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Immunological Markers of Surgical Bowel Diseases in Children

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Abstract The article is devoted to the development of immunological indicators of intestinal inflammation in children, which is of great importance for health authorities when organizing specialized pediatric and surgical services. The proposed method contributes to the early diagnosis and prevention of complications of inflammatory surgical bowel diseases in children, which is of great practical importance. The authors conducted an immunological study of 91 pediatric patients. All children underwent immunological blood tests: cellular and humoral immunity, cytokines (TNF-α, IFN-α, IL-8, MCP-1 and vascular endothelial growth factor VEGF-A) were studied. For the prevention of postoperative complications of CKD in children, it is recommended to determine INF-α in the blood serum in the period before surgery to solve the indications for immunocorrection.

Keywords Cellular immunity, Cytokines, Surgical intestinal diseases, Chronic constipation, Children, Intestinal obstruction

1. Introduction

In the structure of mortality of patients with acute surgical pathology of the abdominal organs, this disease occupies one of the first places, amounting to 4.3–18.9%, and among people over 70 years of age – up to 36.0% [1].

In acute intestinal obstruction (AIO) complicated by peritonitis, the mortality rate approaches 100% [5].

Among acute surgical diseases of the abdominal cavity, acquired intestinal obstruction ranks second in frequency, second only to acute appendicitis, at the same time, the number of deaths in it is greater than in other acute surgical diseases of the abdominal cavity combined. The frequency of intestinal obstruction in relation to acute surgical diseases of the abdominal cavity can reach 9.4%. Intestinal intussusception and adhesive intestinal obstruction are most common in children, much less often - obstruction on the basis of Meckel's diverticulum, inversions and nodules of the small and large intestine, strangulated internal hernias [2].

Despite significant achievements in modern surgery, the development and introduction of new methods of early diagnosis and surgical treatment of patients with AIO, there is a large number of unsatisfactory results and deaths in this pathology. All this ultimately necessitates the search and clinical application of reliable methods for determining the type and level of intestinal obstruction, the choice of adequate surgical aids in each case, and the improvement of existing diagnostic and treatment algorithms that help save patients' lives [4].

Inflammatory bowel diseases (IBD) often develop in patients with pathology of adaptive immunity. Numerous genetic defects that can disrupt T- and B-differentiation and activation eventually lead to the development of complex dysfunctions of adaptive immunity, including immunodeficiency and autoimmune inflammation. Diseases manifested by IBD-like symptoms include B-lymphocyte defects, such as general variable immunodeficiency, hyperimmunoglobulinemia M, agammaglobulinemia. A number of severe combined primary immunodeficiencies (Wiskott–Aldrich syndrome, Omenne syndrome) may also be accompanied by IBD-like intestinal inflammation [6].

Understanding the pathophysiology of a disease caused by a genetic defect can serve as a justification for choosing an unconventional therapy due to specific pathogenetic effects. For example, patients with mevalonate kinase deficiency or chronic granulomatous disease accompanied by an increase in IL-1ß levels may be indicated therapy with an IL-1ß receptor antagonist. In cases of phagocytosis and/or neutropenia disorders, the introduction of a granulocyte colony-stimulating factor may be effective. This is not a standard therapy for IBD, but it is justified from the point of view of pathophysiology and, in the future, may be very effective in relation to this group of patients [3].

2. The Purpose of the Study

To develop immunological indicators of complications of surgical bowel diseases in children.

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3. Materials and Methods of Research

A retrospective analysis of 867 case histories of children who received inpatient treatment at the Department of Pediatric Surgery of the Bukhara branch of the Republican Scientific Center of Emergency Medical Care from 2019 to 2022 for surgical diseases of the gastrointestinal tract was carried out.

The total number of hospitalized sick children for 3 years was 5,650, in 2019 – 1,551 (27.5%), in 2020 – 1,149 (20.4%), in 2021 – 1,353 (23.9%), in 2022 - 1,597 (28.3%).

