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Role of Active Inflammatory Mediators in Helicobacter Pylori Associated Chronic Gastritis in Children

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Annotation: To evaluate the efficacy of triple eradication therapy versus symptomatic therapy in children with Helicobacter pylori–associated chronic active gastritis. The aim of this study was to show whether there is a relationship between fecal calprotectin levels and Helicobacter pylori (H pylori) gastritis in children and to determine the association of fecal calprotectin levels with gastric biopsy results in terms of chronic inflammation and neutrophil activity.

Keywords: gastritis, child, gastrointestinal disease, helicobacter pylori, infection, celiac disease, gastroenteritis.

Methods: Symptomatic patients with *H pylori* (n = 41) were randomly assigned into two groups: (1) patients infected with *H pylori* who were treated with triple eradication therapy (n = 22); and (2) patients infected with *H pylori* who were treated with symptomatic therapy (n = 19)

Persistent stomach infection with Helicobacter pylori causes chronic mucosal inflammation (gastritis), which is widely recognized as an essential precursor to gastric cancer. The IL-1 interleukin family cytokines IL-1β and IL-18 have emerged as central mediators of mucosal inflammation. Here, we review the regulation and functions of these cytokines in H. pylori-induced inflammation and carcinogenesis. Upon infection, *H. pylori* interacts with host cells within the gastric mucosa, resulting in activation of multiple innate immune signaling pathways, leading to pro-inflammatory cytokine production and immune cell recruitment [1]. The Interleukin-1 (IL-1) family comprises 11 cytokines that act as important mediators of host mucosal immune responses against microbial pathogens . Two of these members, IL-1β and IL-18, have been shown to recruit innate immune cells, direct adaptive immune responses and modulate tissue homeostasis, thereby determining the outcome of *H. pylori* infection. Moreover, genetic polymorphisms in the *IL1B* and *IL18* genes strongly correlate with an increased risk of *H. pylori*-associated diseases. El-Omar et al. showed that polymorphisms in the promoter region of the *IL1B* gene are associated with higher secretion levels of IL-1β and gastric atrophy, leading to carcinogenesis. In addition, certain *IL18* genetic variants were reported to determine the susceptibility to *H. pylori* infection in the Korean population. Despite the important roles of IL-1β and IL-18 in *H. pylori*-related disease, our understanding of the cellular and molecular processes involved are still poor. This review will discuss recent findings on the regulation and physiological functions of these cytokines in *H. pylori*-induced inflammation and gastric cancer [2].

The Sydney System of classification and grading of gastritis, first created in 1994 and subsequently upgraded in 1999, provides pathologists with a framework to review gastric biopsies in a reproducible manner. However, due to the lack of a universally accepted number of mononuclear inflammatory cells in the gastric mucosa, the definition of chronic inflammation is vague. This has resulted in the use of interchangeable terms like “mild chronic gastritis” (MCG) or “non-specific gastritis” (NSG), which are often noted on histopathology reports, but have questionable clinical relevance.

It is known that HP can actively recruit macrophages, monocytes and dendritic cells to the gastric mucosa. HP forces these cells to secrete pro-inflammatory cytokines and chemokines, causing inflammation and gastric mucosal injury. Several studies report the influence of HP infection on the macrophage polarization due to promotion of free radicals induced oxidative processes [1]. According to the results of a number of research studies, bacterial factors contribute to the increased production of reactive oxygen species and hypoxia-inducible factor 1 a. Furthermore, HP is able to synthesize large amounts of inducible nitric oxide synthase (iNOS), contributing to macrophage polarization into M2 phenotype, which, in contrast to M1, exhibit a rather low phagocytic activity, thus facilitating the further pathogen persistence [4].

Gastritis is a histological diagnosis, characterized by the presence of inflammatory cells, identified on endoscopic gastric biopsies; gastropathy, on the other hand, is a term used to describe abnormalities in the gastric mucosa that can be identified on endoscopy, with or without histological changes. The most common cause of chronic gastritis in children is Helicobacter pylori infection. Other less frequent causes include systemic stress, bile reflux, non-steroid anti-inflammatory drug use, Crohn’s disease, eosinophilic disease, autoimmune gastritis, lymphocytic gastritis, and rarely Zollinger-Ellison Syndrome.

It has been noted that in children of the first year of life, stool liquefaction occurs when the rules for introducing complementary foods are violated; in children who are only breastfed - if the mother's diet is violated. In addition, the process of teething in young children can also be accompanied by diarrhea. There is an opinion that age-related inhibition of the lactase enzyme is associated with the excitation of genes responsible for dentition, which causes stool thinning in the baby [4].

