

RAPID COMMUNICATION

Prevalence of celiac disease in adult patients with refractory functional dyspepsia: Value of routine duodenal biopsy

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tients and suggests the routine use of duodenal biopsy in this type of patient undergoing EGD.

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Abstract

AIM: To investigate the prevalence of celiac disease (CD) in adult patients referred to an open access gastroenterology clinic in the south of Italy and submitted to esophago-gastro-duodenoscopy (EGD) for evaluation of refractory functional dyspepsia.

METHODS: Seven hundred and twenty six consecutive dyspeptic patients (282 male, 444 female; mean age 39.6 years, range 18-75 years) with unexplained prolonged dyspepsia were prospectively enrolled. Duodenal biopsies were taken and processed by standard staining. Histological evaluation was carried out according to the Marsh-Oberhuber criteria.

RESULTS: The endoscopic findings were: normal in 61.2%, peptic lesions in 20.5%, malignancies in 0.5%, miscellaneous in 16.7%. CD was endoscopically diagnosed in 8 patients (1.1%), histologically in 15 patients (2%). The endoscopic features alone showed a sensitivity of 34.8% and specificity of 100%, with a positive predictive value (PPV) of 100% and a negative predictive value (NPP) of 97.9%.

CONCLUSION: This prospective study showed that CD has a high prevalence (1:48) in adult dyspeptic pa-

INTRODUCTION

Celiac disease (CD) has been considered for years to be a rare pathology that affects, in particular, pediatric patients who present with a clinical picture of malabsorption^[1]. The development of sensitive and specific serological tests and their administration to subjects who are apparently healthy has shown that: CD is still under diagnosed in all age groups; the form with obvious symptoms is found in only a limited number of cases; in most patients, particularly adults, the disease has an atypical symptomatology or is completely silent^[2-5]. The latter characteristics are responsible for a the length of time needed to have a correct diagnosis and expose patients to the possible development of severe pathologies. With the aim of discovering the hidden proportion of subjects with CD^[6] two different diagnostic approaches have been proposed: to carry out a screening on the apparently healthy population, or to apply case-finding in subjects that are believed to be at high risk for the disease^[7,8].

As regards mass screening, at the moment there is no evidence that supports this approach, since in the apparently healthy population the prevalence of

CD varies in relationship with geographical areas^[9]. Furthermore, a cost-effectiveness analysis in support of a mass screening program has not been performed.

Case-finding is believed to be the most appropriate diagnostic approach to adopt for asymptomatic patients or for patients with subtle clinical features. This approach is particularly effective and becomes more so if in the selection of subjects to be investigated their family doctors are involved^[10-12]. The activation of a celiac awareness program in the primary-care setting focusing on selective serological screening of high risk groups has doubled the number of cases diagnosed from among the adult asymptomatic population^[13].

It was recently observed that CD had a greater prevalence, with respect to the general population, in dyspeptic patients^[14,15] and that 30%-40% of CD patients have dyspeptic symptoms^[2]. These findings suggested that it would be useful to carry out, in subjects undergoing esophago-gastro-duodenoscopy (EGD), biopsies of the descending duodenum independently of the endoscopic aspect of the mucosa^[16-20]. The aim of our study was to determine, by means of duodenal biopsies, the prevalence of CD in dyspeptic patients submitted to EGD in an open access Gastroenterology Outpatient Clinic of a University Hospital in the south of Italy.

MATERIALS AND METHODS

From January 2005 to June 2007, 5413 patients underwent EGD at the Gastroenterology Unit of the University Hospital Policlinic of Catania.

The study was approved by the Bioethical Committee of the Polyclinic and carried out on 726 patients (282 male, 444 female; mean age 39.6 years, range 18-75 years) prospectively enrolled.

All patients gave their written informed consent before being enrolled in the study. During the entire period of the study, the first two dyspeptic patients admitted in our unit to undergo an EGD for the first time were included.

Patients with a positive family history for CD, those affected by pathologies known to be associated with CD^[21] and patients with gastroesophageal reflux disease were excluded. Dyspeptic symptomatology was classified according to Roma II criteria as: Ulcer-like Dyspepsia, Dysmotility-like Dyspepsia, and Indeterminate Dyspepsia.

During EGD, other than the observation of the esophageal and gastric mucosa, a precise evaluation of the duodenal mucosa up to the distal duodenum was carried out and any anomalies were classified as: micro nodular pattern; mosaic pattern; scalloped folds and loss or decrease of duodenal folds^[22].

