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The role of cytokines in the pathogenesis of infectious complications in surgical treatment of obstructive jaundice of gallstone origin

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ABSTRACT

Aim. To study the content of cytokines in the blood serum of patients with obstructive jaundice of gallstone origin before and after surgical treatment, depending on the development of postoperative complications.

Materials and methods. The treatment group consisted of 70 patients with the diagnosis of obstructive jaundice of gallstone origin, verified following a comprehensive clinical and instrumental examination. In 54 patients, the postoperative period was uncomplicated, and in 16 patients, various infectious complications in the postoperative period were revealed. The control group consisted of 125 healthy volunteers. The concentration of six cytokines (interleukin (IL)-2, IL-4, IL-18, IL-10, tumor necrosis factor alpha (TNF α), and interferon gamma (INF γ)) was determined using reagent kits manufactured by Vector-Best LLC (Novosibirsk, Russian Federation) by enzyme-linked immunosorbent assay on the Thermo Scientific analyzer (BioMerieux, France).

Results. We identified significantly high concentrations of proinflammatory cytokines in the blood serum of patients with obstructive jaundice of gallstone origin upon admission, compared with the data obtained in the study of blood serum in the control group and in patients with obstructive jaundice after surgery. In the postoperative period in patients with obstructive jaundice without complications, the proinflammatory cytokines are significantly reduced and IL-4 is increased, whereas with the development of infectious complications, the level of proinflammatory cytokines is significantly elevated.

Conclusion. In the pathogenesis of obstructive jaundice, a local inflammatory process plays an essential role. This is confirmed by statistically significant changes in the studied cytokines. The established increase in the concentration of IL-4, which has anti-inflammatory activity, indicates its importance in the mechanisms underlying the absence of infectious complications in the postoperative period of obstructive jaundice of gallstone origin. The revealed increase in the levels of IL-18, TNFα, and INFγ in the blood serum of patients suggests their role in the pathogenesis of infectious complications in the postoperative period of obstructive jaundice of gallstone origin.

Key words: cytokines, pathogenesis, postoperative complications, inflammation, obstructive jaundice.

Conflict of interest. The authors declare the absence of obvious or potential conflicts of interest related to the publication of this article.

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Conformity with the principles of ethics. All participants signed an informed consent to take part in the study. The study was approved by the local Ethics Committee at Research Institute of Medical Problems of the North (Protocol No. 7 от 16.11.2012).

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Роль цитокинов в патогенезе инфекционных осложнений при хирургическом лечении механической желтухи желчнокаменного генеза

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РЕЗЮМЕ

Цель. Изучить содержание цитокинов в сыворотке крови пациентов с механической желтухой желчнокаменного генеза до и после хирургического лечения в зависимости от развития послеоперационных осложнений.

Материалы и методы. Основная группа состояла из 70 пациентов с верифицированным на основании комплексного клинико-инструментального обследования диагнозом «механическая желтуха желчнокаменного генеза». У 54 больных послеоперационный период был без осложнений и у 16 больных выявлялись различные инфекционные осложнения в послеоперационном периоде. Контрольную группу составили 125 практически здоровых добровольцев. Концентрацию шести цитокинов (интерлейкина (IL) 2, IL-4, IL-18, IL-10, фактора некроза опухоли α (TNFα), интерферона γ (INFγ)) определяли с использованием набора реагентов производства ЗАО «Вектор-Бест» (г. Новосибирск) методом иммуноферментного анализа на иммуноферментном анализаторе Thermo Scientific (BioMerieux, Франция).

Результаты. Установлено наличие статистически значимо высоких концентраций провоспалительных цитокинов в сыворотке крови пациентов с механической желтухой желчнокаменного генеза при поступлении относительно данных, полученных при исследовании сыворотки крови контрольной группы и больных с механической желтухой после операции. В послеоперационном периоде у пациентов с механической желтухой без осложнений статистически значимо снижаются показатели провоспалительных цитокинов и увеличивается IL-4, а при развитии инфекционных осложнений – статистически значимо увеличивается уровень провоспалительных цитокинов.

Заключение. В патогенезе механической желтухи важную роль играет локальный воспалительный процесс. Это подтверждается статистически значимыми изменениями изучаемых цитокинов. Установленное нарастание концентрации IL-4, обладающего противовоспалительной активностью, свидетельствует о его значимости в механизмах отсутствия развития инфекционных осложнений в послеоперационном периоде механической желтухи желчнокаменного генеза. Выявленное повышение в сыворотке крови уровня IL-18, TNFα, INFγ позволяет предположить их участие в патогенезе инфекционных осложнений в послеоперационном периоде у пациентов с механической желтухой желчнокаменного генеза.

