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THE ROLE AND PLACE OF LACTOFERIN IN THE IMMUNE RESPONSE TO GASTRODUODENAL DISEASES ASSOCIATED WITH HELICOBACTER PYLORI IN CHILDREN

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Abstract. *Introduction* The significant prevalence of gastroduodenal diseases, including those with an asymptomatic course [1,2] highlights the necessity of investigating the specific features of their pathogenesis to optimize diagnosis and treatment.

Purpose: To study the role of lactoferrin as a component of the immune response in diseases of the upper gastrointestinal tract associated with H. pylori in children.

Methods. The study included 60 patients aged 9 to 17 years. The first subgroup included 30 children (mean age 14.72±1.9 years) with morphological changes in the gastroduodenal region associated with H. pylori. The second subgroup included 30 children (mean age 14.76±2.5 years) with morphological changes in the gastroduodenal region not associated with H. pylori. The control group consisted of 20 conditionally healthy children, representative for age and gender. For diagnosis, endoscopic, laboratory, and histological examinations were performed.

Results. Serum lactoferrin levels in children in the study group were six times higher than those in the control group ($p<0.05$). Peptide levels increased fourfold in erosions and sevenfold in ulcers compared to the control group ($p<0.05$).

The increase in lactoferrin levels corresponded to the severity of the inflammatory process, which was independent of the presence or absence of H. pylori infection. This was confirmed by a direct correlation between lactoferrin levels and inflammatory activity ($r=0.51$, $p<0.05$). Serum iron levels did not differ between subgroups 1 and 2. A negative relationship was established between lactoferrin levels and serum iron ($r=-0.33$, $p<0.05$). A relationship was demonstrated between the occurrence of false-negative SHUT results and gastric acidity and lactoferrin levels.

Conclusions. Chronic inflammation of the upper gastrointestinal mucosa and its compromised integrity are accompanied by elevated serum lactoferrin levels, which is likely due to its protective effect. Elevated lactoferrin levels are associated with decreased urease activity of H. pylori, indicated the peptide's possible influence on the bacterial enzymatic activity and can be used to optimize infection diagnostics.

Key words: children, adolescent, lactoferrin, immune system, Helicobacter pylori, gastroduodenal region, diagnostics, peptic ulcer.

Роль та місце лактоферину в імунній відповіді на гастродуоденальні захворювання, пов'язані з Helicobacter pylori, у дітей

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Резюме. *Вступ.* Значна поширеність гастродуоденальних захворювань, зокрема тих, що мають безсимптомний перебіг [1,2], підкреслює необхідність дослідження особливостей їх патогенезу для оптимізації діагностики та лікування.

Мета дослідження. Дослідити роль лактоферину як складової імунної відповіді при захворюваннях верхніх відділів шлунково-кишкового тракту, асоційованих із H. Pylori, у дітей.

Матеріали та методи. У дослідження включено 60 пацієнтів віком від 9 до 17 років. До першої підгрупи увійшли 30 дітей (середній вік 14,72±1,9 року), що мали морфологічні зміни гастродуоденальної зони, асоційовані з H. pylori. Друга підгрупа включала 30 дітей (середній вік 14,76±2,5 року), які мали морфологічні зміни гастродуоденальної зони, неасоційовані з H. pylori. Групу контролю склали 20 умовно здорових дітей, репрезентативних за віком і статтю. Для діагностики було проведено ендоскопічне, лабораторне та гістологічне дослідження.

Результати досліджень. Встановлено, що рівень лактоферину в сироватці крові дітей основної групи в 6 разів перевищував показники дітей групи контролю ($p<0,05$). Визначено підвищення рівня означеного пептиду при ерозіях у 4 рази, при виразках – у 7 разів порівняно з групою контрою ($p<0,05$).

Підвищення рівня лактоферину відповідало ступеню запального процесу, який не залежав від наявності або відсутності інфікування H. pylori, як підтвердження – наявність прямої кореляційної залежності рівня лактоферину та активності запального процесу (r=0,51, p<0,05). У 1 та 2 підгрупі рівні сироваткового заліза не відрізнялися. Встановлено негативний взаємозв'язок між рівнем лактоферину та сироватковим залізом (r=-0,33, p<0,05). Показано наявність залежності між виникненням хибно негативного результату ШУТ та кислотністю шлункового вмісту і рівнем лактоферину.

