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NON-SPECIFIC ULCERATIVE COLITIS: EPIDEMIOLOGY, ETIO-PATHOGENESIS AND ISSUES OF SURGICAL TREATMENT

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Abstract: Non-specific ulcerative colitis (NUC) is a chronic autoimmune inflammatory disease of the colon with a relapsing course, characterized by mucopurulent and bloody discharge from the intestine, abdominal pain and systemic manifestations. The incidence of UC has traditionally been high in Western countries, but in recent decades its growth has been observed in the regions of Asia and the CIS. The mechanisms of development of UC include genetic predisposition (many polymorphisms of interleukins and HLA), immunoregulation disorders (imbalance of Th1/Th2 response, excessive expression of TNF-α, IL-13, etc.) and dysbiosis of intestinal microbiota . The leading method of radical treatment of UC is colectomy with formation of ileoanal anastomosis (IAA), which is used in severe exacerbations and complications (toxic megacolon, uncontrolled bleeding, perforation, dysplasia/carcinoma) or in relapses refractory to therapy. Modern minimally invasive technologies (laparoscopy , robots) can reduce postoperative complications and shorten the duration of hospitalization. The review considers international and regional epidemiological data on UC, modern concepts of etiopathogenesis , clinical picture and indications for surgery, as well as modern surgical approaches and unresolved issues.

Key words: nonspecific ulcerative colitis, epidemiology, pathogenesis, surgical treatment, minimally invasive technologies, intestinal microbiota .

Introduction

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) and is characterized by a persistent, relapsing course. It is characterized by chronic inflammation of the colonic mucosa, primarily affecting the rectum and spreading further, and in severe cases, total colon involvement [1,5,6]. The disease usually debuts at a young age (15–30 years), but a secondary peak in incidence is also possible in old age. Ulcerative colitis is estimated to account for approximately 20–30% of all IBD cases and causes hundreds of thousands of visits to physicians each year; in the United States, annual direct medical costs for UC reach several billion dollars. Constant exacerbations reduce the quality of life of patients, and surgical treatment is required for a significant number of patients: according to large studies, only about 10% of patients with UC require colectomy within 20 years of diagnosis . The increase in the incidence of IBD, including UC, in countries with low and medium levels of development (Asia, the Middle East, the CIS) increases the relevance of studying this pathology at the international and regional levels [11,12,14]. In this regard, the review presents current data on the epidemiology of UC, the main pathogenetic mechanisms, clinical manifestations and indications for surgical treatment, existing approaches to surgery and prospects for further research.

Epidemiology of UC

UC is widespread, but there are significant geographical differences. The highest incidence is traditionally observed in Northern Europe and North America – up to 20–25 new cases per year per 100,000 population. For comparison, in Eastern Europe and Asia these rates are significantly lower (approximately 5–12/100,000 per year). According to meta-analyses and reviews, the current prevalence of UC in Western countries reaches 150–300 per 100,000 population. At the same time, in many regions with low incidence, a steady increase has been observed in recent decades. For example, in South Korea, the annual incidence of UC increased from 0.33 to 6.58 cases per 100,000 population during 1986–2015, and in Japan, from 0.03 to 12.2/100,000 during 1955–2014. According to the review, in East Asia, about 0.1–0.2% of the population has IBD. In South Asian countries (India, Pakistan, Sri Lanka), the average incidence is lower (several cases per 100,000).

Data for the CIS and Central Asian regions are limited. In Kazakhstan, the prevalence of UC is 84.4 cases per 100,000 population (total IBD is 113.9/100,000). In Uzbekistan and other Central Asian countries, there have been virtually no specialized epidemiological studies, so there are no accurate statistics. In general, there are few studies in Central Asia, which makes it difficult to assess the actual incidence of IBD. Thus, global trends show stabilization or a slight decrease in incidence rates in developed countries, while there is rapid growth in developing regions of the world.

Etiopathogenesis

The causes of UC are complex and include the interaction of genetic factors, immune disorders, changes in microbiota and external factors. It is generally accepted that UC develops against the background of genetic predisposition and immune regulation disorders . Thus, having a close relative with UC increases the risk of the disease by approximately 4 times. Many polymorphisms of genes associated with inflammation regulation (IL23R, IL12B, IL10, HLA, etc.) have been identified; genetic studies of recent years emphasize the influence of variations in interleukins and their receptors on the predisposition to UC.

Immunopathogenesis of UC is characterized by an excessive inflammatory response to environmental factors and microbial antigens. In UC, a predominantly Th2-type response is observed (in contrast to Th1/Th17 in Crohn's disease) - cytotoxic CD4^+^ Th2 cells are activated, levels of IL-13, as well as TNF-α and other proinflammatory cytokines are increased. Innate components of immunity play an important role: patients have been shown to have dysfunction of the epithelial barrier (impaired mucin composition and cellular contacts), as well as increased expression of TL receptors on dendritic cells of the mucosa [2,3,15,26]. Against the background of barrier impairment, commensal intestinal bacteria can provoke an excessive immune response. The result is a chronic disruption of the "microbe - immune system" homeostasis: the composition and diversity of the microbiota changes , which further stimulates inflammation and damage to the intestinal mucosa. In particular, with UC, there is a decrease in the number of beneficial bacteria (Faecalibacterium prausnitzii , etc.) and an increase in opportunistic strains, which can be both a cause and a consequence of inflammation [30,32,34].

