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Gastroduodenal Involvement in Asymptomatic Crohn's Disease Patients in Two Areas of Emerging Disease: Asia and Eastern Europe

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Abstract

Background: The incidence of Crohn's disease [CD] is increasing in Asia and Eastern Europe. Limited studies have reported on the frequency of upper gastrointestinal [GI] involvement in patients with CD in non-Western countries. This prospective study compared the rate of macroscopic and microscopic upper GI manifestations and *Helicobacter pylori* positivity in asymptomatic CD patients in Asia and Eastern Europe.

Methods: Consecutive asymptomatic CD patients were prospectively recruited for upper GI endoscopy between 2013 and 2015 in Hong Kong and in Hungary. Endoscopy and biopsy findings were recorded and histology was performed to assess for *H. pylori* and microscopic signs characteristic for CD, using standardized diagnostic criteria.

Results: One hundred and eighty CD patients [100 Hong Kong; 80 Hungary; 70.6% male; mean age, 38.5 years] and 189 controls [100 Hong Kong; 89 Hungary; 57.7% male; mean age 41 years] were included. Gastroduodenal involvement of CD was significantly higher in Hungary than in Hong Kong [16.5% vs 2.0%, $p \leq 0.001$]. *H. pylori* positivity was significantly higher in Hungarian than Chinese CD patients [13.9% vs 4.0%, $p \leq 0.001$]. Granulomas were detected in 1% in Hong Kong and 7.6% in Hungary [$p \leq 0.001$]. Chinese CD subjects had a significantly lower *H. pylori* positivity compared with controls [6% vs. 15%; $p \leq 0.001$].

Conclusions: Upper GI CD was significantly higher in Eastern Europe than in Asia. The detection of granuloma in Hungary was similar to the literature data, whereas focal gastritis was lower than expected in both cohorts.

Key Words: Asia; Crohn's disease; Eastern Europe; upper gastrointestinal tract

1. Introduction

The incidence of Crohn's disease [CD] has been increasing in previously low incidence areas, including Asia and Eastern Europe.[1,2,3] Susceptibility genes and disease phenotype may differ in CD patients between the East and the West.[4] Male predominance and the absence of nucleotide-binding oligomerization domain-containing protein 2 [NOD2]/caspase recruitment domain-containing protein 15 [CARD15] gene mutations in ileal CD have been reported in CD in an Asian population.[5] A lower proportion of isolated colonic CD and an increased proportion of ileocolonic CD in Asia and Eastern Europe[2,4] have been described when compared with Western European CD patients.[6,7] Observational studies have reported a higher proportion of upper gastrointestinal [GI] involvement in Chinese CD patients.[8,9]

Unlike in children with CD whereby upper endoscopy is advocated irrespective of the presence or absence of upper GI symptoms,[10] in adults with CD, upper GI endoscopy is not routinely performed in patients who do not have symptoms. Studies that included multiple upper GI biopsies on endoscopy have shown that the diagnosis of CD may be missed in 11–29% of cases.[10] In a Hungarian study of paediatric CD, macroscopic lesions have been found on oesophageal gastroduodenoscopy [OGD] in 64% of patients with CD. Characteristic lesions for CD were noted in 31% of CD patients, and the diagnostic yield of OGD proved to be 9% of CD patients.[11]

Chow *et al*. have reported that CD patients with upper GI involvement have worse clinical outcomes including increased need of hospitalization and are associated with stricturing and penetrating behaviour.[9] Therefore, there is a need to assess the frequency of upper GI involvement among CD patients as it may represent a distinct or worse phenotype.

This prospective study aimed to compare the prevalence of macroscopic and microscopic upper GI manifestations in asymptomatic CD patients in Asia and Eastern Europe in comparison with non-irritable bowel disease [IBD] controls. Secondly, we also compared the rates of *Helicobacter pylori* positivity among CD patients and matched controls.