Of these, 2853 sick children were admitted for IBD, which is 50.5% of all hospitalized in the surgery department. To develop informative indicators of complications of surgical bowel diseases in children, patients were divided into 3 groups:

- 1 control group consists of 30 healthy children;

Group -2 consisted of 31 sick children with intestinal obstruction (IO);

- group 3 consisted of 30 sick children with chronic constipation (CC).

All children underwent immunological blood tests: cellular and humoral immunity, cytokines (TNF-α, IFN-α, IL-8, MCP-1 and vascular endothelial growth factor VEGF-A) were studied.

The study was conducted in accordance with the Helsinki Declaration.

Statistical processing of the results was carried out using Excel programs from the Microsoft Office XP application package (Microsoft, USA), correlation analysis was performed using the Pearson method and evaluated on the Cheddock scale.

4. Results

The relative number of CD3 lymphocytes was reduced in patients of both the main group and the comparison group to 46.3±0.31% and 34.2± 0.47%, respectively, against the control indicators-51.7±0.62% (P<0.05 - 0.001). The relative percentage of CD4 helper lymphocytes was significantly reduced in patients of the main group to 27.0±0.41% versus the control - 34.4±0.43% (P<0.01).

When studying the level of CD8-immunoregulatory subpopulation of T-suppressors/cytotoxic lymphocytes, a significantly reduced content was revealed at IO to -19.5±0.59% (P<0.05), and at CC in patients of the main group there was a statistically significant increase to 28.0±0.94% (P<0.05).

Thus, at IO in children have a deficiency of cellular immunity. There is a decrease in the relative number of CD3, CD4 and CD8 lymphocytes.

The B-system is represented by the quantitative content of B-lymphocytes with CD20 and CD23 molecules and the level of immunoglobulins of IgG, IgA, IgM and IgE classes. CD20+ lymphocytes are known to be directly involved in specific immune defense reactions of the body.

A comparative assessment of the content of circulating CD20+ cells in the blood showed that with IO and CC, the level of these cells significantly increased to 31.7±0.52% and 28.9±0.5%, respectively (P<0.01) compared with the control group-23.2±0.63%. Our research data showed that in the main group of patients, the level of relative values of CD23+ cells was significantly increased by 2.3 times (P<0.001).

A study of the concentration of the main classes of IgG, IgA and IgM, as well as IgE, showed that with CC, there was a 3.2-fold decrease in IgG against the background of an increase in IgM to 1.7±0.09 g/l versus control-1.2±0.13 g/L. In the main group of patients with IO, IgG concentration was at the level of control values, and IgM was increased to 1.6±0.11 g/l versus control-1.2±0.13 g/L.

As is known, this type of antibodies is produced against infectious agents, activates complement and enhances phagocytosis.

It is possible that the increased synthesis of IgM in the main and comparative group of patients with IO and with CC is associated with the addition of an infectious process. Very important properties of IgM are their attraction of phagocytic cells to the location of the antigen or to the focus of infection and activation of phagocytosis.

IgG is the primary antibody of the secondary immune response. The main biological function of immunoglobulins of this class is to protect the body from pathogens of infection and their waste products. Being thymus-dependent, IgG is produced only with the obligatory participation of T-lymphocytes.

As can be seen from the above data, the most increased synthesis of IgA occurs in the group of patients with IO -1.4±0.08 g/l (P<0.01), and in the comparative group its concentration was increased to 0.9±0.04 g/l, against the control-0.4±0.03 g/l, P<0.05.

With an immediate type of hypersensitivity reaction, specific antibodies (reagins) with the ability to sensitize their own tissues are detected in the body. Its concentration in the blood serum in the control group averaged 105.4±11.4 ng/ml. In all groups of examined patients, its concentration was at the level of control values.

The special attention of researchers is attracted by the class of immunocompetent cells, which performs a killer function. We are talking about natural killer cells - NK cells - (CD16+).

The control group contains natural killer cells (CD16+ cells) with an average of 16.4±1.0%. The absolute value of this indicator averaged 182±9.0 in 1 µl. The relative content of NK cells in the bloodstream of patients with CN and CD was increased to 23.2 0.9% and 20.6 0.23%, respectively, in relation to the data of the control group - 17.1 0.44% (P<0.05).

