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Improvement of Treatment and Prevention of Liver Echinococcosis

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The purpose of the study was to determine optimal pathogenetically justified methods and means to improve the results of diagnosis and treatment of liver echinococcosis.

Materials and methods. During treatment, on the 1st, 3rd, 5th, and 10th day of the postoperative period, patients were examined for the functional state of the liver by blood analysis for the amount of proinflammatory cytokines TNF-α, IL-6, IL-4 and IL-10, IL-1. The activity of humoral immunity was assessed based on the level of immunoglobulins IgA, IgG and IgM.

Results and discussion. On the 1st day after the operation, the level of IgA increased and amounted to 5.56 ± 0.1 q/L. The improvement in the dynamics of indicators was observed on the 5th day of observations, and this trend persisted up to 10 days after surgical treatment. On day 5, a significant decrease in the concentration of the main proinflammatory cytokines TNF-α, IL-6 and IL-4 was revealed, compared with the indicators before treatment and on the first day after treatment – 12.5 ± 0.6 pg/ml; 11.7 ± 0.3 pg/ml and 4.0 ± 0.2 pg/ml, respectively. This treatment regimen resulted in a marked decrease in TNF-α, IL-6 and IL-10 levels on day 10.

The initial level of cytokines and immunoglobulins indicates a pronounced immunosuppressive effect on the body of a parasitic disease. A significant decrease in cytokines IL-1, IL-6 and IL-10 in patients after surgery and a decrease in indicators after maintenance therapy can serve as a potential immunological marker for evaluating its effectiveness. When studying the cytokine profile in the patients we examined, there was a significant increase in the level of TNF-α and IL-6 in blood serum relative to the control values, which is directly dependent on the severity of the pathological process and the functional state of the liver and suppresses the secretion of anti-inflammatory cytokines, which was confirmed by data from foreign authors. As well as the works published earlier, the data of our studies show that Echinococcus granulosus cysts induce a strong antibody response in most patients, causing, at the same time, a reaction of antigen-specific antibodies of various classes with different intensity and specificity against the background of their synthesis and increased secretion. It is necessary to note an increase in quantitative and qualitative indicators of IgG, IgM and IgA levels in the blood serum of patients with liver echinococcosis, with IgG predominance.

Conclusion. A comprehensive study of inflammatory mediators and the dynamics of cytokine levels makes it possible to diagnose complications in time and prevent possible relapses of the disease. The data obtained made it possible to justify the further use of imunofan and to develop recommendations for the management of patients with liver echinococcosis in the postoperative period.

Keywords: liver echinococcosis, imunofan, biochemical blood test, cytokines, immunoglobulins.

Introduction. Echinococcosis, which belongs to the group of the most common helminthiases and severe and life-threatening diseases, is included by the World Health Organization (WHO) in the list of diseases requiring priority elimination [1, 2]. Despite numerous studies on echinococcosis, the difficulty of early diagnosis, preventive and therapeutic measures, the use of only surgical methods of treatment, the problem is still debatable. For liver echinococcosis, according to various authors, in contrast to the susceptibility of other organs, in recent years there has been a significant increase in the incidence – from 30 to 95% of cases, and the number of patients with complicated forms of this pathology in some cases reaches 35–40% [3, 4, 5, 6]. Postoperative complications of the disease are possible in 54% of cases, and mortality was recorded, according to various sources, in 2–5% of cases [7, 8]. The increase in the prevalence of echinococcosis and the associated increase in many medical and social problems, the importance of developing and conducting optimal preventive, sanitary and educational work raise the urgent question of further

search for etiopathogenetic causal risk factors for infection and, thus, a clear understanding of the ways of infection, methods of diagnosis and prevention of this serious disease, the long-term existence of an echinococcal cyst of the liver causes various complications, among which suppuration of a parasitic cyst is often found [9, 10]. The above explains the relevance of numerous studies on the prevention and timely complex treatment of this parasitic disease [11, 12].

Difficulties in the diagnosis of pathology, especially in the initial stage, are created by a wide variety of symptoms of liver echinococcosis, which often depend on the location, size of the lesion and the stage of its development [13, 14, 15]. Echinococcosis of the liver is characterized by the presence of some local symptoms, in particular, moderate soreness with a dull character, thickening of the liver, patients' complaints of paroxysmal pain, sometimes simulating calculous cholecystitis, in the upper abdomen, in the epigastric region, sometimes there are signs of jaundice, shortness of breath.

The results of instrumental methods for the study of echinococcal cysts presented by the authors, for example, ultrasound semiotics, depending on the phase of the life of the parasite, the presence and nature of complications, can to some extent improve the accuracy of diagnostic measures and plan the optimal tactics in the management of patients before and after surgical treatment.