Висновки. Хронічне запалення слизової оболонки верхніх відділів шлунково-кишкового тракту та порушення її цілісності супроводжується підвищенням рівня лактоферину в сироватці крові, що вочевидь зумовлено його протективною дією. Підвищення рівня лактоферину асоціюється зі зниженням уреазної активності H. pylori, що вказувало на можливий вплив пептиду на ферментативну активність бактерії і може бути використаним для оптимізації діагностики інфекції.

Ключові слова: діти, підлітки, лактоферин, імунна система, Helicobacter pylori, гастродуоденальна зона, діагностика, пептична виразка.

Introduction

The significant prevalence of gastroduodenal diseases, including those with an asymptomatic course [1,2] highlights the necessity of investigating the specific features of their pathogenesis to optimize diagnosis and treatment. The bacterium H. pylori, which is prevalent both worldwide and specifically in European countries, plays a key role in the progression of these diseases [1,3]. One of the components of the immune response during inflammatory processes is the release of antimicrobial peptides from azurophilic granules of neutrophils, which includes the multifunctional glycoprotein lactoferrin [4,5]. This peptide has a bactericidal effect and implements mechanisms of action on the LPS of gram-negative bacteria, which contributes to the destabilization of microorganism membranes [6]. Lactoferrin has the ability to bind iron and limit bacteria's access to this important component of their vital activity [5].

Analyzing laboratory parameters and morphological findings in children with H. pylori-associated gastroduodenal diseases, in conjunction with assessing lactoferrin levels, will contribute to a deeper understanding of its role in the immune response to the inflammatory process associated with H. pylori. Furthermore, determining the relationship between the results of instrumental examinations and lactoferrin levels will contribute to improved diagnostics of H. pylori infection.

Purpose

To study the role of lactoferrin as a component of the immune response in diseases of the upper gastrointestinal tract associated with H. pylori in children.

Materials and methods

A total of 60 patients aged 9 to 17 years, 11 months, and 29 days (including 25 girls and 35 boys) were examined, with an average age of 14.74±2.2 years. All children were hospitalized between 2022 and 2024. If they had any relevant complaints, they underwent fibroesophagogastroduodenoscopy (FEGDS), rapid urease test (RUT), and histological examination.

In accordance with the standards of medical care "Peptic ulcer of the stomach and duodenum in adults and children" (Order of the Ministry of Health of Ukraine No. 1514 dated August 25, 2023), diagnostics and verification of the clinical diagnosis were carried out [7]. During the study, five biopsy samples were taken from different sections of the stomach for further analysis. Gastric acidity was determined by using an acidogastrometer «AGM-03».

Diagnosis of H. pylori infection was based on a rapid urease test – a commercial kit Ure Hp-test (Erba Lachema, Czech Republic) [8] and histological examination. Histological examination was performed on the prepared preparations with the PAS reaction, stained with hematoxylin and eosin, and according to Romanovsky [9].

According to the Updated Sydney System, 1994, the bacterial load of Helicobacter pylori was determined taking into account the degree of colonization density, as well as a histological assessment of the chronic inflammatory process in the gastric mucosa using a semiquantitative analysis of lymphoplasmacytic density and the activity of the inflammatory process. In the absence of lymphoplasmacytic infiltrate and neutrophils, minimal inflammatory changes were detected [10].

In this regard, the main group consisted of 60 children with gastroduodenal diseases. Chronic gastroduodenitis was diagnosed in 34 patients (56.7%), and gastric or duodenal ulcers were diagnosed in 26 patients (43.3%). In 19 patients (31.7%), the development of ulcers or erosions occurred without association with H. pylori, indicating a different etiology for these changes.

The division into 2 subgroups was performed depending on the presence of H. pylori infection. It should be emphasized that the results of the rapid urease test (RUT) differed from the histological examination data. The rapid urease test allowed us to establish the presence of H. pylori infection in 20 (33.3%) children, a negative result occurred in 40 (66.7%) children, a false negative result occurred in 10 (16.7%) cases. The first subgroup included 30 children (mean age 14.72±1.9 years) with morphological changes in the gastroduodenal region associated with H. pylori. The second subgroup included 30 children (mean age 14.76±2.5 years) who had morphological changes in the gastroduodenal region not associated with H. pylori. The control group consisted of 20 children who did not have morphological changes according to the histological examination method and were representative in terms of age and gender.

