:63) had histological confirmation of villous atrophy. These eight patients (all female) had mosaic pattern mucosa, with scalloped folds in four and reduction in number of folds in three: all had EmA compared with neither who had suspicious endoscopic appearances but normal histology. Prevalences of coeliac disease in subgroups were 3% in females (8 of 260), 0% in males (none of 240), 1% in patients under 45 years (2 of 178), 2% in patients aged ≥45 years (6 of 322), 1% in patients with ulcer type symptoms (3 of 316), 2% with reflux symptoms (4 of 256), 3% with nausea and/or vomiting (4 of 139) and 8% with weight loss (3 of 37). Endoscopic abnormalities included mosaic mucosa in all patients; three in addition had scalloping of duodenal folds and two loss of folds (Chapter 10). Clinical details are listed in the Table.
Table. Clinical characteristics of patients diagnosed coeliac at OAE.

<table>
<thead>
<tr>
<th>Patient; age</th>
<th>Symptoms, duration</th>
<th>BMI</th>
<th>Abnormal blood tests</th>
<th>Past history</th>
</tr>
</thead>
<tbody>
<tr>
<td>1; 55</td>
<td>Nausea, weight loss 6 m</td>
<td>21.3</td>
<td></td>
<td>Infertility</td>
</tr>
<tr>
<td>2; 37</td>
<td>Reflux 6 m</td>
<td>22.7</td>
<td>RDW 16.4; ferritin 5.4</td>
<td>Anaemia</td>
</tr>
<tr>
<td>3; 53</td>
<td>Reflux &gt;20 y</td>
<td>28.8</td>
<td></td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>4; 76</td>
<td>Vomiting, weight loss 4 m</td>
<td>21.3</td>
<td></td>
<td>Anaemia</td>
</tr>
<tr>
<td>5; 61</td>
<td>Reflux, nausea 15 y</td>
<td>22.7</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>6; 55</td>
<td>Reflux, abdominal pain 4 y</td>
<td>32.7</td>
<td>None</td>
<td>Anaemia</td>
</tr>
<tr>
<td>7; 18</td>
<td>Nausea, abdominal pain 12 m</td>
<td>26.0</td>
<td>None</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>8; 57</td>
<td>Weight loss, abdominal pain 3 m</td>
<td>19.4</td>
<td>Ferritin 9.3</td>
<td>Anaemia</td>
</tr>
</tbody>
</table>

BMI: body mass index; m: months; y: years; RDW: red cell distribution width (normal range 9-15.5); serum ferritin normal range 10-130 ng/ml
Only one patient (1) had diarrhoea at diagnosis which was long-standing and had not prompted referral: it had previously been attributed to irritable bowel syndrome. Although half gave a past history of anaemia, all eight had satisfactory haemoglobin concentrations (>11 g/dl) and mean cell volumes at diagnosis, the only indicators of deficiency being an elevated red cell distribution width (1 patient) and low serum ferritin (2 patients). No other biochemical abnormalities were noted. Two patients had hypothyroidism and two had had obstetric problems. No patient had a family history of coeliac disease. BMI was in the underweight (<20) range for only one patient; three were overweight (≥25). Three patients (patients 3, 5 and 6 in the Table) had previously undergone (reported normal) upper GI endoscopy for the symptoms prompting OAE.

Patients have now been followed up for a minimum of three months after starting dietary gluten exclusion. All have reported resolution of symptoms with disappearance of serum EmA in five.

Over the study period the author confirmed coeliac disease in a further 33 patients, seen as inpatients, outpatients or undergoing endoscopy following referral from hospital consultants: thus a fifth of newly diagnosed patients (8 of 41) were identified at OAE.

Discussion

Endoscopy and forceps biopsy of the distal duodenum have replaced x-ray guided suction capsule biopsy in the diagnosis of coeliac disease in most centres and allow careful inspection of the duodenal mucosa. Stevens and McCarthy [8] first described a flat mosaic appearance in untreated coeliac patients, which could be accentuated by indigocarmine dye spray. With later higher resolution endoscopes dye spray is no longer necessary and other abnormalities have been noted. Brocchi et al [9] looked for reduction or loss of duodenal folds in 65 patients referred for biopsy and found this sign to have 88% sensitivity and 83% specificity for subtotal villous atrophy; similarly McIntyre et al [10] reported 73% sensitivity, 97% specificity and 85% positive predictive value for this finding. Magazzu et al [11] sought both mosaic pattern and loss of duodenal folds in 14 patients suspected coeliac and 146 having endoscopy for peptic disease and found the presence of either abnormality to have a sensitivity of 100%, specificity of 99% and positive predictive value of 91% for coeliac disease. Scalloping of the folds appears to be a manifestation of mosaic pattern mucosa on
close inspection of the fold edge and was present in 16 of 19 newly diagnosed coeliacs [12].