Methods for diagnosing liver echinococcosis can be divided into laboratory and instrumental, while the analysis of scientific research and medical literature suggests that, despite greater accuracy and resolution of modern methods of radiation diagnostics, and similar, for example, the X-ray picture of most diseases, each of them has its limitations and certain disadvantages, giving a certain number of erroneous conclusions and forecasts [16, 17, 18]. This necessitates the clarification of indications for both classical radiation methods of diagnosis and treatment, as well as the search for new ways to improve complex treatment, prevention and diagnostic tactics using laboratory methods and taking into account modern achievements of medical science in this area.

Thus, from laboratory research methods, a blood test, urine, biochemical tests are used, which determine the general reaction to the presence of a parasite. In recent years, medical science has been actively searching for methods and, at the same time, certain successes have been achieved in the treatment of echinococcosis, while certain advantages are observed when using a combination of a radical surgical and conservative method with the appointment of medications, which, in combination with surgical intervention, significantly increase the effectiveness of treatment [19].

Despite the use of the achievements of modern medical materials science, and against this background, the improvement of the technique of surgical intervention using perfect instruments, the introduction of effective chemical and physical methods of influencing the parasite, the frequency of recurrence and various complications do not decrease. The obtained positive results of drug anti-relapse treatment with the appointment of a course of special antiparasitic drugs, even after an ideally performed operation, make it possible to introduce the technique into widespread practice and reduce the frequency of complications. Thus, chemotherapy or anthelmintic therapy is used to influence small-sized echinococcus [20, 21].

Although the appointment and conduct of several courses of chemotherapy, which is one of the important aspects and a method that contributes to the prevention of recurrence in the pre- and postoperative periods, adversely affects the motor activity of the parasite and subsequently leads to its death. The drugs intended for this may have a toxic side effect, in particular, on the liver and kidneys, which makes this therapeutic tactic inaccessible to patients with these diseases.

Despite certain modern achievements and advances made in the diagnosis and treatment of liver echinococcosis, the frequency of postoperative complications and relapses reaches considerable values, and this problem, with a conflicting attitude towards certain methods, remains unresolved. For this reason, further scientific research and work on the development of new methods that improve the prevention and treatment of echinococcosis and its relapses remains relevant.

The purpose of the study is to determine the optimal pathogenetically substantiated methods and means to improve the results of diagnosis and treatment of liver echinococcosis.

Materials and methods. A total of 114 people were examined during the study. Of these, the control group consisted of 14 practically healthy individuals aged from 18 to 32 years. The main group included 100 patients aged 16–70 years, who, along with surgical treatment, were prescribed medication. Examination of patients for surgical treatment, surgery and further postoperative rehabilitation period took place on the basis of the Surgical Clinic of the Azerbaijan Medical University. The criteria for exclusion of patients from the study were: the age of the patient; the presence of other surgical pathology of the abdominal organs; lack of consent of the patient to participate in the study. The criterion for patients to withdraw from the study was the refusal to further participate in the study. For specific drug treatment of liver echinococcosis in the pre- and postoperative period, we used Imunofan Immunocorrector at average doses

of 10–13 mg/kg/day. The duration of treatment with imunofan, in the pre- and postoperative period, was up to 30 days. In a retrospective analysis clinical, biochemical and instrumental features of the pathology, and the presence and nature of complications and relapses were studied.

To determine the effectiveness of the use of the drug imunofan, the dynamics of changes in some laboratory data before and after treatment was evaluated. Against the background of ongoing therapeutic and preventive measures on the 1st, 3rd, 5th, and 10th day of the postoperative period, the patients underwent a study of the functional state of the liver in terms of the level of total protein and its fractions and a blood test for the amount of pro-inflammatory cytokines TNF-α, IL- 6, IL-4 and IL-10, IL-1.

The activity of humoral immunity was assessed on the basis of the level of immunoglobulins IgA, IgG and IgM. Determination of the concentration of cytokines and immunoglobulins of classes A, M, G was carried out by the method of enzyme-linked immunosorbent assay (ELISA). These studies were carried out in accordance with the principles of bioethics set forth in the Declaration of Helsinki "Ethical Principles for Medical Research Involving Humans", developed by the World Medical Association, "Universal Declaration on Bioethics and Human Rights (UNESCO)" [22]. Statistical processing of the obtained data included the calculation of arithmetic mean values (M) and the error of the representativeness of the arithmetic mean (m). We used the methods of nonparametric statistics [23]. Differences between the compared series were considered significant with a probability level of 95% ($p<0.05$). Statistical processing of the results obtained during the study was carried out using the Statistica 7.0 software application.

Research results. The implementation of complex treatment using imunofan is accompanied by early clinical recovery of patients, as well as the normalization of immunological blood parameters. Immediately on the first day after the start of treatment, the blood levels of IgA, IgM and IgG in all patients remained above the norm. The systemic reaction in patients with liver echinococcosis at the stage of pathology development and surgical and conservative treatment was judged on the basis of the results of the study of the immunoglobulin levels of the IgM, IgG, IgA classes in the blood serum.