The endoscopic observation was completed with a rapid urease test to detect the presence of *H pylori*, 5 biopsies of the gastric mucosa (2 antrum, 1 angulus and 2 body) consistent with the Sydney system recommendations, and 4 biopsies of the descending duodenum. The bioptic duodenal samples were orientated and mounted

villous side up before being immersed in formalin for standard staining (HE). The histological examination was carried out by a pathologist who did not know the clinical details and endoscopic reports of the patients. The pathologist gave a diagnosis of CD based on standard coloration and classified the entity of mucosal damage according to Marsh-Oberhuber criteria^[23,24]. In patients with histological diagnosis of CD the study was completed with a specific antibody test, anti-Tissue Transglutaminase antibodies (tTG) and anti-Endomysial antibodies (EMA), and the determination of the HLA haplotypes (DQ2- DQ8).

Prevalence, the relative risk and 95% CI were calculated using the Biostat Program.

Statistical analysis

The difference between mean and the difference between proportions were evaluated by the *t*-test and the χ^2 test respectively. In the case of abnormal distribution an appropriate non-parametric test was performed. We also estimated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPP) and their 95% CI of the endoscopic examinations, considering the histological evaluation of duodenal biopsies as the gold standard.

RESULTS

Over a 30 mo period 726 dyspeptic patients were enrolled: 102 (14%) ulcer-like dyspepsia, 344 (47.4%) dysmotility-like dyspepsia and 280 (38.6%) indeterminate dyspepsia. No adverse events were reported during the endoscopic procedures and bioptic sampling. The endoscopic findings were normal in 444 (61.2%) patients, peptic lesions (esophagitis, erosive gastritis, peptic ulcer) were present in 149 (20.5%), endoscopic findings suggestive for CD in 8 (1.1%), malignancies in 4 (0.5%) and miscellaneous (chemical gastropathy, lymphocytic gastritis, submucosal mass lesions, hyperplastic polyps, cystic fundal hyperplasia) in 121 (16.7%) (Table 1). Endoscopic markers of CD consisted of a decrease in the number of folds in 5 cases, an association with a mosaic pattern in 2 cases, and in the remaining 3 cases the endoscopic aspect of the mucosa was respectively micro nodular, mosaic and scalloped. These alterations of the mucosa were localized in 3 cases (37.5%) to DI and in 5 (62.5%) both to DI and D II.

The histological diagnosis of CD was made in 15 patients (5 male, 10 female; mean age 39.9 years, range 20-61 years), 8 were already suspected of being affected by CD on endoscopic evidence and 7 had an apparently normal duodenal endoscopic picture. Histological damage was classified as III C category of Marsh (Total Villous Atrophy) in 5 cases, III B (Subtotal Villous Atrophy) in 8 and III A (Partial Villous Atrophy) in 2 cases. None of the patients had histological alterations of Marsh I or II. The general prevalence of CD in dyspeptic patients that we examined was 2% (1/48). As regards *H pylori*, 7/15 (46.6%) CD patients were positive and 322/721

Table 1 Clinical characteristics and endoscopic findings of enrolled patients (*n* = 726)

Dyspepsia	Non CD (%) <i>n</i> = 711	CD (%) <i>n</i> = 15	OR	95% CI	<i>P</i>
Sex (female; male)	434 (61.0) 277 (39)	10 (66.7) 5 (33.3)	1.28	0.45-3.60	0.6
Mean age (yr)	39.5 ± 14.5	39.9 ± 11.2	1.86	0.71-4.65	0.3
Type of dyspepsia					
Dysmotility-like dyspepsia (DD)	336 (47.2)	8 (53.3)	1.27	0.47-3.42	0.6
Indeterminate dyspepsia (ID)	273 (38.4)	7 (46.7)	2.21	0.82-5.97	0.1
Ulcer-like dyspepsia (UD)	102 (14)	0			
Endoscopic findings					
Normal	437 (61.2)	7 (46.7)			/
Peptic lesion	149 (20.5)	/			
Malignancy	4 (0.5)	/			
Miscellaneous	121 (16.7)	/			
CD		8 (53.3)			

Overall prevalence: 2.01% (95% CI 1.2-3.3). Endoscopic evaluation: Sensitivity: 34.8% (95% CI 17.2-57.2); Specificity: 100% (95% CI 17.2-57.2); PPV: 100% (95% CI 59.8-100); NPV: 97.9% (95% CI 96.5-98.8).