In children of subgroup 1 – with gastroduodenal diseases associated with H. pylori, chronic gastroduodenitis was present in 23 (76.7%) patients. Mucosal integrity was compromised in 7 (23.3%) children: duodenal bulb ulcer was diagnosed in 1 (3.3%) child, gastric body erosions in 6 (20%) children. According to histological examination, chronic inflammation was mild in 10 (33.3%) children, moderate in 17 (56.7%), and severe in 3 (10%) children.

Out of 30 children in subgroup 2 – those with gastroduodenal diseases not associated with H. pylori – chronic gastroduodenitis was present in 11 (36.7%) patients. Mucosal integrity impairment was detected in 19 (63.3%) children, including gastric or duodenal ulcers (DU) diagnosed in 8 (26.7%) patients and gastric body erosions in 11 (36.7%) children. Histological examination revealed mild chronic inflammation in 12 children (70.6%), moderate chronic inflammation in 5 (29.4%) children, and minimal inflammatory changes in 13 (43.3%) children.

The level of lactoferrin in blood serum was determined by the ELISA method using a commercial kit Human LTF/LF (Lactoferrin) ELISA Kit, manufactured by Elabscience Biotechnology, USA.

Mathematical analysis and statistical processing of data were performed on a PC using a licensed software package Statistica for Windows 13.0, serial number JPZ8041382130ARCN10-J with the definition of the arithmetic mean (M), standard deviation (σ) and mean errors (m) for indicators, the distribution corresponding to the criteria of normality.

The Pearson χ^2 test was used to analyze the relationships between categorical variables. The relationships between indicators were assessed using Spearman's rank correlation (r). The Student's t-test was used to assess differences in indicators between the compared groups. Differences were considered significant at $p<0.05$.

The Bioethics Commission of the Zaporizhzhia State Medical and Pharmaceutical University approved the examination protocol based on the ethical principles set out in the Belmond Report of April 18, 1979. The protocol meets the bioethical standards defined in the Helsinki Declaration adopted by the General Assembly of the World Medical Association, the Council of Europe Convention on Human Rights and Biomedicine (1977), as well as the requirements of the World Health Organization, the International Council of Medical Scientific Societies, and the International Code of Human Rights.

Results

According to the results of the study, it was established that the level of lactoferrin in the blood serum of children in the main group was within the range of 11.3±0.8 ng/ml, which was 6 times higher than the level in children in the control group – 1.9±0.34 ng/ml ($p<0.05$).

Given the heterogeneity of the main group, primarily in the presence of H. pylori, the lactoferrin level was examined considering the identified subgroups. The lactoferrin content in the blood serum of children in the first subgroup, that is, in patients with Hp-associated diseases of the upper gastrointestinal tract, was the highest among all groups of children studied and amounted to 13.4±1.1 ng / ml ($p<0.05$). It was noteworthy that the lactoferrin level in children in the second subgroup was significantly lower (8.6±1 ng / ml, $p<0.05$) and statistically exceeded the indicators of the control group (1.9 ± 0.3 ng / ml, $p<0.05$).

When comparing data based on the depth of mucosal damage, the following results were obtained. Lactoferrin levels in erosions and ulcers arising from minimal inflammatory changes were 4 times higher than in the control group, at 7.9±1.05 ng/ml. Lactoferrin levels in ulcers and erosions associated with inflammation were 1.7 times higher, at 12.73±1.8 ng/ml ($p<0.05$). Further analysis revealed that lactoferrin levels also differed in children with upper gastrointestinal mucosal defects. Indeed, we observed a dynamic change in lactoferrin levels depending on the degree of mucosal damage. In children with ero-

sive lesions, its content was significantly lower (7.45±0.8 ng/ml) compared to the level of lactoferrin in children who had ulcers (13.9±1.7 ng/ml, p<0.05).

Considering the physiological role of lactoferrin as a member of the antimicrobial peptide family, we compared serum lactoferrin levels in children with established degrees of chronic inflammation, specifically with the level of lymphoplasmacytic infiltration and activity of inflammatory process. The results are presented in Table 1.