2. Patients and methods

2.1. Patient recruitment

Consecutive asymptomatic CD patients were prospectively recruited for upper GI endoscopy between 2013 and 2015 at the Institute of Digestive Disease, the Chinese University of Hong Kong, China and at the 1st Department of Medicine, University of Szeged, Hungary. All patients from the Hong Kong cohort were ethnically Chinese. The diagnosis of CD was confirmed based on strict criteria in both centres. Both hospitals have a dedicated IBD in- and outpatient clinic. Only patients with a confirmed diagnosis of CD based on clinical evaluation, endoscopic/radiological appearances and histology were recruited for the study.[12] The Montreal classification was used to classify CD location (ileal [L1], colonic [L2], ileocolonic [L3] and upper GI [L4]) and disease behaviour (non-stricturing, non-penetrating [B1], stricturing [B2] and penetrating [B3]) at the time of diagnosis.[13] The date of symptom onset and the diagnosis of IBD were recorded. Data on smoking status, alcohol consumption, concomitant diseases, history of appendectomy, history of tuberculosis [TB], family history of IBD and previous surgeries were collected. OGD and biopsy findings were recorded and histology was performed to assess for *H. pylori*, granuloma, coeliac disease and microscopic signs characteristic of CD. Patients enrolled in the study did not receive eradication therapy at least 6 months prior to inclusion.

OGD evaluated the presence of normal mucosa, macroscopic inflammation, erosions, ulcerations, strictures and fistulas. OGD in each centre was performed by two experienced gastroenterologists-endoscopists. Both centres used Olympus endoscopic equipment: an Olympus EXERA II series in Szeged and EXERA III series in Hong Kong. To reduce inter-observer variations, both teams agreed on predefined criteria on macroscopic definition based on photos and discussion prior to the start of the study. A shared common database was used to collect clinical and endoscopic data from both sites based on a standardized reporting system. This system captures macroscopic appearance in the oesophagus, stomach and duodenum. The presence of macroscopic inflammation, erosions, ulcerations, strictures and fistulas was recorded. Both centres used the same standardized proforma, which is prospectively collected. The endoscopic interpretation was based on agreed and clear definitions prior to study initiation. In each patient, two biopsies were taken from each of the corpus, the antrum and the proximal part of the duodenum for histological assessment by a single GI pathologist blinded to the endoscopic findings. Both pathologists assessed the biopsy samples based on well-defined histopathological criteria for the diagnosis of IBD.

The endoscopic criteria for diagnosis of CD included discontinuous [skip] inflammatory lesions, mucosal nodularity or 'cobblestoned' mucosa, thickened gastric folds, multiple aphthous-like ulcerations and/or linear ulcerations, presence of fistula opening and/or stricture. Anatomical criteria of severity were defined as deep ulcerations eroding the muscle layer.[14] On OGD, [a] macroscopic inflammation was defined as mucosal hyperaemia or erythema, oedema or mucosal nodularity; [b] aphthous erosion was defined as a superficial mucosal break 2–3 mm in diameter; and [c] ulcer was defined as a linear or serpiginous mucosal break ≥3 mm in diameter.[15] Histological examination assessed the presence of histological features of chronicity and severity of the inflammation, assessed the presence of focally active gastritis, and evaluated the presence of *H. pylori*, granuloma and coeliac disease. For the purpose of this study, upper GI CD was defined according to established criteria, defined as macroscopic alteration of the stomach or the duodenum consistent with CD on histology.[16] Histological features for CD included the presence of non-caseating granulomas, *H. pylori*-negative focally enhanced gastritis, crypt abscesses or lymphoid aggregates.[16]

The control group was also recruited prospectively during the same period. The control group consisted of age- and sex-matched non-IBD participants who underwent OGD for different indications including dyspepsia, epigastric pain and regurgitation.

The primary outcome of this study was a difference in upper GI CD between Hungarian and Chinese CD patients. Secondary outcome included *H. pylori* positivity in CD in Hungary and Hong Kong.