Analysis of the results showed that with IO, there was a significant increase in the expression of activation markers of early activation - CD25+ cells to 20.4± 0.28% in patients of group 2 and to 25.2±0.62% in patients of group 3 of the examination, against control values-18.0±0.41%, P<0.05.

The level of lymphocytes with a receptor for apoptosis (CD95) in our studies in the main group of patients with

IO was at the level of control values, and in patients with CC was significantly increased by 1.65 times. Thus, the maximum increase in their relative number is observed, where the level is increased by 1.65 times and averages 29.8±0.47% (P <0.001).

During the immunological assessment of blood parameters in patients, a statistically significant decrease in the level of INFa with CC was found to 10.7± 0.23 pg/ml compared to the control-11.6±0.22 pg/ml, which is explained by the chronization of the pathological process and the depletion of the body's defense mechanisms with the formation of a state of immunodeficiency.

In patients of the main group, the INFa was at the level of control values, which confirms the acute onset of IO.

To study the nature of inflammation in the intestine, IL-8 was studied in the blood serum of patients and healthy children. Its significant increase in patients of the main group was found to be 1.33 times, on average up to 48.7±3.39 pg/ml compared to the control values -36.8±1.44 pg/ml. At the same time, in patients with IO, a tendency to decrease IL-8 to 32.6±1.93 pg/ml was revealed, which confirms the importance of dysbiosis in constipation in children.

As a result of apoptosis and cell death, the intestines disintegrate and destructurize, which is confirmed paraclinically by the level of TNF-α in the blood serum. In our studies, the greatest increase in its level was found in patients of the 3rd group (comparison) to 149.7±1.29 pg/ml, and in the main group to 136.7±10.89 pg/ml against the control-58.4±1.84 pg/ml (p<0.001). The results obtained, obviously, prove the disintegration of tissue at the intestinal level in our studies by the formation of megacolons or other secondary changes in the intestinal tract in CC and IO in case of obstruction.

Taking into account the above facts, the assessment of the chemotaxis process in patients selected for the study showed an increase in the level of MCP-1 in patients of the main group by 1.3 times (366.7±20.69 pg/ml), compared to the control-279.8±28.6 pg/ml, which confirms the presence of an acute inflammatory process and activation of macrophages. In patients of the comparative group, MSR-1 was reduced to 183.1±25.17 pg/ml, which is 1.5 times lower than the control values. The obtained result indicates the chronization of the pathological process and a decrease in macrophage activity.

In the study, we found a tendency to increase VEGF-A to 208.4±13.05pg/ml in patients of the main group and a statistically significant decrease to 144.3±9.48 pg/ml in patients of the 3rd group in relation to the indicators of the control group-191.3±14.76 pg/ml. Consequently, with IO, activation of chemotaxis with the participation of endothelial growth factor is noted.

One of the promising directions for improving the quality of diagnosis and stratification of patients according to the severity of the condition in scientific and practical research is the determination of the concentration of procalcitonin (PCT), a marker of systemic inflammatory reaction and bacterial infection [2].

The study of the nature of inflammation and the activity of inflammatory markers made it possible to determine bacterial infection. Thus, in patients of the main group, there was a 7.25-fold increase in PCT (up to 2.9±0.64 ng/ml) in relation to the control group -0.4±0.44 ng/ml (p<0.05) and 3.2-fold increase against the comparison group - 0.9±0.06 ng/ml (p<0.05).

Thus, with IO, an increase of IL-8 by 1.33 times, TNF-α by 2.4 times, MCP-1 by 1.3 times, PCT by 7.25 times was found against the background of activation of chemotaxis with the participation of endothelial growth factor VEGF-A. The obtained results of the immunological study indicate the activation of the body's defense system in children with IO and allow determining the prognosis of the outcome of surgical corrections and postoperative complications. Therefore, for the prevention of postoperative complications in IO, it is important to take into account the immune status.

To develop indicators of postoperative complications, a correlation analysis of immunological parameters was performed in patients of the main group (Fig. 1).