Table 1

Serum lactoferrin levels with different morphological changes in children with diseases of the gastroduodenal region (M±m)

Parameter	Main group n=60	Subgroup 1 n=30	Subgroup 2 n=30	Control group, n=20
Lymphoplasmacytic infiltrate (points)	1,5± 0,1	1,8 ± 0,1	1,3 ± 0,1*	0
Activity of inflammation (points)	1,3± 0,1	1,5±0,1	1±0,1*	0
Lactoferrin level (ng/ml)	11,3 ± 0,8	13,4±1,1	8,6±1*	1,9±0,3
Lactoferrin/lymphoplasmacytic infiltrate ratio (a.u.)	7,5±0,4	7,4±0,4	6,6±0,3	-
Lactoferrin/activity of inflammation ratio (a.u.)	8,7±0,3	8,9±0,4	8,6±0,3	-

*Note. * – p<0,01 – compared with the parameters of subgroup 1.*

As can be seen from the data presented in Table 3, higher inflammation levels corresponded to increasing lactoferrin levels. This trend was maintained in both subgroups. However, calculating the lactoferrin ratio to the inflammatory activity index and the degree of lymphoplasmacytic infiltration revealed a slightly different picture. The calculated ratios showed that the level of lactoferrin synthesis corresponded to the degree of inflammation, emphasizing the protective role of this antimicrobial peptide, independent of the presence or absence of H. pylori infection. This hypothesis is supported by the presence of a direct correlation between lactoferrin levels and inflammatory activity (r=0.51, p<0.05).

The next step in our work was to analyze laboratory parameters. Serum iron levels in children in the main group were within the range of 11.45±1 μmol/L, which was 33% lower than in the control group (17.1 μmol/L). Serum iron levels in subgroups 1 and 2 were virtually identical, at 12.3±1.1 μmol/L and 10.6±1.1 μmol/L, respectively. Lactoferrin levels showed a negative correlation with serum iron (r=-0.33, p<0.05). We also found a positive correlation between bacterial load and serum iron levels (r=0.57, p<0.05). When comparing the results of the pH assessment of gastric contents, we found a negative relationship between the acidity of gastric contents and the bacterial load of H. pylori (r=-0.82, p<0.05), as well as a positive correlation between the acidity of gastric contents and the level of lactoferrin (r=-0.58, p<0.05).

Subsequently, we tested the urease activity of H. pylori. A rapid urease test (RUT) is a diagnostic method based on the determination of the microorganism's urease activity. A negative RUT result, when bacteria are detected histologically, indicates the absence of urease and may indicate an inability of H. pylori to synthesize it.

It was established that a false-negative result of the RUT was associated with the acidity of the gastric contents (r=0.82, p<0.05). Comparison considering the RUT data showed that in the blood serum of children with the presence of H. pylori and a positive RUT result, the lactoferrin level was 10.7±1.1 ng / ml, and in children with the presence of H. pylori and a false-negative RUT result, this indicator was 1.6 times higher and amounted 17.4±0.8 ng / ml. According to further analysis, a negative relationship was determined between the lactoferrin level and the RUT result (r=-0.53, p<0.05), which probably indicates the influence of lactoferrin on the reliability of this diagnostic method.

Discussion. Lactoferrin is an acute phase protein of neutrophil origin, that is, it is released from neutrophil granules and has bactericidal and bacteriostatic properties [6,11,12]. Since lactoferrin is an important component of immune defense, its level clearly correlates with the intensity of acute and chronic inflammation [13]. At the same time, published data devoted to the

study of the role of lactoferrin in diseases of the upper gastrointestinal tract in children are rare and contradictory.

We found that the development of chronic inflammation in the upper gastrointestinal tract in children was accompanied by a marked elevation in the observed peptide level, nearly 10-fold compared to the control group. Additionally, we found that serum lactoferrin levels were clearly correlated with the degree and depth of damage to the gastrointestinal mucosa. We found a 4-fold increase in the level of this peptide in erosions and a 7-fold increase in ulcers compared to the control group. According to literature, lactoferrin has a protective effect in chemically induced ulcer models in rats, specifically, it reduces the number of mucosal defects and lowers markers of oxidative stress and inflammation, while simultaneously increasing protective factors [14].

Increased lactoferrin levels in subgroup 1, i.e., children with gastroduodenal diseases associated with H. pylori, indicated the antimicrobial properties of the peptide. Its activity against gram-negative bacteria is also confirmed by the established positive correlation between the presence of H. pylori and lactoferrin ($r=0.41$, $p<0.05$).

After calculating the ratios of lactoferrin levels to inflammatory activity and chronic inflammation indicators, somewhat different data were obtained. Thus, despite the absolute increase in lactoferrin levels in the group of children with inflammation caused by H. pylori, the relative increase in this antimicrobial peptide did not change across groups, remaining relatively stable. This finding supports the multifaceted effect of lactoferrin on the course of inflammation in the upper gastrointestinal tract.

