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The Gut-stomach Axis: *Helicobacter pylori* and Celiac Disease

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Abstract Abnormalities in the gastric and duodenal eco-systems have been proposed as contributing to the pathophysiology of celiac disease (CD) and *Helicobacter pylori* (*Hp*) infection, respectively. Lymphocytic gastritis and lymphocytic duodenitis cohabit in *Hp* and celiac disease and also in *Hp*- or non-CD respective conditions. The present editorial discusses those entities, concentrating on the pathophysiological pathways, highlighting the *Hp*-CD relationship in the contest of the gut-stomach axis.

Keywords: *helicobacter pylori, celiac disease, lymphocytic gastritis, lymphocytic duodenitis, enteritis, immunopathology, stomach-gut axis*

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1. Introduction

We congratulate Lupan I et al. for summarizing the current literature on the immunopathology of pediatric celiac disease (CD) and *Helicobacter pylori* (*Hp*) infection [1]. As concluded, "There are many "for" and "against" conclusions on immunopathological association between CD and *Hp* infection". In fact, the relationship between the two entities is far from being elucidated. However, new emerging knowledge might help us to understand those complex cross-talks between infectious and autoimmune diseases [2,3]. The present editorial will clarify some of those connections, trying to explore the background for the lymphocytic gastritis (LG) in CD and the lymphocytic duodenitis (LD) in *Hp* infection. Before starting, Table 1 and Table 2 summarize the wide differential diagnosis of LD and LG in non-celiac and non-*Hp* diseases, respectively [4-9].

Table 1. Etiologies of proximal small bowel non-celiac intraepithelial lymphocytosis

Disease class	Etiology
Food allergy	Cow's milk, cereals, rice, fish, chicken, soy etc.
Infections	Helicobacter pylori, Giardiasis, Cryptosporidia, tropical sprue, viral and parasitic gastroenteritis, bacterial over growth
Drugs	NSAID's, olmesartan, proton pump inhibitors
Autoimmune diseases	Autoimmune thyroiditis, rheumatoid arthritis, SLE, Crohn's disease, ulcerative colitis
Immune deficiency/dysregulation	IgA deficiency, CVID, GVHD, lymphocytic/collagenous colitis
Oncogenic	Intestinal lymphoma
Gluten related	Non-celiac gluten sensitivity
Peptic disease	peptic duodenitis
Miscellaneous	Irritable bowel disease, pediatric recurrent abdominal pain, idiopathic, persistence despite gluten free diet

Adapted from ref. [4,5,6].

Table 2. Etiologies of Helicobacter pylori negative lymphocytic gastritis

Disease class	Etiology
Gastric infections	Tuberculosis, CMV, Helicobacter suis, EBV
Inflammatory conditions	Russell body gastritis, microscopic colitis, Ménétrier's disease
Autoimmune diseases	Autoimmune atrophic gastritis, Crohn's disease
Collagenous gastroenteropathies	Collagenous colitis
Reactive gastropathy with focal activity	Chemical gastropathies (bile reflux, NSAIDs, etc.)
Focally active gastritis and carditis	gastroesophageal reflux
Granulomatous gastritis	Crohn's disease, tuberculosis
Oncogenic	Gastric lymphoma

Adapted from ref. [7,8,9].

2. The Pathophysiology of Lymphocytic Gastritis in CD

Abnormalities in the gastric eco-system have been proposed as a contributor to the pathophysiology of CD. Inversely, use of proton pump inhibitors and lack of colonization with *Helicobacter pylori* have been association with an increased risk of CD.

LG appears to be associated with CD, appearing in up to 30-45% of such patients [5,10,11,12]. Since CD is a classical proximal small bowel disease and the majority of the immuno-pathological abnormalities are described locally, one wonders what the current hypotheses for LG development in CD. Are.

a. The retrograde theory: Strong association between LG prevalence and the degree of intestinal atrophy was described recently [13]. Taking in account that *Hp* status is not associated with LG, in CD patients [5,13], it seems that the small bowel mucosal events override the gastric *Hp* presence, in CD LG development.

b. The Th1 cytokine profile theory: CD and *Hp* gastritis affect the systemic immune profile. It is generally accepted that the major cytokine response in both entities has a Th1-type profile. Those pro-inflammatory messengers can impact the gastric inflammatory reaction [5,14].

c. The CD8+ T cells theory: An increase in intestinal intraepithelial lymphocytes (IELs), composed of both CD8+ αβ T cells and γδ T cells, is a hallmark of CD [6]. IELs are responsible for the detrimental consequences of CD, including tissue damage development. CD8+ TCRαβ+ IELs (CD8+ IELs) function as effectors in protective immunity to pathogens (potentially including *Hp*), and in CD they assume a natural killer-like phenotype to kill intestinal epithelial cells [15]. Interestingly, several authors described increased population of the CD8+ lymphocytes in *Hp* gastritis [5,16]. The question arises is if the CD8+ T cells that home the celiac intestinal mucosa, populate the gastric one to produce LG?