Chronic HP-associated gastritis is accompanied by the dynamic increase in the size of the general monocyte/ macrophage population, since it is known that HP actively triggers the cytokine cascade playing a vital part in realization of chronic inflammatory and destructive processes in the gastric mucosa [2]. During the acute inflammatory response, macrophages are usually polarized into M1 phenotype by interferon-y and microbial products, such as lipopolysaccharide, and exhibit strong antimocrobial activity due to production of bactericidal components (nitric oxide and oxygen radicals) [1]. However, this bacterium can inhibit the effects of active substances produced by macrophages due to neutralizstion of these substances with catalase and superoxide dismutase, which provides survival of the bacteria. However, the reactive oxygen species, abundantly secreted by macrophages, cause the death of the gastric mucosal cells, which contributes to the risk of atrophy.

It is well established that full-length pro-IL-1β and pro-IL-18 are not biologically active and, due to the absence of a signal peptide, cannot be secreted into the external cell compartment through the canonical endoplasmic reticulum and Golgi pathway. The processing and secretion of mature/active cytokines remain unclear, but it is speculated to require a “second signal” that induces the formation of protein complexes, collectively known as “inflammasomes”.

Inflammasome complexes serve as platforms to recruit pro-caspase-1, which undergoes proteolysis and becomes subsequently active. As a result, active caspase-1 cleaves precursor IL-1β and IL-18 into their mature forms, which are secreted and then able to exert their biological functions on target cells.

In innate immune cells, H. pylori was reported to induce both the priming and second signals required for IL-1β and IL-18 secretion. The formation of inflammasome complexes involves the participation of NLR family members, including several belonging to the pyrin domain (PYD)-containing subfamily, as well as the interferon-inducible protein, absent in melanoma 2 (AIM2). Upon activation by ligand, PYD-containing proteins (i. e. NLRP1, NLRP3, NLRP6, AIM2) oligomerize and bind to apoptosis-associated speck-like protein containing a CARD (ASC) through homotypic PYD–PYD interactions. ASC molecules form “ASC specks” and link the PYD domain of the NLR or AIM2 sensors to the CARD domain of pro-caspase-1, resulting in cleavage of pro-caspase-1. On the other hand, ASC is dispensable for inflammasome formation by the NLR family member NLRC4, which detects bacterial flagellin or rod proteins delivered by type III or type IV secretion systems. Instead, NLRC4 was shown to directly recruit and activate pro-caspase-1 through homotypic CARD–CARD interactions

The bacterium Helicobacter pylori leads to the launch of the cytokine cascade. In our study, we studied the performance of some cytokines (IL-2, IL-4, IL-8, TNF-a, interferon-y) in patients with chronic gastritis and chronic atro-phic gastritis in the background of Helicobacter pylori infection. In all groups of patients with chronic gastritis and chronic atrophic gastritis with H. pylori infection, an increase in pro-inflammatory (IL-2, interferon-y, IL-8) and anti-inflammatory (IL-4) cytokines was recorded [3].

Histamine receptors are involved to regulate lipid metabolism, so the hypothesis will arise that pathological states with abnormal histamine levels are associated with altered plasma lipids. Objectives: To study the profile of plasma lipids in patients with gastritis and peptic ulcer (GPU). Methods: In a case-control study, 70 dyspeptic patients were selected according to clinical criteria and using gastroduodenoscopy and compared with sex and age matched normal subjects. Results: There were no significant differences in age, sex, and the prevalence of hypertension and diabetes between two groups. But allergy, the familial history of allergy and dyspeptic and H. pylori infection were more prevalent in case group compared with controls. The levels of the indices of inflammation and body hydration were the same in two groups. Patients with dyspeptic compared with the controls had the lower concentrations of serum.

Therefore, the attentions have been paid mainly on H. pylori infection and the role for histamine has been ignored. They concluded that H. pylori infection has extra gastric metabolic effects such as modifying lipid metabolism which may play a role in promoting atherosclerosis [3, 5]. Nevertheless, the findings are controversial and do not offer any mechanism. Moreover, they do not show a causative relationship between H. pylori infection and plasma lipids.

It is generally thought that gastric inflammatory responses are in large part mediated by H. pylori delivery of virulence factors into host cells via a type IV secretion system (T4SS). The H. pylori T4SS is a pilus structure encoded by the cag pathogenicity island (CagPAI) that consists of approximately 30 genes. In vivo studies in the Mongolian gerbil model showed that infection with H. pylori strains possessing an intact T4SS led to more severe gastric immunopathology and development of precancerous lesions than that caused by T4SS-defective strains. The H. pylori T4SS delivers bacterial effector molecules into host cells, specifically the Cytotoxicity-associated gene A (CagA) protein and cell wall peptidoglycan (PGN) fragments, known as muropeptides.

Chronic H. pylori-associated gastritis is accompanied by the dynamic increase in the size of the general macrophage population with the progression of atrophic and metaplastic processes. Atrophic gastritis and adenocarcinoma are characterized by vector redistribution of macrophages into the 2nd functional type. Increased expression of CD163 marker of monocytes/macrophages can serve as a predictor of chronic gastritis malignancy together with histological study of the glandular epithelium atrophy and metaplasia degree.

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