2.2. Statistical analyses

Statistical analysis was performed by an experienced biostatistician. Baseline characteristics, endoscopic findings and histological findings between Asian IBD patients and East European IBD patients were compared. A χ^2 test was used for categorical variables and Mann–Whitney U-test for continuous variables. Values of $p < 0.05$ were considered statistically significant.

2.3. Ethical statement

All patients gave informed consent, and the study was approved by the Regional and Institutional Human Medical Biological Research

Ethics Committee of the University of Szeged and by the ethics committee of the New Territory East Cluster with site-specific approval from each participating hospital trust. The study was carried out according to the Declaration of Helsinki.

3. Results

3.1. Patients with CD

One hundred and eighty CD patients [100 Hong Kong, China; 80 Szeged, Hungary; 70.6% male; mean age: 38.5 years] were included. The clinical demographics of CD subjects are summarized in Table 1. The mean age of CD patients from Hong Kong and Hungary was 41 and 36 years [$p = 0.62$], respectively. There were more current smokers amongst CD patients in Hungary than in Hong Kong [33.8% vs 11%; $p = 0.001$]. History of appendectomy, time of symptom onset and time to diagnosis did not differ between Hungarian and Chinese CD patients [Table 1].

There was no difference in disease location between Hungary and Hong Kong. Non-stricturing, non-penetrating CD was less common in Chinese than in Hungarian patients [41.3% vs 57%, $p = 0.036$]. The proportion of subjects with stricturing or penetrating disease did not differ between the two cohorts. There were also no differences in the rates of perianal disease, family history of IBD and surgery [Table 1].

At endoscopy, there was no difference in the presence of macroscopic inflammation in the stomach between the two cohorts [Hungary 39.2% vs Hong Kong 31%; $p = 0.213$]. However, gastric erosions were identified in a significantly higher proportion of Chinese than Hungarian CD patients [19% vs. 2.5%; $p < 0.001$]. Macroscopic inflammation in the duodenum and duodenal erosions occurred more frequently in Hungarian than in Chinese CD patients [13.9% vs 2%, $p \leq 0.001$ and 10.1% vs 1%, $p \leq 0.001$] [Table 2].

At the time of the study, macroscopic finding of OGD suggested the presence of CD in 24% of the Hungarian cases and 4% of the Chinese cases [$p \leq 0.001$]. Histological inflammation suggestive of CD was present in 25.3% of the Hungarian patients and 28% of Chinese patients [$p = 0.658$]. Combining the macroscopic and microscopic features, CD was proved to be present in 16.5% vs 2% of the Hungarian and Chinese patients, respectively [$p \leq 0.001$].

Overall 12 patients [6.7%] were re-classified due to OGD. In the Chinese cohort three patients without upper GI manifestation at diagnosis were classified to have upper GI involvement after endoscopy. In addition, three patients with an initial diagnosis of L4 disease had no evidence of upper GI disease on OGD performed during the study and thus they were reclassified as not having upper GI manifestation of CD. These patients were under immunosuppressive therapy and remained asymptomatic. In the Hungarian cohort four patients without the initial diagnosis of L4 disease were classified to have upper GI involvement after endoscopy, while two patients with upper GI manifestation at diagnosis were reclassified as not suffering from upper GI disease.

On histological examination chronic inflammation was the most common finding in both groups, with a greater proportion in the Hungarian patients [100% vs. 77%, $p \leq 0.001$]. Focally active gastritis was present in 2% of the Chinese and 23.8% of the Hungarian patients [$p \leq 0.001$]. Granulomas were detected in 1% of the Chinese patients and 7.6% of the Hungarian patients [$p \leq 0.001$]. In subjects with macroscopic inflammation, *H. pylori* positivity was found in 33.3% and 7.1% of the Hungarian and the Chinese patients, respectively. Overall, *H. pylori* positivity was significantly higher in the Hungarian than in the Chinese CD patients [13.9% vs 4%, $p \leq 0.001$]. In total, 2.5% of the Hungarian and none of the Chinese CD patients were diagnosed with coeliac disease [$p = 0.748$]. All the Chinese patients with upper GI manifestation received maintenance azathioprine therapy. In the Hungarian cohort, 40% of the patients with upper GI CD were on azathioprine, 50% were treated with 5-aminosalicylate and 35% with corticosteroid therapy.

