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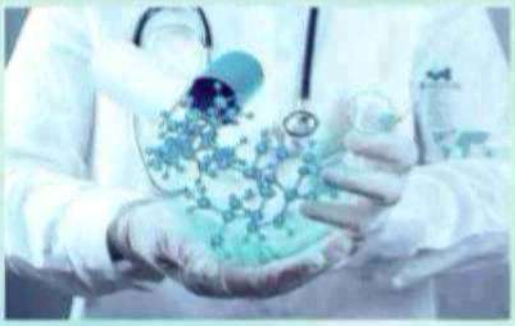

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MULTI-FACTOR ETIOPATHOGENESIS OF GASTRIC AND DUODENAL PEPTIC ULCER DISEASE

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✓ ***Resume***

Gastric and duodenal peptic ulcer disease is a multifactorial pathology, in the etiopathogenesis ofwhich the general and local reactions of the body to external and internal risk factors play a role. Psychoemotional stress is the main cause of the pathology of nervous and humoral regulation (general reaction), and the local reaction is expressed in a violation of the ratio between the factors of aggression and protection factors in the mucous membrane of the stomach and / or duodenum. The combined action of these components leads to the formation of an ulcerative defect.

Key words: peptic ulcer disease, factors of aggression and protection factors, acid-peptic factor, Helicobacter pylori, heredity, stress

МНОГОФАКТОРНЫЙ ЭТИОПАТОГЕНЕЗ ЯЗВЕННОЙ БОЛЕЗНИ ЖЕЛУДКА И ДВЕНАДЦАТИПЕРСТНОЙ КИШКИ

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✓ ***Резюме***

Язвенная болезнь желудка и двенадцатиперстной кишки представляет собой многофакторную патологию, в этиопатогенезе которой важную роль играют как общие, так и местные реакции организма на внешние и внутренние факторы риска. Психоэмоциональный стресс является основной причиной нарушения нервной и гуморальной регуляции (общая реакция), тогда как местная реакция выражается в нарушении соотношения между факторами агрессии и факторами защиты в слизистой оболочке желудка и/или двенадцатиперстной кишки. Совместное действие этих компонентов приводит к формированию язвенного дефекта.

Ключевые слова: язвенная болезнь, факторы агрессии и защиты, кислотно-пептический фактор, Helicobacter pylori, наследственность, стресс.

OSHQOZON VA O‘N IKKI BARMOQLI ICHAK YARA KASALLIGINING KO‘P OMILLI ETIOPATOGENEZI

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✓ ***Rezyume***

Oshqozon va o‘n ikki barmoqli ichak yara kasalligi ko‘p omilli patologiya bo‘lib, uning etiopatogenezida tashqi va ichki xavf omillariga organizmning umumiy hamda mahalliy reaksiyalari muhim rol o‘ynaydi. Psixoemotsional stress nerv va gumoral regulyatsiya patologiyasining asosiy sababi (umumiy reaksiya) hisoblanadi, mahalliy reaksiya esa oshqozon va/yoki o‘n ikki barmoqli ichak shilliq qavatida agressiya omillari bilan himoya omillari o‘rtasidagi nisbatning buzilishi orqali namoyon bo‘ladi. Ushbu komponentlarning birgalikdagi ta’siri yara nuqsonining shakllanishiga olib keladi.

Kalit so‘zlar: yara kasalligi, agressiya va himoya omillari, kislota-peptik omil, Helicobacter pylori, irsiyat, stress.

Relevance

Peptic ulcer disease of the stomach and duodenum (PUD) is a chronic, polyetiological, and recurrent disease. The development of this condition is based on complex nervous, hypothalamic–pituitary, hypothalamic–pituitary–adrenal, and local gastroduodenal mechanisms that lead to trophic disturbances in the gastric and duodenal mucosa [1].

The morphological substrate of PUD is a recurrent ulcer of the stomach or duodenum [2].

There are numerous risk factors and causes that contribute to the development of ulcerative defects: stress; infection with Helicobacter pylori (H. pylori); intake of medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, bisphosphonates, and immunosuppressants; pathology of nervous and/or humoral regulation; endocrine disorders; Zollinger–Ellison syndrome; age-related decline in prostaglandin levels; excessive gastric acid secretion (acid-peptic factor); circulatory and hypoxic lesions; disturbances in diet and meal patterns (dry meals, eating "on the go," late dinners, long intervals between meals, consumption of very hot and/or cold food, excessive intake of salty foods, spicy seasonings and condiments, meat broths, chocolate, strong coffee and tea); alcohol use; smoking; biliary reflux; toxic and allergic lesions; and heredity [2–14].