Table 2 Demographic, clinical, endoscopic and histological data of celiac patients

Pts	Gender M/F	Age (yr)	Clinical findings	Endoscopic markers	Histological findings	Marsh
1	F	20	ID	RF/NM	TVA	III C
2	F	27	DD	NM	TVA	III C
3	F	54	ID	Normal	PVA	III B
4	M	44	DD	Normal	STA	III B
5	F	26	DD	RF	STA	III B
6	F	36	ID	Normal	STA	III B
7	F	41	DD	Normal	STA	III B
8	M	34	ID	RF + SII	TVA	III C
9	F	29	DD	Normal	APV	III A
10	M	54	DD	Normal	STA	III B
11	F	52	ID	Normal	PVA	III A
12	M	56	DD	MM	TVA	III C
13	F	39	DD	RF	STA	III B
14	M	41	ID	RF	STA	III C
15	F	45	ID	SII	STA	III B

PVA: Partial villous atrophy; STA: Subtotal villous atrophy; TVA: Total villous atrophy; DD: Dysmotility-like dyspepsia; ID: Indeterminate dyspepsia; UD: Ulcer-like dyspepsia; RF: Reduced folds; SII: Scalloped folds; NM: Nodular mucosa; MM: Mosaic mucosa.

(45.3%) patients with normal duodenal mucosa histology were positive. We did not find differences in clinical features and in mean intraepithelial leucocyte (IEL) count in *H. pylori*-negative and *H. pylori*-positive patients.

Of the 15 patients diagnosed as celiac, 8 reported dysmotility-like and 7 indeterminate dyspepsia. The type of dyspepsia, endoscopic findings and histological diagnoses are shown in Table 2.

The EMA and tTG antibodies were both present in all but one case, in which only EMA was positive; the HLA associated haplotypes were, respectively, DQ2 in 12 patients, DQ2-DQ8 in 2 patients and DQ8 in one patient.

DISCUSSION

Over the last thirty years it has been established that CD is not a rare disease, rather it should be considered as a global health problem. It is estimated that CD currently affects 2.5/3 million in both American and European populations^[25]. This observation confirms that the awareness for this under-diagnosed disease in clinical practice should be increased.

Recent investigations have shown that most patients affected by CD, in particular adults, do not have the typical symptoms of the disease, thus they remain misdiagnosed, delaying the diagnosis until an older age. In a study conducted on paucisymptomatic patients over 65 years old that had seen both family doctors and specialists, it was documented that the correct diagnosis was made with an average delay of 28 years^[26].

The misdiagnosis of CD for such a long period exposes patients to the risk of developing severe gluten-related complications such as intestinal lymphoma, autoimmune disorders or neurological diseases^[27-29].

To identify the sub-clinical or silent forms of CD, the suggested algorithm consists of the search for specific antibodies in categories of patients known to be at risk. The definitive confirmation of the disease will, however, come from the histological evaluation of the duodenal mucosa.

In recent publications^[11,30,31] a high prevalence of CD has also been found in adult patients classified as functional dyspeptic who did not respond to an adequate pharmacological therapy. To identify in this particular population the subjects whose symptoms are really due to CD, three alternate approaches have been proposed: (1) Carry out biopsies from the descending duodenum^[16,17] in all functional dyspeptic patients undergoing EGDS even if endoscopy does not reveal any lesions typical of CD^[22]; (2) Use magnification tools or immersion techniques to better characterize the duodenal mucosa^[32]; (3) Test for specific antibodies and, if positive, carry out EGD with biopsies of the descending duodenum^[33].

The first approach has been criticized due to its cost for the limited number of CD cases that could be identified and for the amount of work for the pathology services^[34,35]. The second approach, a modified version of the so-called immersion technique (MIT), which based on recent data has a sensitivity and specificity of 100%, is considered impractical though further studies are needed to assess its efficacy in routine practice as a screening or case-finding tool^[36]. The third approach has diagnostic limitations, since the test for anti-tTG and anti-EMA antibodies^[37] are relatively poor for adult smoker patients^[38,39] or in the presence of a slight or medium (Marsh I to II) histological damage.

The above cited observations suggest that for both asymptomatic risk groups and symptomatic risk groups in the general population the threshold for biopsies must become lower^[38]. In Spain duodenal biopsy performed during upper GI endoscopy has been incorporated in daily practice in digestive endoscopic services^[40]. This choice should be adopted especially in geographical areas

where there is a high prevalence of CD in an apparently healthy population.