3.2. Control patients

In total, 189 controls [100 Hong Kong; 89 Hungary; 57.7% male; mean age 41 years] were recruited in the study. Table 3 shows the basic demographic data of the control subjects. The main indication

Table 1. The clinical demographics of the Hungarian and Chinese CD patients enrolled in the study.

	Hungarian CD patients [$n = 80$]	Chinese CD patients [$n = 100$]	p-Value
Gender [male/female]	51/29	76/24	0.74
Mean age at present [years]	36	41	0.602
Mean age at time of symptom onset [years]	28	30	0.568
Mean age at diagnosis [years]	29	33	0.458
Smoking habits			
Current smoker	27	11	0.001
Ex smoker	8	14	
Never smoked	43	75	
History of appendectomy	10	10	0.602
Family history of IBD	3	3	0.465
Previous bowel surgery	25	28	0.864
Location at diagnosis			
L1 [ileal]	26	27	0.747
L2 [colonic]	16	21	0.648
L3 [ileocolonic]	38	51	0.682
L4 [upper GI]	12	4	0.011
Behaviour at diagnosis			
B1 [non-stricturing non-penetrating]	33	57	0.036
B2 [stricturing]	20	23	0.783
B3 [penetrating]	23	26	0.132
Perianal manifestation	22	33	0.400
H. pylori positivity [%]	13.9	4	≤0.001

Table 2. Endoscopic and histological findings of the Hungarian and Chinese CD patients enrolled in the study.

	Hungarian CD patients [n = 80]	Chinese CD patients [n = 100]	p-Value
Endoscopic findings of the stomach			
Macroscopic inflammation [%]	39.2	31	0.213
Erosions [%]	2.5	19	≤0.001
Ulcers [%]	0	3	0.302
Strictures [%]	0	0	0.452
Fistulation [%]	0	1	0.346
Endoscopic findings of the duodenum			
Macroscopic inflammation [%]	13.9	2	≤0.001
Erosions [%]	10.1	1	≤0.001
Ulcers [%]	0	0	0.214
Strictures [%]	0	0	0.402
Fistulation [%]	1.3	1	0.426
Histological findings			
Chronic inflammation [%]	100	77	≤0.001
Severity of the inflammation [%]			
- Mild	87.3	71	0.231
- Moderate	11.1	14	0.202
- Severe	1.6	1	0.110
Focally enhanced gastritis [%]	23.8	2	0.001
Presence of granuloma [%]	7.6	1	≤0.001
H. pylori positivity [%]	13.9	4	≤0.001

Table 3. Demographic data of the Hungarian and Chinese control patients enrolled in the study.

	Hungarian controls [n = 89]	Chinese controls [n = 100]	p-Value
Gender [male/female]	41/48	68/32	0.408
Mean age at present [years]	41	41	0.726
Indication of OGD			
Epigastric discomfort	25	46	
Dyspepsia	7	25	
Regurgitation	15	19	
Abdominal bloating	14	2	
Dysphagia	4	2	
History of GI bleeding	1	0	
Anaemia	7	4	
Others	4	2	
H. pylori positivity [%]	14.6	15	0.564

for OGD was epigastric discomfort in both the Chinese and the Hungarian cohort. Macroscopic inflammation of the oesophagus and the stomach was more frequently reported in the Chinese than the Hungarian controls [16% vs. 4.5% and 76% vs. 27%, $p \leq 0.001$], although oesophageal and gastric erosions occurred more frequently in the Hungarian than the Chinese patients [24.7% vs 0% and 10.1% vs 3%, $p \leq 0.001$]. No difference was shown in *H. pylori* positivity between the two control populations [Hungary 14.6% vs Hong Kong 15%, $p = 0.564$]. Granuloma did not occur on histological examination, and no difference was revealed in the rate of coeliac disease. However, none of the patients were diagnosed with coeliac disease in Chinese patients [2.2% vs 0%].