The mechanism of ulcer disease development is quite complex. In its pathogenesis, an important role is played by both general and local reactions of the organism to the combined influence of various risk factors [1].

The general reaction consists of pathology of nervous and humoral regulation. The coordinating role of the cerebral cortex over subcortical structures—the intermediate brain and hypothalamus—is disrupted. This leads to excitation of hypothalamic–pituitary centers and increased vagal tone. The effect of the vagus nerve is realized through an increase in acid-peptic activity and disturbances in gastric and/or duodenal motility. When gastric emptying accelerates or when pyloric contractions become irregular, the contact time between hydrochloric acid and the buffering components of food is reduced, allowing active gastric juice to enter the duodenal lumen. In another scenario, the rate of gastric emptying does not change, but the passage of chyme through the duodenum slows down, resulting in duodenostasis. In both cases, an ulcer defect forms, localized mainly in the pyloroduodenal region [1, 15, 16].

According to the Global Burden of Disease (GBD) 2023 data, peptic ulcer disease affects about 8–10% of the adult population, or roughly 8.4 million people worldwide each year. The infection with Helicobacter pylori is detected in 70–90% of patients with duodenal ulcers and in 50–70% of patients with gastric ulcers. The use of NSAIDs and low-dose aspirin contributes to about 20–25% of new ulcer cases, particularly among the elderly.

The annual incidence of ulcer disease is estimated at 0.1–0.3% of the global population. The recurrence rate after treatment remains around 5–15% per year, depending on the effectiveness of eradication therapy and lifestyle modification. Complications such as bleeding, perforation, and stenosis occur in 10–20% of all ulcer cases, with ulcer bleeding causing 5–10% mortality, especially in older patients with comorbidities.

In Central Asia, including Uzbekistan, the prevalence of peptic ulcer disease reaches 9–12%, with H. pylori infection rates exceeding 70% among adults.

Pathophysiology:

Thus, peptic ulcer disease of the stomach and duodenum is a multifactorial pathology resulting from the combined influence of systemic neurohumoral disturbances and local mucosal defense impairment. Despite advances in acid suppression and eradication therapy, risk factors such as stress, NSAID use, smoking, and dietary habits continue to sustain the high prevalence of this disease worldwide.

In gastric body ulcers, the hypothalamic–pituitary centers are suppressed, and the tone of the vagus nerve decreases. The activity of the acid-peptic factor and gastric motility are reduced or remain unchanged, while local pathogenic factors play a decisive role in the development of the disease [1, 15].

Etiology

Many authors consider that the triggering factor in the development of peptic ulcer disease is psychoemotional stress, to which individuals with a high level of anxiety and predominance of astheno-depressive traits are particularly susceptible. These problems arise, for example, in various conflict situations, during military actions, with prolonged pain syndrome, overwork, and lack of sleep [1, 4, 10, 15–19].

In stress-induced ulcers, the mucous membrane of the stomach and duodenum is damaged secondarily in relation to other acutely developing severe diseases. For example, Curling's ulcers are secondary to systemic burns, and Cushing's ulcers – to acute traumatic brain injuries. Most often, stress ulcers form in the body and fundus of the stomach, but they also occur in the antral part of the stomach and in the duodenum. The main risk factors for the development of this type of ulcers are: artificial ventilation of the lungs for more than 48 hours, coagulation abnormalities (decrease in the number of platelets), sepsis and septic shock, use of vasopressors and large doses of steroids, hepatic, renal, multiple organ failure, burn injuries of more than 30% of the body surface, head trauma, gastrointestinal bleeding during the previous year. Their cause may also be the damaging effect of bile salts and uremic toxins on the mucous membrane [20].

The local reaction of the organism during the development of the disease is usually represented as a model called "Shea's balance," according to which the disease occurs when the balance between the protective and aggressive factors shifts toward the predominance of the latter [16, 21, 22]. The aggressive factors include infection with H. pylori, increased activity of the acid-peptic factor, and the use of medications (mainly NSAIDs). The protective factors include bicarbonates, prostaglandins, the mucous barrier, and adequate blood circulation of the mucous membrane [11, 13].

An increase in the activity of the acid-peptic factor occurs both as a result of disturbances in nervous-humoral regulation (as mentioned above) and as a result of hereditary (hyperplasia of parietal cells and an increase in the number of gastrin-producing cells) and external (smoking, alcohol consumption, disturbance of diet and nutritional structure) risk factors. The principle of K. Schwarz "no acid – no ulcer" underlies both therapeutic (pharmacotherapy with antacids, cholinolytics, proton pump inhibitors, H2-histamine receptor blockers) and surgical (vagotomy, subtotal gastrectomy) methods of treatment of peptic ulcer disease [3, 15, 21].

