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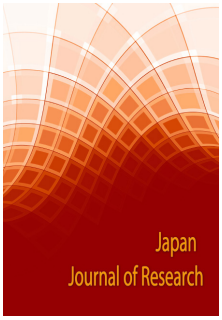

Helicobacter pylori (Hp) infection and upper gastrointestinal mucosal changes in Crohn's disease patients from the population with high prevalence of Hp

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Background

Crohn's disease (CD) is a type of inflammatory bowel disease (IBD) that may affect any segment of the gastrointestinal tract from the mouth to the anus. Helicobacter pylori (Hp) infection and upper gastrointestinal mucosal changes in Crohn's disease patients from the population with high prevalence of Hp disease pathogenesis involves genes and environment as cofactors in inducing autoimmunity; particularly the interactions between enteric pathogens and immunity are being studied. While the lower gastrointestinal (GI) tract has been well studied in CD patients, the upper GI tract has attracted less attention. The prevalence of upper GI involvement of CD was considered to be relatively low (0.5–16.0%) [1-4], but not far ago prospective researches have revealed that a considerable percentage of CD patients (24–56%) exhibit upper GI lesions [5-8]. Gastroscopy with biopsies is considered the gold standard in the diagnosis of gastroduodenale CD. The gastric antrum and duodenal bulb are most frequently involved, while proximal gastric and distal duodenal involvement are uncommon [9-12]. Endoscopic findings in CD may include aphthous ulceration, erosions, patchy erythematous mucosa, thickened folds, fistulae and bamboo joint-like appearances . Bamboo joint-like lesions are specific for CD, appearing as erosive grooves intersecting longitudinal edematous gastric folds. The duodenum in CD may also exhibit a cobblestone appearance, polypoid lesions and duodenal notching of Kerckring's folds, which is considered to be a pathognomonic sign [13]. Detecting epithelioid cell granulomas in biopsy specimens from the gastroduodenal mucosa is generally considered to be diagnostic of Crohn's disease. Recently, the focal enhanced gastritis (FEG) and multinucleated giant cells has been reported as the main histological findings in gastroduodenal CD. Focally enhanced gastritis consists of focal collections of histiocytes and lymphocytes surrounded by gastric foveolae [14-16].

Even though gastric CD can have suggestive features that can help in the diagnosis, they are not pathognomonic. In this regard, many histological characteristics found in gastric CD are also associated with Hp infection and this infection can constitute a confounding factor. Helicobacter pylorus (HP) is a gram-negative, spiral-shaped pathogenic bacterium responsible for chronic gastritis. That mucosal inflammatory process is most likely driven by a cellular immune response to the on-going stimulation of the host's immune system caused by the bacterium. This results in high production of interleukin (IL)-12, leading to a T helper type 1 (Th1)-polarized response and elevated levels of Th-1 cytokines.

Previous research found an inverse prevalence association between HP and CD, suggesting a potential protecting role of HP from IBD [17]. The recent study of the prevalence of Hp infection among patients with IBD and the control group in the Brazilian population with a high prevalence of Hp didn't reveal significant differences [15]. In Belarus, there is a high prevalence of Hp infection and since Hp is associated with several of the histological features recognized in gastric CD, its presence could play a confounding role in the histological diagnosis of IBD patients with gastric involvement.

The aim of the study was to clarify endoscopic and histological gastroduodenal mucosa changes in Hp- negative and Hp-positive patients with CD.

Methods

For clarification and comparison, we conducted own special study of gastroduodenal changes in patients with CD with simultaneous endoscopic and histological evaluation. We carried out high resolution Narrow band imaging (NBI) endoscopy of the stomach and duodenum with biopsies in 73 CD patients (41 men, 32 women; mean age, 30 years) and 45 age- and gender-matched patients without CD (control group).

Demographic and clinical characteristics of the patients with Crohn's disease are presented in table 1.

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Table 1. Demographic and clinical characteristics of the patients with Crohn's disease (n=73)