We found a strong positive correlation between lactoferrin levels and inflammatory activity ($r=0.51$, $p<0.05$), which is likely related to its protective effect. Additionally, a moderate negative relationship was found between bacterial load and inflammatory activity ($r=-0.45$, $p<0.05$), which obviously indicates a decrease in H. pylori colonization of the gastric mucosa with greater inflammatory activity due to an enhanced immune response.

The action of lactoferrin is realized in several ways – by binding iron and by directly affecting membranes by increasing their permeability, which is consistent with our data on the determination of the presence of a feedback loop between lactoferrin and serum iron ($r= -0.33$, $p<0.05$) [13]. Furthermore, a positive correlation was observed between bacterial load and serum iron levels ($r=0.57$, $p<0.05$), confirming increased H. pylori growth in the gastric mucosa under favorable conditions, as iron plays a key role in enzyme synthesis. Moreover, the effect of lactoferrin, associated with limited access to iron, is aimed at reducing the activity of bacterial virulence factors, including urease activity [13].

The H. pylori is resistant to the effects of acid because it has a protective mechanism – urease activity, which allows the bacterium to provide a favorable microenvironment [15]. However, a negative correlation was observed between gastric acidity and the bacterial load of H. pylori ($r=-0.82$, $p<0.05$), which does not provide a cause-and-effect relationship. The hypothesis that the decrease in acidity is due to the action of H. pylori and is a consequence of intensive colonization of the stomach is unlikely, as urease activity is localized and cannot neutralize significant quantities of hydrogen ions throughout the entire gastric environment, which contains liters of acidic contents. H. pylori colonization of the gastric mucosa begins in the antrum, where acidity is lower, and therefore it is acidity that determines the ability of H. pylori to colonize more intensively [16,17]. Important data show that lactoferrin exhibits the greatest antibacterial activity at a slightly acidic pH of 5.0-6.0 and is capable of binding iron at pH values up to 3.0, which is typical for inflamed areas [6]. This explains the strong negative association between gastric acidity and bacterial load ($r=-0.82$, $p<0.05$).

The effect of lactoferrin on the enzymatic activity of H. pylori has been studied separately in recent literature. In addition to iron binding, an indirect mechanism of action on urease activity has been mentioned. A direct effect of lactoferrin has not been described, but there is information about a derivative peptide, lactofercin, which occurs as a side effect due to lactoferrin degradation by gastric pepsin and can inhibit H. pylori urease activity [18].

A false negative RUT result correlated with gastric acidity. A strong positive correlation was found ($r=0.82$, $p<0.05$), meaning that in a more acidic environment, instead of an increase in urease activity, which would be logical if the bacteria changed the pH in its favor, a decrease in urease activity was observed and, as a result, a disruption of defense mechanisms against an acidic environment. Moreover, among the protective mechanisms of H. pylori for survival in an ag-

gressive acidic environment is the ability of the microorganism to transition from a metabolically active form (S-form) to an intermediate ovoid (U-form) and then to a coccoid form (C-form) [19]. The C-form of H. pylori is resistant to increased acidity, but it is immobile, incapable of division and growth, and has reduced metabolic activity [20]. These data allow us to conclude that in an acidic environment, lactoferrin reduces the urease activity of H. pylori.

Our results may contribute to the optimization of diagnostic approaches. Correlation analysis revealed a negative association between lactoferrin levels and RUT results ($r=-0.53$, $p<0.05$), confirming the influence of this peptide on the reliability of the RUT. The reliability of the rapid urease test in children is known to be lower than in adults, meaning the diagnostic issue remains relevant. It is believed that the main cause of false positive results is a low bacterial load and uneven colonization of the gastric mucosa [21].

Conclusions

1. Chronic inflammation of the upper gastrointestinal mucosa and damage to its integrity are accompanied by elevated serum lactoferrin levels, which is clearly due to its protective effect. In cases of gastrointestinal diseases associated with H. pylori, its action as an antimicrobial peptide is realized, aimed at eliminating the pathogen.

2. An increase in lactoferrin levels is associated with a decrease in the urease activity of H. pylori, which indicated a possible influence of the peptide on the enzymatic activity of the bacterium and can be used to optimize the diagnosis of infection.

Conflict of interest: The authors report the absence of any conflict of interest.

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