PREDICTION OF CROHN'S DISEASE RELAPSES AND THEIR PREVENTION

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Resume

The effectiveness of the developed method for predicting recurrence of CD in the postoperative period, due to the importance of including immunological criteria, allows increasing the sensitivity of the test by 3.5 times, specificity - by 1.9 times, and the prognostic value of the method - by 3.3 times. The use of the developed treatment and diagnostic algorithm for the prevention of recurrence of CD made it possible to reduce the frequency of its development in a mild form from 31% to 27.5%, in a moderate form from 21.4% to 12.5% and completely avoid its severe forms under the influence of pathogenetically substantiated differentiated and targeted anti-cytokine, hormonal and immunosuppressive therapy.

Keywords: crohn's disease, the traditional method.

Relevance

Treatment of Crohn's disease (CD) is interdisciplinary (1,3,5,7,9,10,12,13,14,15,16,17,18,19,20). At the same time, if drug treatment of Crohn's disease is aimed at healing the mucous membrane and reducing the symptoms of the disease, then surgical intervention plays a key role in the treatment of such complications of the disease as stenosis, perforation, intestinal fistulas and abscesses of the abdominal cavity and cellular spaces (2,4,6,8,3,11,21).

Relapse of CD in the postoperative period develops in more than 80% of operated patients (12,13).

Numerous studies in this area have allowed us to develop various options for surgical strategies aimed at improving treatment results and reducing the frequency of relapse of CD in the postoperative period (6).

Some improvement in the results of surgical operations for CD was achieved after the introduction of laparoscopic technology. However, they could not affect the regression of the frequency of relapse of CD in the postoperative period (8,10). All this influenced the formation of a certain concept about the purpose of performing surgical operations for CD as creating conditions for slowing the onset of relapse, which is considered inevitable in the long term.

The aim of the study is to improve the treatment results of patients with CD by developing pathogenetically substantiated clinical and immunological criteria for predicting and preventing relapse of this disease.

Material and methods. The results of a comprehensive examination and treatment of 82 patients with Crohn's disease (CD) are analyzed. The patients were divided into 2 study groups: control (42 patients) and main (40 patients). A distinctive feature of the patient groups was the use of different approaches to predicting and preventing relapse of CD.

The study design was based on an open, cross-sectional retrospective and prospective cohort study.

All patients included in the study were operated on by us for complications of CD. In this regard, the complex of examination of patients was not only preparatory, but also dynamic, aimed at assessing the general condition of the patient, the course of the postoperative period and the features of changes in cellular and humoral immunity in CD.

For immunological studies, blood was collected from the cubital vein into a centrifuge tube treated with 5.0 ml of heparin.

Blood for immunological studies was collected in the preoperative period and on days 7, 14, 30, 90, and 180 of the postoperative period. In this case, the results obtained on days 7-14 were interpreted by us as the results of the early postoperative period, and on days 30-180 - the late postoperative period.

Instrumental diagnostic methods were mandatory. The entire range of instrumental research methods included the following methods: ultrasound examination of the abdominal organs and perineum; multispiral computed tomography with intravenous contrast and enterography; magnetic resonance imaging of the abdominal organs according to individual indications in case of questionable MSCT data; video colonoscopy with mandatory examination of the Baugin valve and the terminal ileum. This made it possible to assess the degree of CD development using a simple endoscopic scale (SES-CD).

When assessing the immediate treatment results, we used the scale developed by A.O. Okhunov and A.D. Sapaev (2018). According to this method, good, satisfactory and unsatisfactory immediate treatment results were distinguished.

Relapse of CD was determined by the appearance of typical symptoms of the disease at the stage of clinical remission - spontaneous or drug-supported.

The severity of relapse of CD was determined according to the criteria of the Society for the Study of Inflammatory Bowel Diseases at the Association of Proctologists of Russia (2009).

Results and discussion. The causes of Crohn's disease relapse and the criteria (markers) for their prediction were identified using direct and cross-correlation analysis of the obtained data, dividing them into early and late postoperative periods.

The nature of the correlation between the dynamics of changes in CD3+ and CD4+ cells in the blood in Crohn's disease in the postoperative period, both in the remission phase and in the relapse phase of the disease, did not have any special differences except for a decrease or

increase in the ratio. This nature of changes was apparently associated with the early reaction of the body's immune system in differentiating naive T-lymphocytes and T-helpers when macrophages presented primary antigens. The participation of T-suppressors in the development of a relapse of Crohn's disease was minimal, and its participation in the immune response was characterized by the general course of the postoperative period. At the same time, the activity of natural killer cells was more important already in the late postoperative period, in which we noted a high proportion of the development of a relapse of Crohn's disease. These changes were apparently associated with the active attraction of CD16+ cells to the immune response in patients with a relapse of Crohn's disease in the late period after surgery. The correlational nature of changes in T-regulatory lymphocytes and dendritic cells was multidirectional and was determined by the timing of the postoperative period in Crohn's disease.

Analysis of the dynamics of changes in blood cytokines in terms of the correlation coefficient of 15 indicators revealed the presence of a high direct relationship in the overall dynamics of the postoperative period in 10 (66.7%) cases. In the remaining 5 cases, the correlation was inverse and was associated with the dynamics of the transforming growth factor. In this case, we noted the maximum difference in the dynamics of TGF-β to IL-4 (R = -0.562) and then in descending order to TNF-α (R = -0.415), to IL-21 (R = -0.402), to INF-γ (R = -0.396) and to IL-17 (R = -0.304). An interesting fact is the identity of the dynamics of changes in TGF-β and IL-17 between patients with different phases of Crohn's disease in the late postoperative period (R = -0.932 and R = -0.980, respectively), which indicates a single mechanism of their transformation in the pathogenesis of this disease.