Parameter	N, proportion	Confidence interval(CI)
Gender		
male	41/73, 56.2%	95% CI 40.3-76.2
female	32/73, 43.8%	95% CI 30.0-61.9
Median age (range, years)	30	95% CI 27.7-30.3
BMI		
< 18,4 kg/m^2	15/73, 20.6%,	95% CI 11.5-33.9
18,5-24,9 kg/m^2	35/73, 47.9%,	95% CI 33.4-66.7
>25 kg/m^2	23/73, 31.5%,	95% CI 20.0-47.3
CD phenotype, Montreal classification		
Age at diagnosis		
A1	6/73, 8.2%	95% CI 3.0-17.9
A2	52/73, 71.2%	95% CI 53.2-93.4
A3	15/73, 20.6%	95% CI 11.5 -33.9
Location		
L1	8/73, 11.0%	95% CI 3.5-15.8
L2	8/73, 11.0%	95% CI 3.5-15.8
L3	19/73, 26.0%	95% CI 15.7-40.6
Isolated L4	1/73, 1.4%	95% CI 0.35-7.63
L4 in combination with other localization	37/73, 50.6%	95% CI 35.7-69.9
Behaviour		
B1	48/73, 65.8%	95% CI 48.5-87.2
B2	13/73, 17.8%	95% CI 6.9-22.2
B3	12/73, 16.4%	95% CI 8.5-28.7
“p” phenotype	13/73, 17.8%	95% CI 6.9-22.2
Clinical Disease Activity (CDAI)		
Remission	33/73, 45.2%	95% CI 31.1-63.5
Mild	21/73, 28.8%	95% CI 17.8-44.0
Moderate	14/73, 19.2	95% CI 10.5-32.2
Severe	5/73, 6.8%	95% CI 2.2-16.0
Endoscopic Disease Activity,(SES-CD)		
Remission	33/73, 45.2%	95% CI 31.1-63.5
Mild	16/73, 21.9%	95% CI 12.5-35.6
Moderate	11/73, 15.1%	95% CI 7.5-27.0
Severe	13/73, 17.8%	95% CI 6.9-22.2
Hp-status CD-patients		
Hp -positive CD patients	27/73, 37.0%	95% CI 24.4-53.8

The group of CD patients had the following predominant characteristics: BMI more than 18,5 – 79,4%, age at diagnosis between 17 and 40 years – 71,2%, ileocolonic location in concomitant upper gastrointestinal disease -76,6%, non-stricturing and non-penetrating behaviour – 65,8%, remission with mild Clinical Disease Activity – 74,0%, remission with mild on Endoscopic Disease Activity – 67,1%.

The CD diagnosis was established on the basis of international guidelines. Endoscopic disorders such as erythema/edema, erosions, ulcers/scarring, nodularity, hemorrhages/ vulnerability, atrophy and metaplasia of gastroduodenal mucosa and intestinal lymphangiectasia were analyzed and compared between CD and control patients. Histological findings were examined as follows: chronic gastritis, active gastritis (cryptitis, crypt-abscess), FEG, lymphoid infiltration of gastric mucosa, lymphoid follicles, duodenitis, active duodenitis, metaplastic and non-metaplastic atrophy. Histological findings of upper gastrointestinal tract were compared between CD and control patients. The H.pylori status was evaluated histologically.

Statistical analysis was carried out using statistical software Winpepi, Graph Pad Prism 5. χ2-Test and Fisher's exact test were used to evaluate differences between CD and control groups.

Results

TH. pylori infection was recognized in 27 cases of CD patients (37.0% (95% CI 24.4-53.8)) and in 14 cases of control patients – 31.1% (95% CI 17.0-52.2), p>0.05.

As expected in a country with high prevalence of Hp, the infection ratio in the IBD subjects was not lower than in controls. In fact, there were no differences in Hp prevalence among the study groups.

There was no significant difference in the prevalence of endoscopic disorders in the gastric mucosa between CD and control patients - 94,5% (95% CI 73.5-119.6) vs 84,4% (95% CI 59.7-115.9), P=0.10. The prevalence of erythema/edema; erosions; ulcers/scarring; nodularity; hemorrhages/vulnerability, atrophy and intestinal metaplasia of gastric mucosa in CD patients and Hp-negative CD patients was correspond to control patients and Hp-negative control patients, P>0.05. Gastric ulcers/scarring were observed in three CD patients and had no H. pylori infection. In control patients a scar of the gastric mucosa was revealed in one patient and scar was associated with H. pylori infection.

Duodenum endoscopic disorders occurred at significantly higher rates in CD patients compared with control – 75.3% (95% CI 56.7-98.07) vs 51.1% (95% CI 32.4-76.7), P<0.01. Ulcers/scarring and nodularity of duodenum were more frequently diagnosed in CD patients in comparison with control -15.1% (95% CI 7.5-27.0) vs 2.2% (95% CI 0.1-12.4), P <0.05 and 15.1% (95% CI 7.5-27.0) vs 0.0% (95% CI 0.0-8.2), P < 0.01 respectively. Furthermore, most of the cases ulcers/scaring (10/11 (90.9% (95% CI 43.6-167.2)) as well as nodularity 10/11 (90.9% (95% CI 43.6-167.2) of duodenum in CD patients had no H. pylori infection. Non Hp -associated ulcers/scarring as well as nodularity were revealing in 13. 7% (95% CI 6.6-25.2) CD patients; in control group ulcers/scarring and nodularity of duodenum were strongly associated with Hp-infection and wasn't identified in Hp-negative control patients (P = 0.01). There was no significant difference in the prevalence of such endoscopic findings as erythema/edema, erosions, hemorrhages/vulnerability, atrophy and metaplasia of duodenum between CD and control patients (P>0.05) as well as Hp-negative CD and Hp-negative control patients, (P>0.05). Intestinal lymphangiectasia was reveal with a comparable frequency between CD and control patients – 24.7% (95% CI 14.6-39.0) vs 22.2% (95% CI 10.7-40.9), P>0.05.