According to modern epidemiological data, stress-related and secondary ulcers account for about 5–10% of all peptic ulcer cases. The incidence of Curling's ulcers among patients with severe burns exceeds 20–25%, while Cushing's ulcers occur in up to 15% of patients with traumatic brain injury. Among critically ill patients in intensive care units, stress ulcers develop in 75–100% of cases without preventive therapy, although only 5–10% lead to clinically significant bleeding due to the widespread use of proton pump inhibitors and H2 blockers. Mortality associated with ulcer bleeding in intensive care patients remains at 15–20%, especially in those with multiple organ failure. Helicobacter pylori infection continues to affect more than 50% of the world's population, playing a role in 60–70% of all ulcer cases, while NSAID-induced ulcers account for about 25% of new cases each year.

The main aggressive factor is the spiral-shaped bacterium Helicobacter pylori (H. pylori), discovered by B. Marshall and R. Warren in 1983. For a long time, peptic ulcer disease was considered a manifestation of a local reaction to bacterial infection, and the most radical gastroenterologists claimed that without H. pylori, the development of the disease was impossible, and that the main therapy should be aimed at eradication of the pathogen. However, this postulate cannot explain the occurrence of H. pylori–negative forms of the disease [3, 7–9, 15, 23].

On the other hand, H. pylori infection affects more than 60% of the population, while only 10–15% suffer from peptic ulcer disease. From this, it can be concluded that H. pylori plays a role in the pathogenesis of ulcer disease but is not its only cause [15, 16, 21, 24].

Initially, H. pylori was a commensal microorganism, i.e., a representative of the conditionally pathogenic microflora. However, as a result of the uncontrolled use of antibacterial drugs, resistant strains emerged, carrying cytotoxicity genes such as cytotoxin-associated gene A (CagA) and vacuolating-associated cytotoxin A (VacA) [15, 21].

H. pylori resides in the layer of supraepithelial mucus and, using its flagella, reaches the epithelial cells of the gastric mucosa. The enzyme mucinase (protease) destroys the glycoproteins of gastric mucus, providing access to epithelial cells. Through the enzyme urease, H. pylori breaks down urea into ammonia, which forms a "cloud" that protects the bacteria from the acidic gastric environment [12, 15].

Although hydrochloric acid is a factor of aggression, it suppresses H. pylori activity in the gastric body, causing the bacteria to colonize the antral part of the stomach and induce inflammation. Gastric secretion changes toward an increase in gastrin and chloride concentrations, which leads to acidification of the duodenal lumen and the formation of ulcers. Conversely, at low hydrochloric acid concentration, H. pylori spreads throughout the gastric mucosa, causing more extensive inflammatory lesions [3].

Epithelial cells of the gastric mucosa respond to the invasion of H. pylori by secreting cytokines (interleukin-1, tumor necrosis factor-alpha). Interleukin-1 triggers the local inflammatory reaction by activating effector cells to eliminate the pathogen and repair the damaged tissue. After brief vasoconstriction mediated by thromboxane A_2 and catecholamines, vasodilation occurs through the action of nitric oxide, produced by endothelial cells in response to proinflammatory cytokines (TNF-α, IL-1, IL-6, interferon-γ) and bradykinin. Bradykinin, in turn, increases vascular permeability, promoting tissue edema [2, 12, 25–29].

Peptidergic nerve fibers involved in pain sensitivity release neuropeptides, which contribute to vasodilation, expression of adhesion molecules on endothelial and leukocyte surfaces, and enhanced cytokine production by macrophages. From damaged cytoplasmic membranes, lipid mediators are formed: prostacyclins, prostaglandins, leukotrienes, thromboxanes, platelet-activating factor, and lipid peroxides. As vascular permeability increases, pain develops at the site of inflammation [25].

Aggressive properties are also characteristic of medications, mainly nonsteroidal anti-inflammatory drugs (NSAIDs). Their role lies in inhibiting cyclooxygenase-1 (COX-1) and disrupting the synthesis of prostaglandins, which are one of the protective factors of the mucosa against ulcer formation. This pathological effect is more pronounced with the use of non-selective drugs [11, 13].

The next defense factor is the mucosal barrier, which consists of three parts: mucus (mucin and sialic acids), the epithelial lining and its membranes, and subepithelial structures. When this barrier is disrupted, the back diffusion of hydrogen ions increases, stimulating gastrin and histamine production, and causing microcirculatory and trophic disturbances of the gastric mucosa [17].