CD subjects in Hong Kong had significantly lower *H. pylori* positivity compared with the matched controls [6% vs 15%; $p \leq 0.001$], whereas no difference was found in *H. pylori* positivity between the Hungarian CD and control population [13.9 vs 14.6%; $p = 0.159$] [Tables 2 and 3].

4. Discussion

To our knowledge this is the first study that has prospectively examined and compared the prevalence of macroscopic and microscopic upper GI manifestations and *H. pylori* positivity in asymptomatic adult CD patients in two populations of different ethnicities and emerging CD incidence. The presence of upper GI CD confirmed by established criteria was 16.5% of the Hungarian patients and 2% of the Hong Kong patients; however, the presence of histological inflammation suggestive of CD did not differ between the Hungarian and Hong Kong CD subjects. When considering endoscopic appearance, gastric erosions occurred more frequently in Hong Kong CD patients, while duodenal inflammation and erosions were more common in Hungarian than in Chinese CD patients.

These results can be discussed from at least two different views: on the one hand, the histological criteria of mild upper GI CD are quite accurate and the frequency of upper GI CD is almost the same in both areas, although the endoscopic interpretation of macroscopic lesions of suspected CD is completely different. On the other hand, the presence of macroscopically obvious CD may differ significantly in the two regions. In controls, macroscopic inflammation of the upper GI tract was more frequent in Hong Kong patients and erosions occurred more frequently in the Hungarian patients. No difference was shown in *H. pylori* positivity between the two control populations. However, *H. pylori* infection was more commonly detected in Hong Kong controls versus CD patients.

The prevalence of gastroduodenal involvement of CD patients varies between 0.5 and 13%.[16,17,18] In an Italian study, upper GI CD was found in approximately 19% of CD subjects, a value similar to our results.[19] Macroscopic and histological findings of CD were detected in 48.7% and 59.7% of CD patients, respectively, and *H. pylori* was found in 8.4% of CD subjects, which appeared also to be comparable to the present Hungarian results.

Focally active gastritis proved to be low in both groups. According to a recently published review about the prevalence of upper GI CD and its histopathological changes, focal gastritis was present in 31% of the patients, a very similar value to that of the Hungarian cohort.[20] The review included 20 studies mainly from European countries or the US. Only two studies came from Japan, showing that data from Asia are extremely limited. Moreover, because focal gastritis may present in 12% of ulcerative colitis patients and 19% of healthy individuals undergoing gastroscopy, it cannot distinguish between CD and ulcerative colitis.[20,21]

CD has been reported with an increasing frequency in some Asian countries in the recent years. The review by Wang *et al*. summarized proportions of patients with only small intestinal involvement, colonic involvement or both varying in the ranges 28.6–53.8%, 26.9–27% and 19.2–44.4%, respectively, in Chinese patients compared with developed countries for which values were 30%, 15% and 55%, respectively.[22] However, data on upper GI tract involvement in Asian CD patients are generally lacking. The study by Leong *et al*. revealed 19% of the patients having involvement proximal to the terminal ileum, suggesting a higher frequency of upper GI tract CD.[8] Notably, in our study we evaluated involvement of the upper GI tract between the oesophagus and the duodenum, so comparing the data of these two studies is difficult. The Hungarian cohort of Lovasz *et al*. revealed upper GI tract involvement to be 4.8%, while isolated upper GI tract involvement was only 0.7%,[23] which is consistent with our findings that none of the patients had isolated upper GI tract involvement. In our study, 6.7% of the patients were re-classified based on OGD.