In our study granulomas were not found in any CD and control group patients. Chronic gastritis and non- Hp associated chronic gastritis were more often identified in CD than control patients- 75,3% (95% CI 56,8-98,1) vs 51,1% (95% CI 32,4-76,7) and 51.1% (95% CI 32.4-76.7) vs 29,0% (95% CI 13.3-55.1) P<0.01 and P = 0.01 respectively. Chronic gastritis was reveals in all Hp-positive CD and control patients. Active inflammation of gastric mucosa occurred in 48.0% (95% CI 33.4-66.7) CD patients and 31.1% (95% CI 17.0-52.2) patients control group, P > 0.05. However, non Hp -associated active inflammation of gastric mucosa was reveal in 30.4% (95% CI 16.6-51.1) CD patients and only in 9.7% (95% CI 2.0-28.3) control cases, P = 0.01. There was no significant difference in the prevalence of active inflammation of gastric mucosa Hp-positive CD and control patients 77.8% (95% CI 48.2-118.9) vs 78,6% (95% CI 39.2-140.6), P = 1.00. There was no significant difference in the prevalence of non-metaplastic and metaplastic atrophy in gastric mucosa between CD and control patients (p>0.05).

Lymphoid follicles were revealed in 12.3% (95% CI 5.64-23.4) CD patients and in 11.1% (95% CI 3.6-25.9) cases control, P>0.05. In Hp-negative CD patient's lymphoid follicles were diagnostic in 13.1% (95% CI 4.9-29.0) cases and lymphoid follicles weren't identified in Hp-negative control patients, P<0.05. There was no significant difference in the prevalence of lymphoid follicles of gastric mucosa Hp-positive CD and control patients 11.1% (95% CI 2.3-32.5) vs 35,7% (95% CI 11.6-83.4), P = 0.10.

FEG occurred in 27.4% (95% CI 16.7-42.3) CD patients; non Hp -associated FEG was reveal in 15.1% (95% CI 7.5-27.0) Hp-negative CD patients; in control group FEG (8.9% (95% CI 2.4-22.8) was strongly associated with Hp-infection and wasn't identified in Hp-negative control patients. The Hp-negative CD patients with FEG are characterized predominance of cryptitis (63.6% (95% CI 25.6-131.1), p<0.01), crypt-abscess (27.3% (95% CI 5.6-79.7), p=0.05) and non-metaplastic atrophy (54.6 % (95% CI 20.0-118.7) p<0.05) in comparison with Hp-negative CD patients with non-FEG gastritis.

There were no differences in prevalence of duodenitis - 39.7% (95% CI 26.6-57.1), active duodenitis - 27.4% (95% CI 16.7-42.3), atrophy – 32.9% (95% CI 21.1-48.9) and metaplasia – 28.8% (95% CI 17.8-44.0) between CD and control patients, P>0.05. However, in Hp-negative CD patients duodenitis - 43.5% (95% CI 26.6-67.2), active duodenitis - 30.4% (95% CI 16.6-51.1), atrophy – 34.2% (95% CI 18.2-58.5) were observed significantly more frequently than in Hp-negative controls, P<0.01 P<0.05 and P<0.01 respectively.

Discussion

The lower gastrointestinal (GI) tract has been well studied in CD patients, but the upper GI tract has attracted less attention. In MEDLINE database (PuMed) contains 244 publications (1968-2020) using keywords "Crohn Disease/anatomy and histology"[Mesh] AND gastric": 10 years – 54, 5 years - 25 results. Among these publications, there is no Meta-Analysis, Randomized Controlled Trial, Systematic Review and there are only 4 Clinical Trial. In ScienceDirect database contains 117 publications (1987-2020), predominantly Conference abstracts - 60, Research articles -21. Our risk of bias assessment found that most studies had small sample sizes and reported insufficient methodological detail (in particular, simultaneous assessment by endoscopy and histology) to enable robust assessment gastric and duodenal mucosa. Moreover, there is significant heterogeneity in the ethnicity of patients. However, some results can be noted. Primarily it is indicated that, the prevalence of upper GI involvement of CD was considered to be relatively low (0.5–16.0%), but not far ago prospective researches have revealed that a considerable percentage of CD patients (30–56%) exhibit upper GI lesions.