The initial data obtained made it possible to determine that the studied pathological process in the liver has a significant impact on the indicators of general immunity. Statistical analysis of the data obtained showed that all patients before treatment had a significant increase in the levels of IgG, IgA compared with practically healthy people, with the simultaneous appearance of IgM. Comparative analysis revealed a high degree of differences in immunoglobulin blood profiles in the main and control groups.

The decrease in the concentrations of IgM, IgG, IgA in the studied biological media at various stages made it possible to judge the positive dynamics in reducing the severity of the inflammatory process. When studying the state of antibody genesis in the blood of patients after the start of treatment, a statistically significant decrease in the content of immunoglobulins A, M and G against the background of an increased level of anti-inflammatory cytokines was revealed. Thus, as a result of treatment courses in patients with a pronounced clinical picture of the studied pathology, a positive trend was recorded in the dynamics of changes in the quantitative indicators of IgM and IgG. According to the results of a statistical analysis of the data obtained, the concentration of IgA in the blood of practically healthy individuals was recorded at the minimum values, while in the main group of patients with background pathology before the start of the course of maintenance treatment, the indicators were almost by 1.5 times higher (**Table 1**).

On the 1st day after the operation and the start of therapeutic and preventive measures, the level of IgA increased and amounted to 5.56 ± 0.1 q/L ($t = 39.6$ and $p<0.001$). An improvement in the dynamics of indicators for this factor was observed at a later date, that is, on the 5th day of observation, and this trend continued until the 10th day after surgical treatment and the start of conservative therapy – 2.34 ± 0.1 q/L and 1.72 ± 0.04 q/L, respectively, on the 5th and 10th days of observations. The level of IgG in the group of practically healthy individuals was 11.5 ± 0.5 q/L, in patients with echinococcosis, on the contrary, a very high level of this immunoglobulin was detected – 16.05 ± 0.3 q/L. On the 5th and 10th days after the start of observations, the level of IgG in the blood serum approached the values found in the control group of individuals without somatic pathology.

Data on IgM underwent significant changes at certain stages. In the control group, this indicator was 1.08 ± 0.1 q/L, and in patients with liver echinococcosis at the initial stage, it increased to 1.54 ± 0.06 q/L and reached a maximum one day after surgery and the start of a course of conservative maintenance therapy – 2.24 ± 0.1 q/L ($t = 11.6$ and $p<0.001$). On the 5th day, the level of the studied immunoglobulin gradually decreased, but by the 10th day it turned out to be lower than the values recorded in the control group, that is, it remained within the normal range (0.94 ± 0.03 q/L, versus 1.08 ± 0.1 q/L, that is, the values recorded in the control group of healthy individuals) ($t = 1.4$ and $p>0.05$). Thus, when studying some indicators of general immunity in patients with liver echinococcosis before and after surgery, and at various stages of the course of basic conservative

Table 1 – The activity of humoral immunity and the level of immunoglobulins in the blood before and after the completion of treatment

Data	Control	Before treatment			After day 1			After day 5			After day 10		
İgA		**q/L**	**t**	**P**		**t**	**P**		**t**	**P**		**t**	**P**
Vmax	2.5	4.7			8.7			6.4			2.6		
Vmin	0.5	1.8			3.9			1.5			1.1		
M	1.6	2.92			5.56			2.34			1.72		
±m	0.1	0.1	13.2	<0.001	0.1	39.6	<0.001	0.1	7.4	<0.001	0.04	1.2	>0.05
İgG		q/L											
Vmax	14.9	20.9			29.6			17.6			15.4		
Vmin	5.8	11.8			14.8			12.5			5.1		
M	11.5	16.05			20.6			13.6			10.9		
±m	0.5	0.3	7.6	<0.001	0.5	18.2	<0.001	0.2	4.2	<0.001	0.4	1.0	>0.05
İgM		q/L											
Vmax	1.9	2.8			4.3			2.4			2.0		
Vmin	0.7	0.9			1.6			1.2			0.8		
M	1.08	1.54			2.24			1.32			0.94		
±m	0.1	0.06	4.6	<0.001	0.1	11.6	<0.001	0.03	2.4	<0.05	0.03	1.4	>0.05

therapy, activation of the main parts of the immune system was revealed.

In patients of the main group, against the background of pathological changes in the functional state of the liver, some fluctuations in the biochemical parameters studied by us, in particular, the level of immunoglobulins and cytokines, were revealed.

The work was carried out under standard conditions using enzyme-linked immunosorbent assay of blood taken from the examined patients on an empty stomach on the 1st, 5th, and 10th day of the postoperative period. According to the data obtained, interleukins, in particular, IL1, IL-4, IL-6, IL10, and tumor necrosis factor (TNF-α) react most pronouncedly to the effect of surgery and the drug used.