Looking for all described endoscopic markers, Maurino et al [5] studied 100 consecutive patients undergoing duodenal biopsy and found that of 36 with villous atrophy, 27 had loss of folds, 12 scalloped folds, 14 mosaic pattern and 5 visible underlying blood vessels: overall, the presence of any of these markers had a sensitivity of 94%, specificity of 92% and positive predictive value of 84%.

Presentation of coeliac disease with mild or atypical symptoms is now well recognised, with less than half of patients having diarrhoea in two recent series from Northern Ireland [13,14], and non-specific upper gastrointestinal symptoms are common. Over 20% of male patients and 40% of female patients complained of dyspepsia in one series [1], while of 36 adult coeliacs in a questionnaire study [15] 50% reported dysphagia, 30% vomiting, and 14% noncardiac chest pain. These symptoms are probably due to gut dysmotility. Duodenal and jejunal manometry showed abnormal discrete clustered contractions, giant jejunal contractions, and bursts of nonpropagated contractions in 89% of adult coeliac patients [16]. Oesophageal manometry in 18 adult coeliac patients showed motor abnormalities, including nutcracker oesophagus, repetitive contractions and a hypotonic lower oesophageal sphincter in 67% [15]; the yield of pH monitoring for pathological reflux was low.

Most studies of endoscopic markers for coeliac disease have involved patients suspected of having coeliac disease; few have assessed their value in an unselected dyspeptic population or in the setting of OAE. Brocchi et al [9] found four patients among 873 undergoing upper gastrointestinal endoscopy who had loss of folds and villous atrophy, giving a prevalence of 1:218. Of the 146 patients undergoing endoscopy for suspected peptic disease studied by Magazzu [11] only one had an endoscopic marker (mosaic mucosa) but did not prove to have villous atrophy.

Coeliac disease is common in western Europe, affecting 1:300 Italian schoolchildren [2], 1:250 Swedish blood donors [3] and 1:150 of a general population in Northern Ireland [4]. Based on the last figure, there should be approximately 10,000 coeliacs in Northern Ireland’s population of 1.6 million, yet there were only 909 members of the Coeliac Society with Northern Ireland addresses in December 1996 (Coeliac Society, personal communication). Although lack of clinician awareness of the clinical presentations of coeliac disease accounts for some of this shortfall [13], many patients have no, trivial or non-specific symptoms. None of seven coeliacs identified from Swedish blood donor screening had symptoms apart
from slight bloating [3]. It is unlikely that the five patients here without weight loss would have had the diagnosis made had they not undergone OAE, unless symptoms had changed or deteriorated, particularly as there was no evidence of malabsorption on blood tests or BMI and none had a family history which might have prompted serological testing or biopsy. Nevertheless the diagnosis appears to have been worthwhile in view of the clinical improvement on gluten-free diet and the possibility that future complications will be prevented. The design of this study did not allow assessment of sensitivity of the endoscopic markers in the setting of this non-selected population and it is possible that the prevalence of coeliac disease was even higher; a study including either duodenal biopsy irrespective of endoscopic appearance or EmA testing of all patients having OAE would be needed to explore this further. A policy of routine duodenal biopsy, irrespective of endoscopic appearances, would have significant workload and financial implications for histopathology services. Furthermore, our OAE protocol was designed to optimise diagnosis of peptic and malignant conditions. The population studied is therefore unrepresentative not only of the general population but also of patients with reflux or dyspepsia. Many young patients, particularly if H pylori negative or with symptoms controlled on empirical medication, will not be referred for OAE, and the question of whether these should have routine EmA testing begs further research.

In conclusion, OAE represents a further opportunity to improve diagnosis rates for coeliac disease, which may present with non-specific symptoms of dyspepsia.
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References