Ключевые слова: цитокины, патогенез, послеоперационные осложнения, воспаление, механическая желтуха.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Исследование проводилось за счет средств государственного задания НИИ МПС ФИЦ КНЦ СО РАН.

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INTRODUCTION

Obstructive jaundice (OJ) is an acute clinical condition caused by the appearance of an obstacle to the outflow of bile in the duodenum [1]. OJ of benign genesis is commonly caused by gallstone disease. Currently, many researchers point to the increasing number of patients with OJ in many countries of the world, therefore, OJ is a medical and social problem of modern society [2, 3]. The pathogenesis of OJ is complex; the development of a local and systemic inflammatory response and endotoxicosis contributes to destruction and disorganization of the gastrointestinal tract and requires urgent surgical aid to restore patency of the bile ducts and eliminate all complications [4–7]. Considering the data of numerous studies on the leading role of the destructive and inflammatory process in the pathogenesis of OJ, which directly involves cytokines, it can be assumed that signs of imbalance in cytokine production affect the course of the postoperative period in patients with OJ. The data of such studies are ambiguous and few in number [8–10].

Following tissue infection in the postoperative period, a patient with OJ develops a complex, multicomponent sequence of reactions aimed at isolating and destroying the pathogen, preventing tissue destruction, triggering repair processes, and restoring homeostasis. The initiation and development of the inflammatory response is controlled by proinflammatory cytokines produced by T cells, neutrophils, and macrophages in response to a bacterial pathogen. Cells of the immune system produce IL-2, TNF-α, INF-γ, and IL-8. Proinflammatory cytokines play a protective role by stimulating the phagocytic and bactericidal activity of neutrophils and macrophages and triggering antigen-specific immunity aimed at eliminating the pathogen. The protective role of proinflammatory cytokines is carried out when mediators work locally in the focus of inflammation, while systemic overproduction of these cytokines contributes to the appearance of toxic shock syndrome and organ dysfunctions. To overcome excessive manifestations of systemic inflammation in a patient with OJ, negative regulation mechanisms are activated due to the production of anti-inflammatory cytokines (IL-4 and IL-10) and soluble inhibitors of proinflammatory cytokines. The basis of the pathogenesis of infectious complications in the postoperative period in OJ is the development of cytokine storm, which includes pro-inflammatory and anti-inflammatory mediators. The balance between the two opposite groups largely determines the course and outcome of infectious complications in OJ in the postoperative period [11, 12].

Therefore, the above-stated data allow to make an important conclusion about the relevance of a comprehensive study of the content and balance of cytokines before and after surgical treatment of patients with OJ of gallstone origin in order to understand the molecular mechanisms of the development of postoperative complications in OJ and formulate the aim of this study.

The aim of the study was to determine the content of cytokines (IL-2, TNF-α, INF-γ, IL-18, IL-4, and IL-10) in patients with OJ caused by gallstones before and after surgical treatment, depending on the development of postoperative complications.

MATERIALS AND METHODS

To accomplish this aim, 70 patients were examined (the average age was (44.02 ± 14.88) years) with the diagnosis of OJ of gallstone origin, verified following a comprehensive clinical and instrumental examination. All the patients were admitted to the surgical department of the clinic of the Research Institute of Medical Problems of the North of FRC of the KSC SB RAS. All the patients were diagnosed on the basis of a standard examination, including history taking, clinical presentation, detailed blood count, biochemical parameters (bilirubin level, alanine aminotransferase (ALT), alkaline phosphatase, total protein, etc.), and an instrumental examination (ultrasound, MRI, etc.).

In the postoperative period, 16 out of 70 patients (22.8%) developed inflammatory infectious complications that required additional drug correction. As control values of the cytokines in the blood serum determined in the present study, we used the data obtained from 125 practically healthy volunteers, comparable in sex and age with the group of the examined patients, who were selected during regular health checkups in Krasnoyarsk medical facilities. The examination of the participants was approved by the Ethics Committee of the Research Institute of Medical Problems of the North (Protocol No. 7 of November 16, 2012). Each participant signed an informed consent for the examination. When working with the examined patients, we followed the ethical principles set out in Art. 24 of the Constitution of the Russian Federation and the Declaration of Helsinki developed by the World Medical Association.