In our study the biopsies were carried out in patients where EGD was used to clarify a functional dyspeptic symptomatology that did not resolve after an adequate pharmacological treatment. It should be noted that as regards *H pylori* positivity the percentage of *H pylori*-positive celiac patients is similar to non-celiac patients and, as recently shown^[41], clinical features of CD patients are unrelated to simultaneous presence of *H pylori* gastritis.

In this population the prevalence of CD was 2% (1/48 patients) two/four times more than that found using serological tests in the general population^[42-45] and more than that reported in two studies conducted in Italy and Brazil on dyspeptic patients^[14,30]. The data is, however, similar to that obtained in a study conducted on patients who reported chronic abdominal pain^[46].

Concerning the demographic characteristics of the 15 celiac patients (mean age 39.9 years; male/female ratio 2:1) our data are in agreement with what has already been observed in a multicenter retrospective study^[3] and in a screening study^[47], both carried out in Italy. A higher prevalence of females among celiac patients (3% vs 1%) has also been reported in a retrospective evaluation^[40] of adult patients referred to an endoscopy unit with mild digestive symptoms (dyspepsia, abdominal discomfort) or analytical alterations (anemia, iron deficiency or hypertransaminasemia).

The greater prevalence of CD among patients who reported dysmotility or indeterminate dyspepsia may be related to autoimmune damage of the extrinsic autonomic system^[48] and/or to an increase in neurotensin and enteroglucagon plasma levels which inhibit the motility of the upper gastrointestinal tract^[49,50]. Moreover a delayed oro-cecal transit time^[51] and a post-prandial decrease in gallbladder emptying rate^[52] have been found in untreated CD patients. Normalization of oro-cecal transit time was observed after gluten withdrawal using a hydrogen lactulose breath test^[50]. The diagnostic precision of the endoscopic observations [8/15 (53%)] was similar to that observed in other samples of dyspeptic patients^[14] but lower than that found in patients at high risk of CD^[23,33,53]. The discrepancy of our study compared with the latter could be explained by the fact that the operator paid more attention to the observation of the duodenal mucosa in the patients affected by pathologies already recognized as being at risk for CD.

In conclusion, based on the results that we have obtained it can be hypothesized that in patients who have been diagnosed as having refractory functional dyspepsia and for whom an EGD has been prescribed, endoscopic observation should be routinely completed with a biopsy of the descending duodenum as suggested by the guidelines of the working group on CD^[24]. Particular attention should be given to females who report dysmotility or indeterminate dyspepsia. Such an approach could reveal another submerged part of the "Celiac Iceberg" but it must be validated as regards the cost effectiveness, bearing in mind the variable prevalence of the disease in

different geographical areas. The development of new and more precise serologic and/or immunohistochemical tests^[54] would allow correct selection of subjects who need a bioptic examination of duodenal mucosa.

COMMENTS

Background

Celiac disease (CD) has been considered for years to be a rare pathology that affects, above all, pediatric patients presenting with a clinical picture of malabsorption. The development of sensitive and specific serological tests and their administration to subjects who are apparently healthy has shown that: CD is still under diagnosed in all age groups; the form with obvious symptoms is found in only a limited number of cases; in most patients, particularly adults, the disease has an atypical symptomatology or is completely silent. It was recently observed that CD had a greater prevalence, with respect to the general population, in dyspeptic patients and that 30%-40% of CD patients have dyspeptic symptoms. These findings suggested that it would be useful to carry out, in subjects undergoing esophago-gastro-duodenoscopy (EGD), biopsies of the descending duodenum independently of the endoscopic aspect of the mucosa.

Research frontiers

Based on the results that authors have obtained it can be hypothesized that in patients who have been diagnosed as having refractory functional dyspepsia and for whom an EGD has been prescribed, endoscopic observation should be routinely completed with a biopsy of the descending duodenum as suggested by the guidelines of the working group on CD. Particular attention should be given to females who report dysmotility or indeterminate dyspepsia.

Innovations and breakthroughs

This is a prospective study undertaken in the Mediterranean area. All the other related or similar articles are mainly retrospective and from different geographical areas.

Applications

Such an approach could reveal another submerged part of the "Celiac Iceberg" but it must be validated as regards the cost effectiveness, bearing in mind the variable prevalence of the disease in various geographical areas.

Peer review

This is an interesting study, looking into the prevalence of histological and serological proof of CD in consecutive patients undergoing upper GI endoscopy because of dyspepsia. Because of the high CD prevalence found, the authors conclude that duodenal biopsies should routinely be taken at this indication.

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