In Crohn's disease, there is an imbalance between Th1/Th2 cells and Th17/T-regulatory cells, the intensity of which determines the outcome of the disease in the form of remission or relapse. The basis of immunological disorders in relapse of Crohn's disease are the mechanisms of formation of an autoimmune reaction due to increased cell apoptosis against the background of expression of proinflammatory cytokines TNF-α, IL-17 and IL-21 through the induction of natural killer cells against the background of a low concentration of TGF-β. Relatively high stimulation of TGF-β production by naive T-helpers stimulates T-regulatory lymphocytes, increasing their role in the development of tissue regeneration, and, accordingly, creating favorable conditions for the onset of the remission phase of Crohn's disease.

When developing a treatment and diagnostic algorithm for the prevention of relapse of Crohn's disease, along with the results of immunological studies, it is necessary to take into account the clinical manifestations of the disease, which, based on the immediate results of treatment, can determine the likelihood of unsatisfactory results.

We have formed such a conclusion based on the purpose of the surgical treatment methods for Crohn's disease, which are primarily aimed at removing (resecting) intestinal areas that have

undergone morphostructural changes and do not allow for the normal functioning of both food passage and the digestion process as a whole. At the same time, in general, the possibility of relapse of the disease remains very high starting from the 14th day of the postoperative period, acquiring an increasing character in the dynamics of the postoperative period.

The treatment and diagnostic algorithm we have developed allows not only to predict and prevent relapse of Crohn's disease, but also to determine the timing of restorative operations, which have received more opportunities to achieve effective results.

The basis of the treatment and diagnostic algorithm for the prevention of relapse of Crohn's disease is the dynamic monitoring of the level of cytokines (TNF-α, IL-17, IL-21 and TGF-β) in the blood, as well as clinical signs of the postoperative course (frequency of stool per day, body temperature, heart rate, the presence of postoperative complications and their degree according to the Clavien-Dindo classification), which allow us to determine the level (low or high) of the probability of an attack, on the one hand, and to apply differentiated approaches to the scheme of anti-cytokine (Infliximab and Vedolizumab), hormonal (Prednisolone) and immunosuppressive (Azathioprine) therapy, on the other.

The methods for predicting and preventing relapse of Crohn's disease that we developed were used by us among patients of the main group, who did not differ from patients of the control group in their initial clinical and pathognomonic signs. The effectiveness of the criteria developed by us for predicting the recurrence of Crohn's disease in the postoperative period was carried out by the ROC analysis methods according to the principles of evidence-based medicine. In this case, the main leitmotif of such an analysis was to determine the significance of immunological criteria in increasing the prognostic value of the method, which were used among patients of the main group, while in the control group of patients we mainly focused on clinical criteria in the probability of recurrence of Crohn's disease in the postoperative period.

The results of using the clinical criteria for predicting Crohn's disease relapse were, on average, 10.5±5.9% true-positive results, 33.3±2.9% true-negative results, 25.7±5.1% false-positive results, and 30.5±4.4% false-negative results. In general, using the clinical criteria for predicting Crohn's disease relapse allowed us to increase our diagnostic sensitivity from 6.67% on day 14 after surgery to 33.3% on day 180 after surgery, and specificity from 46.15% on day 14 after surgery to 57.14% on day 180 after surgery. The prognostic value of clinical criteria on the 14th day after surgery was 6.3%, on the 30th day after surgery – 14.3%, on the 90th day after surgery – 30.8%, and on the 180th day after surgery – 42.9%. On average, the diagnostic value was 28.9±14.4%.

The effectiveness of the method developed by us for predicting the recurrence of Crohn's disease in the postoperative period is due to the importance of including immunological criteria, which allows increasing the sensitivity of the test by 3.5 times, specificity - by 1.9 times, and the prognostic value of the method - by 3.3 times. The use of the developed

treatment and diagnostic algorithm for the prevention of relapse of Crohn's disease made it possible to reduce the frequency of its development in a mild form from 31% to 27.5%, in a moderate form from 21.4% to 12.5% and completely avoid its severe forms under the influence of pathogenetically substantiated differentiated and targeted anti-cytokine, hormonal and immunosuppressive therapy.

CONCLUSIONS:

1. The basis of the treatment and diagnostic algorithm for predicting and preventing relapse of CD is the dynamic monitoring of the level of cytokines (TNF-α, IL-17, IL-21 and TGF-β) in the blood, as well as clinical signs of the postoperative course (frequency of stool per day, body temperature, heart rate, the presence of postoperative complications and their degree according to the Clavien-Dindo classification), which allow us to determine the level (low or high) of the probability of an attack, on the one hand, and to apply differentiated approaches to the scheme of anti-cytokine (Infliximab and Vedolizumab), hormonal (Prednisolone) and immunosuppressive (Azathioprine) therapy, on the other.
2. The effectiveness of the developed method for predicting recurrence of CD in the postoperative period, due to the importance of including immunological criteria, allows increasing the sensitivity of the test by 3.5 times, specificity - by 1.9 times, and the prognostic value of the method - by 3.3 times. The use of the developed treatment and diagnostic algorithm for the prevention of recurrence of CD made it possible to reduce the frequency of its development in a mild form from 31% to 27.5%, in a moderate form from 21.4% to 12.5% and completely avoid its severe forms under the influence of pathogenetically substantiated differentiated and targeted anti-cytokine, hormonal and immunosuppressive therapy.

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