The exclusion criteria were: persons with HIV, tuberculosis, and drug addiction; refusal to participate in the study; age over 80 years. The material for the study was venous blood which was drawn from the ulnar vein of the patients twice: before the start of etiotropic therapy and 7 days after surgical treatment. Serum samples were frozen and stored in the refrigerator at -70 ° C prior to testing. Once frozen, the blood serum was thawed to room temperature before testing.

The concentration of six cytokines (interleukin (IL)-2, IL-4, IL-18, IL-10, tumor necrosis factor alpha (TNF α), and interferon gamma (INF γ)) was determined using reagent kits manufactured by Vector-Best LLC (Novosibirsk, Russian Federation) by enzyme-linked immunosorbent assay on the Thermo Scientific analyzer (BioMerieux, France).

The concentration of the cytokines was determined in pg / ml [13, 14]. Statistical data were analyzed using the Statistica 10 software package (StatSoft Inc., USA). Non-normal distribution of parameters in all the obtained samples was found using the Kolmogorov – Smirnov test with Lilliefors correction. The statistical significance of the differences was assessed using the nonparametric Wilcoxon test for dependent samples and using the Mann – Whitney test with Bonferroni's correction for independent samples. All data were presented as the median and the interquartile range *(Me)* [Q_1–Q_3]. The differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

In the present study, in the blood serum of the patients with uncomplicated OJ of gallstone origin, statistically significantly high concentrations of the proinflammatory cytokines were detected, compared with the data obtained from practically healthy volunteers (Table 1). An increase in the concentration of TNF α by more than 60 times was revealed in the patients with OJ before the surgery, compared with the control group ($p = 0.0006$); after surgery, the value decreased. This indicates an increase in the natural cytotoxicity of monocytes, macrophages, and natural killer (NK) cells [15, 16]. It plays an important role in inflammation, promotes adhesion of granulocytes to the vascular endothelium, accelerates transendothelial migration of leukocytes to the inflammation focus, and increases the phagocytic activity of neutrophils and monocytes, implementing development of complete phagocytosis [17].

The concentration of INF γ was elevated in all OJ patients with an uncomplicated postoperative period ($p = 0.001$), whereas statistically significant differences were detected in OJ patients before the surgery compared with the control group. Its formation and secretion occur after a repeated response of previously sensitized lymphocytes to the antigen. INF γ stimulates cells of the immune system to develop an immune response.

Overproduction of the cytokine IL-18 was found in the OJ patients before and after surgical treatment ($p = 0.001$); the most pronounced increase in the parameter value was detected in the patients before the pathogen-specific treatment of OJ of gallstone origin. Under the influence of IL-18, antimicrobial resistance of the whole body increased [18].

Overproduction of proinflammatory cytokines in OJ proves the presence of local and systemic inflammation, which aggravate the clinical course of the disease in patients. After surgical treatment, the concentration of proinflammatory cytokines decreases, but does not reach normal control values, proving that the surgery itself is a surgical injury that maintains the inflammatory process in the body [19–21].

The increased content of IL-2, a regulator of cellular antigen-specific immune response, was identified. The median IL-2 concentration was 7 times higher in the OJ patients before the surgery and 5 times higher after the surgery, compared with the control group. By activating various signaling pathways, it causes proliferation and activation of T cells for implementing the immune response.

When assessing the content of cytokines, the increase in which is associated with the activation of type 2 inflammation, a statistically significant decrease in the median concentrations of IL-4 and IL-10 in the patients with OJ before etiotropic treatment was found, compared with the control group. Therefore, in the patients with OJ of gallstone origin before surgical treatment, type 1 inflammation prevailed. At runtime, in the patients with OJ, the concentration of IL-4 increased after surgical treatment, compared with the control group. It is likely that the revealed changes in the content of IL-4 do not exclude its ability to participate in development of connective tissue and fibrosis at the site of surgical injury. The role of anti-inflammatory cytokines in limiting local inflammation and preventing the development of systemic phenomena is not excluded [22, 23].

In 16 patients with OJ of gallstone origin, infectious complications developed in the postoperative period (Table 2). Evaluation of the content of pro- and anti-inflammatory cytokines revealed statistically

significantly higher concentrations of cytokines with pro-inflammatory properties (TNFα, INFγ, IL-18) at baseline and in the postoperative period, while the median concentrations of anti-inflammatory cytokines remained low. Acute overproduction of proinflammatory cytokines in the bloodstream contributes to development of a systemic inflammatory response with corresponding clinical manifestations (cytokine storm), to correct which involvement of all organs and systems of the body is required in case of severe impairment in hemostasis. Prolonged pathologically high concentrations of proinflammatory cytokines cause septic shock and death of the patient [17, 24, 25]. Thus, in conditions when the concentration of cytokines exceeds physiological values for a long time, their protective function changes to a pathological one [15, 26]. Due to inadequate overproduction, cytokines themselves have a histodestructive effect, causing multiple organ failure.