External environmental factors also modify the risk of UC. Among them, smoking has been studied the most: interestingly, smokers are less likely to develop UC, and in former smokers, the disease often proceeds more severely [4,5,6]. Exacerbation of UC may develop upon quitting smoking. Appendectomy at a young age is associated with a decrease in the risk of UC (by about 69%). The attractiveness of the "Western" lifestyle (diet with a predominance of fats and sugars, lack of fiber) and the use of a number of drugs (NSAIDs, oral contraceptives) are discussed as potential risk factors. Thus, it is known that non-steroidal anti-inflammatory drugs often provoke relapses of UC [7,8,13,14]. The influence of warm moist infections and antibiotics, which disrupt the intestinal microbiota , is also assumed . Together, all these factors contribute to the

high variability of the course of UC, but the exact mechanisms are still not fully understood.

Clinical picture and indications for surgery

UC is characterized by a chronic remitting course with acute and latent phases. The main symptoms are diarrhea with blood and mucus, abdominal pain (usually in the left iliac region), tenesmus and false urges (imperative urges without evacuation). Non-specific manifestations are often added - weight loss, subfebrile temperature, anemia, general weakness [18,21,22,30]. The course of UC is variable: from proctitis, in which only the rectum is affected (which occurs in 30-60% of patients at debut), to left-sided colitis (16-45%) and total (pancolitis) (14-35%). On examination, the intestine looks "fragile", with an erased vascular pattern, erythematous and ulcerated areas, evenly spreading from the rectum to the proximal parts. Important markers of activity are elevated ESR, CRP, leukocytosis, and in 60–70% of cases, the presence of perinuclear ANCA (p-ANCA) [9,10,11,18]. UC is often accompanied by extraintestinal manifestations: 10–30% of patients develop arthritis, eye inflammation (episcleritis , uveitis), skin diseases (erythema nodosa , pyoderma gangrenosum), and other inflammations associated with colitis activity. Chronic UC is associated with primary sclerosing cholangitis (PSC), which increases the risk of colorectal cancer.

Despite the improvement of medical treatment (5-aminosalicylates, glucocorticoids, immunosuppressants, biological drugs), a significant proportion of patients sooner or later require surgical treatment [22,23,26,35,38]. Various studies note that from 10% to 30-40% of patients with UC undergo colectomy during their life . Indications for surgery are divided into emergency and planned. Emergency indications include severe complications or a life-threatening condition: acute severe colitis that cannot be relieved with medication, toxic megacolon (extensive expansion of the colon with a toxic state), massive bleeding, intestinal perforation. In such situations, an urgent subtotal colectomy is performed with the formation of an ileostomy , often with preservation of the rectum (Hartmann stages), or a proctocolectomy with an ileostomy or ileoanal anastomosis is performed immediately , depending on the patient's condition. Elective indications for colectomy include failure of long-term drug therapy (relapses after multiple courses of therapy), low quality of life with persistent symptoms, dysplasia or early colon cancer in UC. If high-grade dysplasia or cancer is detected, colorectal risk is considered an indication for total proctocolectomy with ileoanal anastomosis. The choice of surgical tactics is largely determined by the severity and extent of inflammation, as well as the general condition of the patient.

Modern approaches to surgical treatment

Surgical treatment of UC is considered radical and can lead to complete disappearance of intestinal symptoms, but surgery is a serious intervention with its own risks. In UC treatment programs, the main role is given to total proctocolectomy with the formation of an ileoanal anastomosis (IAA), which allows preserving the anal sphincter [14,17,19,25,26]. Classically, this operation is performed in 2-3 stages (to reduce the risk of taking corticosteroids): first, removal of the colon and formation of a temporary ileostomy (preservation of the rectum or its suturing), then removal of the rectum and restoration of the intestine from the ileal loop. In emergency cases, a less radical operation is often performed - subtotal colectomy with ileostomy (Hartman technique) to stabilize the patient, and then, during the second operation, complete the removal of the rectum and form the anastomosis.

In recent decades, laparoscopic technique has become the standard of preparation for colorectal surgery . Laparoscopy in UC has a proven effect of reducing postoperative morbidity, the number of early complications (including incisional infections) and shortens the duration of hospitalization [16,18,20, 31-33]. Randomized and observational studies have shown that with

laparoscopic IARA, the overall complication rate is comparable to open surgery (odds ratio ≈1.12 without statistical difference), but the duration of the operation is usually longer. At the same time, after laparoscopy, the average duration of hospitalization is significantly shorter (in the meta-analysis 11.2 ± 4.8 days versus 26.4 ± 4.3 days with open surgery). In addition, the tolerability of laparoscopy is especially important in young patients with a potentially large number of surgeries. A systematic review showed that laparoscopic intestinal restoration (IARA) provides comparable results with open access in terms of morbidity and mortality. Several studies have noted the benefit of laparoscopy in reducing the incidence of short-term complications in patients who received corticosteroids before surgery.

In addition to classical laparoscopy, robotic technologies and single-laparoscopic access are used in modern proctology. Robotic proctocolectomy allows for more precise work in the pelvis and can reduce the conversion rate in complex cases, although the final results are still limited to small series. Single-incision techniques (SILS) and trans-anal approaches are also being actively introduced for outpatient expansion of indications. An important aspect is the minimization of the number of operations and stages: in a favorable situation, one-stage IARA can be performed, but in high-risk patients (immunosuppression, active inflammation), two- or three-stage options are more often used. In general, modern surgical approaches seek to ensure complete removal of the inflammation focus and adequate intestinal reconstruction with minimal trauma.

Conclusion. Thus, despite the progress in understanding UC, many aspects remain incompletely understood. The etiology of the disease remains unclear: it is unknown which specific environmental triggers initiate the inflammatory cascade in genetically susceptible individuals and how immune and metabolic disturbances influence it. The exact role of the gut microbiota remains to be determined : although dysbiosis in UC has been documented, therapeutic methods of flora correction (e.g. faecal microbiota transplantation) have not yet become standard treatment. Genetic studies are constantly expanding the list of associated loci, but still do not explain all clinical phenotypes of UC.

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