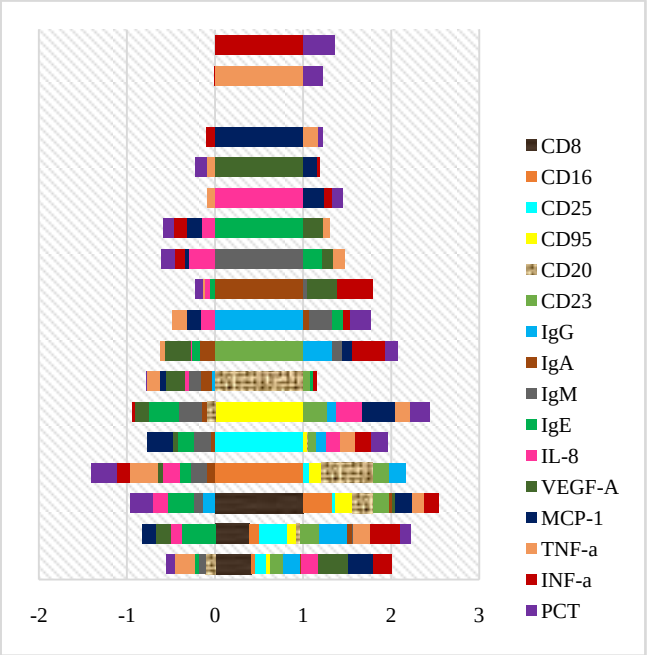

Figure 1. Correlations of immunological parameters of blood in intestinal obstruction in children

As a result, a noticeable positive relationship was established between INF-α and CD8-r=0.34, between INF-α CD23 -r=0.38, between INF-α and IgA-r=0.39, between INF-α and PCT-r=0.36.

At the same time, PCT has a noticeable negative relationship with CD16- r=-0.31 and with CD8- r=-0.31 against the background of a noticeable positive relationship with IgG -r= 0.32 and INF-α- r=0.36.

Consequently, among all the studied immunological indicators, INF-α and PCT with a noticeable correlation dependence were determined to be the most informative indicators. As an indicator of immunity, INF-α has the most noticeable positive association with CD23, with IgA and

PCT. According to the level of INF-α, it is possible to predict the outcome of the postoperative period. And PCT - as an indicator of the activity of inflammation and bacterial infection, due to the noticeable links with the studied immunological parameters of the blood, it acts as an indicator for the indication of antibacterial therapy and its effectiveness.

The greater the activation of protective mechanisms of protection (for example, the level of INF-α), the better the prognosis of the outcome of surgical correction of the intestine in children. That is, the body's response with an increase in the level of the above-mentioned immunological (CD8, CD23, IgA and PCT) indicators confirms the compensatory phase of the immune response.

This leads to the conclusion that INF-α is a more informative indicator of the effectiveness of the immune response, and PCT is an indicator of the effectiveness of antibacterial therapy in surgical bowel diseases in children.

5. Conclusions

1. There was a deficiency of cellular immunity in intestinal obstruction in children, while there was a decrease in the relative number of CD3, CD4 and CD8 lymphocytes against the background of an increase in CD20 and CD23 lymphocytes (2.3 times).
2. Surgical bowel diseases in children aged 6 years and older are characterized by an increase in IgM and IgA against the background of normal IgG and IgE values and an increase in the expression of activation markers of early (CD25) and killer (CD16) activation.
3. With intestinal obstruction, an increase of IL-8 by 1.33 times, TNF-α by 2.4 times, MCP-1 by 1.3 times, PCT by 7.25 times was found against the background of activation of chemotaxis with the participation of endothelial growth factor VEGF-A.
4. A noticeable positive relationship was established between INF-α and CD8-r=0.34, between INF-α CD23 -r=0.38, between INF-α and IgA-r=0.39, between INF-α and PCT- r=0.36. At the same time, PCT has a noticeable negative relationship with CD16- r=-0.31 and with CD8- r=-0.31 against the background of a noticeable positive relationship with IgG -r=0.32 and INF-α- r=0.36.
5. It was found that INF-α is a more informative indicator of the effectiveness of the immune response, and PCT is an indicator of the effectiveness of antibacterial therapy in surgical bowel diseases in children.

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