CONCLUSION

The study made it possible to establish that statistically significantly higher concentrations of proinflammatory cytokines (IL-2, TNFα, INFγ, IL-18) are detected in the blood serum of patients with OJ of gallstone origin before the surgery, which indicates the significance of type 1 inflammation in the pathogenesis of OJ of gallstone origin. It was found that in the blood serum of the patients with OJ with an uncomplicated postoperative period, statistically significantly higher concentrations of IL-4, which action is aimed at compensating the consequences of the inflammatory process and restoring the damaged tissue of the hepatobiliary system, were revealed along with a combination of type 1 and type 2 inflammation. The identified high concentrations of TNFα, INFγ, and IL-18 in the postoperative period of OJ suggest their participation in the development of infectious complications.

Table 1

The content of cytokines in the blood serum of patients with OJ with an uncomplicated postoperative period at runtime, compared with the control group, pg / ml

Parameters	Control group, n = 125 (1)		OJ patients before the surgery, n = 54 (2)		OJ patients after the surgery, n = 54 (3)	
	Me	Q_1–Q_3	*Me*	Q_1–Q_3	*Me*	Q_1–Q_3
IL-2	1.1	0.5–3.05	7.25	4.72–9	5.5	3–7.3
	–		p_{1-2} = 0.001		p_{1-3} = 0.001	
TNFα	0.54	0.38–0.88	35.7	4.82–86.5	8.1	3.1–51
	–		p_{1-2} = 0.0006		p_{1-3} = 0.001	
INFγ	0.6	0.22–4.0	9.2	2.8–21.83	7.3	2.7–8.1
	–		p_{1-2} = 0.001		–	
IL-18	1.6	0.1–2.1	90	56.9–2452.	61.7	53.88–99.3
	–		p_{1-2} = 0.001		p_{1-3} = 0.001	
IL-4	2.15	0.6–4.8	0.01	0.009–2.2	38.4	4.3–377.6
	–		p_{1-2} = 0.003		p_{1-3} < 0.001 p_{2-3} < 0.001	
IL-10	14.8	8.65–26.85	2.6	1.1–5.4	2.1	1.05–2.75
	–		p_{1-2} = 0.001		p_{1-3} = 0.04	

Note: p_{1-2} – statistically significant differences between the control group and the group of patients with OJ before the surgery; p_{1-3} – statistically significant differences between the control group and the group of patients with OJ after the surgery; p_{2-3} – statistically significant differences between the group of OJ patients after the surgery and the group of patients with OJ before the surgery (here and in Table 2).

Table 2

The concentration of cytokines in the blood serum of patients with OJ with a complicated postoperative period at runtime, compared with the control group, pg / ml

Parameters	Control group, n = 125 (1)		OJ patients before the surgery, n = 16 (2)		OJ patients after the surgery, n = 16 (3)	
	Me	Q_1–Q_3	*Me*	Q_1–Q_3	*Me*	Q_1–Q_3
IL-2	1.1	0.5–3.05	9.43	6.12–11.7	12.26	7.96–15.21
	–		p_{1-2} = 0.001		p_{1-3} = 0.001	
TNFα	0.54	0.38–0.88	46.41	6.27–112.5	60.33	8.15–146.19
	–		p_{1-2} = 0.001		p_{1-3} = 0.001	

Table 2 (continued)

	Control group, n = 125 (1)		OJ patients before the surgery, n = 16 (2)		OJ patients after the surgery, n = 16 (3)	
	Me	Q_1–Q_3	*Me*	Q_1–Q_3	*Me*	Q_1–Q_3
INFγ	0.6	0.22–4.0	12.0	3.64–28.4	15.6	4.73–36.9
	–		p_{1-2} = 0.001		–	
IL-18	1.6	0.1–2.1	117	73.97–318.8	80.21	70.04–129.1
	–		p_{1-2} = 0.001		p_{1-3} = 0.0006	
IL-4	2.15	0.6–4.8	0.013	0.012–2.86	0.017	0.015–2.9
	–		p_{1-2} = 0.001		p_{1-3} = 0.00001	
IL-10	14.8	8.65–26.85	2.2	0.19–4.4	0.9	0.85–2.75
	–		p_{1-2} = 0.001		p_{1-3} = 0.001	

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