According to I.A. Litovsky and A.V. Gordienko [22], a limited ulcerative defect (necrosis) can develop only under local ischemia of the gastric or duodenal mucosa. Other etiopathogenetic factors (disturbances of gastroduodenal motility, changes in hydrochloric acid secretion, stress conditions, autonomic disorders, and irregular nutrition with long intervals between meals and dry food intake, as well as H. pylori infection) are considered auxiliary. Their role is to intensify the adverse effects of ischemia to a critical level, followed by mucosal necrosis. Impaired blood circulation in the gastric and duodenal mucosa arises from congenital (in ulcer disease) or acquired (in stress-induced ulcers) hypoplasia of small and medium-caliber vessels.

Seasonal peaks of peptic ulcer disease in autumn and spring, as well as spontaneous or drug-induced remissions during summer, are associated by the authors with the influence of the Earth's geomagnetic field, which affects cell membranes by activating or inhibiting lipid peroxidation (LPO) [22].

Products of lipid peroxidation inactivate sulfhydryl (SH) groups of enzymes, receptors, and hormones, induce histamine release from mast cells, and damage membrane lipids, increasing their permeability and leading to cell destruction and ulcer defect formation [15, 22].

At the same time, hereditary predisposition increases the body's sensitivity to external damaging factors (H. pylori, NSAIDs, stress, alcohol, smoking, poor diet). Individual features such as the number of parietal cells in the gastric mucosa, the tone of the vagus nerve, secretion of gastrin, pepsin, mucus, and bicarbonates, the quantity of IgA immunoglobulins and mucopolysaccharides, as well as the metabolism and blood circulation characteristics in gastric cells, are also genetically determined [15, 30–34].

According to current epidemiological data (2020–2025), H. pylori infection affects about 4.4 billion people worldwide, which corresponds to nearly 55–60% of the global population. However, only 10–15% of infected individuals develop peptic ulcers, indicating the role of additional environmental, genetic, and vascular factors. The prevalence of NSAID-induced ulcers is around 20–25% among all ulcer cases, particularly in elderly patients and those with comorbidities. The annual recurrence rate of H. pylori–positive ulcers is 5–10%, while complications such as bleeding or perforation occur in 10–20% of patients.

In Central Asia, including Uzbekistan, H. pylori infection prevalence reaches 70–75%, with peptic ulcer disease affecting approximately 10–12% of adults, showing a seasonal increase during spring and autumn months.

The role of hereditary predisposition is supported by data from the literature, according to which duodenal peptic ulcer disease occurs 3 to 7 times more often among first-degree relatives compared to the general population [33, 35]. The familial nature of the disease is most accurately demonstrated by twin studies. In monozygotic twins, a similar course of the disease was observed, with simultaneous

spontaneous exacerbations and complications. In dizygotic twins, this pattern was less pronounced, despite similar lifestyles and unfavorable environmental conditions [30].

Further evidence of hereditary predisposition includes early disease manifestation, a pronounced clinical picture with severe pain, serious complications, and frequent relapses [31]. Genetic and epidemiological studies have identified a number of candidate genes that play a role in the development of peptic ulcer disease:

PSCA, ABO, IL1β, IL1RN, TNFα, HSP70–1, GSR, TLR4, TLR2, TLR9, MMP-1, MMP-3, MMP-9, TIMP-3, PGC, MIF, MPO, and COX-1 [5, 6].

Discussion

Etiopathogenesis of peptic ulcer disease involves both external (stress, Helicobacter pylori infection, use of medications, dietary disturbances, smoking, alcohol consumption) and internal (disorders of neural and/or humoral regulation, endocrine abnormalities, acid-peptic factor, decreased prostaglandin levels, circulatory-hypoxic damage of the gastric mucosa, biliary reflux, and heredity) risk factors.

An important role in the development of the disease is played by both general and local reactions of the organism, which lead to a disturbance in the balance between aggressive and protective factors, resulting in trophic disorders of the gastric and duodenal mucosa and the formation of ulcerative defects.

A significant role belongs to hereditary predisposition, since it increases the body's sensitivity to external risk factors and determines individual structural and functional characteristics of the digestive, nervous, endocrine, immune, and other systems, which enhance the effects of internal etiopathogenetic mechanisms.

According to modern genetic studies (2020–2025), familial aggregation of peptic ulcer disease is confirmed in up to 35–45% of cases. The heritability coefficient for duodenal ulcer disease reaches 0.60–0.70, indicating a strong genetic influence. Specific polymorphisms in genes such as IL1β, TNFα, and TLR4 are associated with a higher risk of H. pylori-induced mucosal inflammation and ulcer recurrence. These findings emphasize that genetic susceptibility, in combination with environmental and behavioral factors, remains a key determinant in the multifactorial pathogenesis of gastric and duodenal ulcer disease.

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