As expected in a country with a high prevalence of Hp, the infection ratio in the CD patients was higher then previously published and not lower then in controls (37.0% (95% CI 24.4-53.8) vs 31.1% (95% CI 17.0-52.2), p>0.05.

Our research revealed that the gastric antrum and duodenal bulb are most frequently involved in inflammation in CD patients, then the proximal gastric and distal duodenum (p<0.05) respectively.

Systematic Review L. Diaz et al. [8] demonstrated the most common gastric endoscopic finding in patients with CD was erythema in 5.9%, followed by erosions in 3.7%. In our research gastric erythema and erosions were detected much more offen - 93.2% (95% CI 72.3-118.1) and 13,7% (95% CI 6.6-25.2) respectively, but there was no significant difference

in the prevalence of erythema and erosions in the gastric mucosa between CD and control patients (p>0.05). This fact demonstrates that the endoscopic gastric disorders such as erythema/edema; erosions are nonspecific and common.

The prevalence of ulcers/scarring in gastric mucosae CD patients and Hp-negative CD patients was correspond to control patients as well as Hp-negative CD and Hp-negative control patients. However, gastric ulcers/scarring were observed in three CD patients and had no H. pylori infection. In control patients a scar of the gastric mucosa was revealed only in one patient and scar was associated with H. pylori infection. Further large-scale study of the prevalence of ulcers/scarring in gastric mucosae CD patients is necessary. There was no significant difference in the prevalence of endoscopic disorders such as nodularity; hemorrhages/vulnerability, atrophy and intestinal metaplasia of gastric mucosa between CD and control patients (P>0.05)

A distinctive feature of duodenal mucosae CD patients in comparison with control patients was significantly higher prevalence of ulcers/scarring and nodularity. Non Hp -associated ulcers/scarring as well as nodularity were revealing in 13. 7% (95% CI 6.6-25.2) CD patients; in control group ulcers/scarring and nodularity of duodenum were strongly associated with Hp-infection and wasn't identified in Hp-negative control patients (P = 0.01).

In our study there was no significant difference in the prevalence of such endoscopic findings of duodenum as erythema/edema, erosions, hemorrhages/vulnerability, atrophy and metaplasia of duodenum between CD and control patients as well as Hp-negative CD and Hp-negative control patients.

Detecting epithelioid cell granulomas in biopsy specimens from the gastroduodenal mucosa is generally considered to be diagnostic of Crohn's disease. In our study granulomas were not found in any CD and control group patients. Chronic gastritis and non- Hp associated chronic gastritis were more often identified in CD than control patients (P<0.01 and P = 0.01 respectively).

Focally enhanced gastritis consists of focal collections of histiocytes and lymphocytes surrounded by gastric foveolae. FEG occurred in 27.4% (95% CI 16.7-42.3) CD patients; non Hp -associated FEG was reveal in 15.1% (95% CI 7.5-27.0) Hp-negative CD patients. In our research FEG was exclusive associated with CD when Hp infection was ruled out. In accordance with the present study, several other investigators have found a higher prevalence of FEG in CD [14-16].

There was no significant difference in the prevalence of lymphoid follicles between CD patients and control P>0.05. However, in Hp-negative CD patient's and control lymphoid follicles were strongly associated with CD patients.

While many aspects of quality improvement in IBD are equally relevant across the globe, there are important regional differences with respect to the prevalence of distinct disease phenotypes, genetic drivers of disease manifestations and response to therapy, prevalence of potential "mimickers" and confounding factors of the disease that may warrant specific approaches to diagnostic, treatment, and epidemiology of environmental triggers such as prevalence of concomitance infections and diseases.

Conclusion

Our research allows us to mark some new positions. Even though gastroduodenal CD can have suggestive endoscopic and histological features that can help in the diagnosis, they are not pathognomonic. In this regard, many endoscopic and histological characteristics found in gastroduodenal CD, from the population with high prevalence of Hp, are also associated with Hp infection and this infection can constitute a confounding factor.

In our study endoscopic features such as nodularity, ulcers/scarring of duodenum were exclusively associated with CD when Hp infection was ruled out. Focal enhanced gastritis (FEG) was recognized in Hp-negative patients only in CD and not found in Hp-negative control group. Furthermore, in CD patients FEG is characterized predominance of active inflammation in gastric mucosa (cryptitis, crypt-abscess) and atrophy in comparison with non-FEG gastritis. The results obtained refer to the group of patients with CD having the following characteristics: age at diagnosis 17 - 40 years, ileocolonic location in concomitant upper gastrointestinal disease, with non-stricturing and non-penetrating disease behaviour, in condition as remission and mild activity by Clinical Disease Activity and Endoscopic Disease Activity and it does not extend to other disease forms.

Further large-scale study of the upper gastrointestinal tract in patients with Crohn's disease other phenotypes is necessary for detailed study.

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