Upper GI endoscopy is a regularly performed examination in paediatric IBD but significantly less frequently used in adults CD patients. Although the European Crohn's and Colitis Organization guidelines recommend examination of the location and extent of CD in the upper GI tract, irrespective of the findings at ileocolonoscopy, in routine practice, upper endoscopy is mainly performed in CD patients with symptoms.[14] Confirming the need for routine OGD, routine upper endoscopy has been shown to reveal various rates of macroscopic gastroduodenal lesions in 30–75% of CD patients.[24,25] Microscopic inflammation was detected in 24–70% of patients undergoing upper GI endoscopy.[26] Our results also revealed some macroscopic abnormalities in more than 80% of the patients with mild chronic inflammation on histology. The occurrence of epithelioid granulomas, being the histological hallmark of CD, varies between 10 and 25%.[27,28,29] *H. pylori* infection on histology occurs in about 10% of CD patients.[26] In our study, granulomas and *H. pylori* positivity were more common in Hungarian CD patients. Some studies have found a lower prevalence of *H. pylori* infection in IBD patients versus healthy individuals.[30,31] In the present study, a significant difference in *H. pylori* infection between CD patients and controls was detected only in the Chinese population. The meta-analysis by Castaño-Rodríguez *et al*. also reported a stronger negative association between *H. pylori* infection and IBD in Eastern populations than Western populations.[31] Our consistent findings may be explained by the difference between the *H. pylori* strain in Eastern and Western populations.[31,32]

The incidence of CD lesions in the upper GI tract is frequently underestimated. Although the majority of macroscopic and microscopic abnormalities were independent of CD, macroscopic findings suspicious of CD differed significantly; while histological evaluation of CD was highly similar in the two groups, endoscopy and histology definitively disclosed CD in 16.5% of the Hungarian and 2% of the Chinese patients of our cohorts. This study showed different upper GI tract manifestations in the Hungarian and the Hong Kong cohorts; however, histology suggested CD at a significantly higher than expected rate in asymptomatic patients.

As the majority of the asymptomatic patients whose initial diagnosis of upper GI tract involvement was altered after the study OGD were under immunosuppressive therapy, this suggests that adequate immunosuppressive therapy may reverse the upper GI manifestations of CD.

The strength of our study is that, to our knowledge, it is the first prospective study assessing upper GI CD in two populations of emerging disease incidence studied in parallel over the same period using specific predefined criteria for definition agreed upon prior to start of study. Matched controls were also recruited to assess *H. pylori* prevalence in two different countries of different *H. pylori* background incidence.

There are also some limitations to the study. There may be inter-observer variation between centres on the macroscopic appearance as photos were not routinely captured during the study period. Nonetheless, photos and strict and validated criteria were used to define these lesions. Although central reading for endoscopic mucosal assessment would have provided a more relevant comparison between the two regions, centralized assessment of endoscopic findings usually relates to studies evaluating experimental drugs or novel scoring systems in IBD. Although central reading has been proven to be effective in the assessment of disease activity, it has not been tested in the assessment of upper GI CD. Moreover, video acquisition is not yet the standard of care in clinical endoscopy suites and may require segmental annotation. Moreover, this is a prospective study that included data under real practice collected by trained gastroenterologists and endoscopists. Endoscopic interpretation was based on clear definitions, and statistical analysis was performed by a biostatistician. Our controls underwent OGD for certain symptoms so there may be a higher prevalence of finding lesions; asymptomatic controls are more ideal to enroll, but this would be ethically challenging.

In conclusion, we have shown that upper GI lesions are less common among asymptomatic Chinese versus Hungarian CD patients based upon our endoscopic criteria but did not differ based on histological assessment. Gastric erosions were more common in Hong Kong, and duodenal inflammation was more characteristic for Hungarian CD patients. The detection of granuloma in Hungary was similar to the literature data, whereas focal gastritis was lower than expected in both cohorts.

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Conflict of Interest

None.

Author Contributions

Study design, data collection, supervision of patient selection and manuscript preparation: SCN, TM, KF, HC; data collection: KF, HC, MR, ZS, FN, LT,

WT, GW, RT, AL, CC, SW, RL; data collection and manuscript preparation: SCN, TM, KF, HC; statistical analysis: TN. All authors have approved the final draft submitted.

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