d. The dysbiota and increased production of lysozyme theory: To protect against the tough microenvironment, associated with bacterial proliferation, the epithelia of the gastrointestinal tract react by speeding-up cell exfoliation, by increasing peristalsis, eliminating bacteria through secretion of plasma cell-immunoglobulins and by increasing production of natural antibacterial enzymes (lysozyme) and host defense peptides (defensin-5). Lysozyme was recently found up-regulated in LG and CD [17]. This up-regulation is a direct response towards the special types of bacteria thriving in the microenvironment of the two conditions. The purpose of that up-regulation is to protect the mucosa facing ongoing chronic inflammation. The contribution of the up-regulated lysozymes to the LG or to the LD, is not clear. The increased proliferation of the dysbiota associated with CD and the resulting metabolome, might induce or enhance gastric inflammation through the dysbiotic changes in the stomach [18].

3. The Pathophysiology of Lymphocytic Duodenitis in *Hp* Gastric Infection

Lymphocytic duodenitis is associated with *Hp* gastritis in 6-14% of the cases. In CD with normal architecture of the small bowel, LD was reported in 9-40% [13]. It goes without saying that the classical pathological feature of CD demands > 25 IELs/100 enterocytes, for the diagnosis, despite the ongoing debate on the normal cut-off level [6]. The association between *Hp* infection and LD is controversial and much more is the complex causative relationship [19,20,21,22]. Since *Hp* infection is a classical gastric disease and the majority of the immuno-pathological abnormality are described locally, one wonders what might be the explanations for the LD development in *Hp*+ patients.

a. **The duodenal colonization of *Hp***: Interestingly and strangely enough, *Hp* resides in the proximal small bowel [23] and in gastric metaplastic patches in the duodenum [24]. If substantiate, the duodenal *Hp* presence can activate multiple inflammatory pathways, imitating some of the gastric ones, to induce duodenitis.

b. **Systemic active immune system theory**: Since in both conditions, circulating pro-inflammatory immune factors were described, they might induce or maintain the inflammation in the duodenum and the stomach. Mucosal committed immune cells, post-translational modified proteins, proinflammatory cytokines and lymphokines and antibodies/autoantibodies are circulating via the blood/lymphatic vessels, potentially affecting remote areas, like the stomach or duodenum [25].

c. **Gastric gluten digestion in *Hp* gastritis**: CD is triggered by the ingestion of gluten, digestion of which may be based on the pH and status and function of the gastric mucosa. Abnormal digestion may influence prevalence and intensity of LD in CD patients.

4. Is *Hp* Protective against CD?

Recent cross-sectional studies revealed that *Hp* carriers had a decreased risk of developing immunological diseases, such as inflammatory bowel diseases, asthma and some other atopic diseases. Several recent observations alluded to the protective effect of gastric *Hp* infection on CD incidence [26,27]. Epidemiologically, increased CD prevalence in the United States coincides temporally with declining *Hp* prevalence. If those observations are confirmed, *Hp* gastric colonization should prevent or attenuate LD associated with CD.

5. Unresolved Questions

A plethora of unanswered and unresolved questions exist. Following are some of them:

1. The clinical implications of the above mentioned gastric histologic abnormalities, and how they may affect the natural history of CD, are not known.
2. We do not know if gastritis preceded CD, occurred synchronously, or appeared subsequent to the development of villous atrophy. It therefore cannot be determined whether LG triggers CD in certain individuals, is a consequence of gluten exposure, or reflects an autoimmune process that is independent of CD activity.
3. We have no information about the clinical significance of non-Helicobacter gastritis.
4. Questions arise about the influence of gastric pathology on digestion, drug metabolism or the

microbiome as well on the long-term effect on general health of an individual.

5. In recent years there has been consideration that long term blocking of gastric acid production by PPIs may have a deleterious effect on health. Since *Hp*+ and CD patients chronically consume acid suppressive drugs, those effects disserve more studies.

6. Conclusions

Multiple observations strengthen the gut–stomach axis in CD-*Hp* cross-talks. LG in *Hp* negative and LD in non-celiac patients are etiologically, pathophysiologically and therapeutically challenging. Understanding the gut-stomach axis in *Hp*-CD interrelationship can open avenues of research regarding the role of the stomach in the pathogenesis of CD. Further interrogation of these pathways will provide a greater understanding and guide us to develop novel therapeutic approaches in chronic infections induction of autoimmumnity.

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