After the completion of surgery in the main group of patients, there is a statistically significant sharp increase in the concentrations of the above factors, which is probably associated with the destruction of hepatocytes during exposure to liver tissue and the release of cytokines into the blood. However, as subsequent studies have shown, in the course of using conservative maintenance therapy, their level gradually begins to decrease and in some cases normalizes by the end of observations, that is, by day 10.

The management of patients with liver echinococcosis, taking into account the level of pro- and anti-inflammatory interleukins in the blood serum before and after echinococcectomy, makes it possible to predict the success of the applied course of basic therapy, as well as to reduce the incidence of postoperative complications. Against the background of conservative treatment and the study of the state of the immune status and the results of its correction in the examined patients, there was a decrease in the level of TNF-α, IL-6 and IL-1 and other factors, but at the initial stages of the study they remained still at a high level and were far from intact indicators, which, first of all, can be said about the decrease in the concentration of IL-4 in the blood.

The use of the drug imunofan in the complex treatment of liver echinococcosis led to positive dynamics in terms of pro-inflammatory cytokines. (**Table 2**). So, at the intermediate stage of laboratory studies, a statistically significant decrease in their number was recorded – 12.5 ± 0.6 pg/mL; 11.7 ± 0.3 pg/mL and 4.0 ± 0.2 pg/mL, respectively (t = 11.6 and p<0.001). This treatment regimen led to a pronounced decrease in the level of TNF-α, IL-6 and IL-10 on the 10th day, compared with the same group before the start of therapy and the previous stages of treatment. A comparative analysis of the data obtained before and after the inclusion of the proposed scheme of drug correction of immune disorders in the complex of measures in patients with echinococcosis revealed their greater effectiveness. The obtained results testify to the sufficient effectiveness of imunofan and its use allowed to reduce the number of altered biochemical parameters.

After echinococcectomy with the use of imunofan in the early postoperative period, a positive correlation was established between the duration of treatment and the concentrations of interleukin IL-6 and the level of bilirubin. The detection of postoperative complications is associated with excessive high activity of the pro-inflammatory cytokine IL-4. The study of the synthesis of IL-4 and IL-6 in patients with liver echinococcosis, the peculiarity of the course of reparative processes revealed the reversibility of alternative reactions to restore the functional state of the liver in the early postoperative period, which allows

Table 2 – The level of cytokines in blood serum before and after echinococcectomy and conservative therapy

Data	Control	Before treatment			After day 1			After day 5			After day 10		
İL-1		**pg/mL**	**t**	**P**		**t**	**P**		**t**	**P**		**t**	**P**
Vmax	5.8	13.9			18.6			10.6			7.6		
Vmin	1.1	3.2			5.9			2.6			1.9		
M	3.35	6.3			8.9			5.8			4.9		
±m	0.2	0.3	7.4	<0.001	0.4	18.9	<0.001	0.2	6.1	<0.001	0.2	3.9	<0.001
İL-4		pg/mL											
Vmax	6.4	8.9			10.9			7.5			6.9		
Vmin	1.4	2.6			3.7			2.1			1.6		
M	3.8	4.2			6.5			4.0			3.9		
±m	0.2	0.2	1.3	>0.05	0.2	9.0	<0.001	0.2	0.5	>0.05	0.2	0.2	>0.05
İL-6		pg/mL											
Vmax	5.4	30.4			66.7			18.3			9.7		
Vmin	1.2	3.7			13.6			6.8			2.6		
M	3.27	16.85			30.6			11.7		4.5			
±m	0.2	0.8	16.9	<0.001	1.6	17.1	<0.001	0.3	<0.001	0.2		4.1	<0.001
İL-10		pg/mL											
Vmax	15.7	28.6			32.5			28.6		20.4			
Vmin	2.8	10.5			15.6			8.3		3.9			
M	13.2	19.4			26.4			19.7		15.8			
±m	0.6	0.5	7.9	<0.001	0.5	16.9	<0.001	0.6	<0.001	0.5		3.3	<0.001
TNF-α		pg/mL											
Vmax	5.7	12.4			67.5			24.8		14.9			
Vmin	1.2	2.9			12.8			6.5		3.8			
M	4.2	8.5			27.9			12.5		6.7			
±m	0.2	0.3	10.7	<0.001	1.7	13.9	<0.001	0.6	<0.001	0.3		6.2	<0.001

expanding the indications for the use of imunofan in the complex treatment of liver echinococcosis.

Thus, the determination of the etiopathogenetic relationship between the studied factors and the functional state of the liver makes it possible to assess the severity of the inflammatory process after surgical treatment.

Discussion. The diagnostic efficiency of laboratory research methods in liver echinococcosis significantly increases with the simultaneous use of several immunological tests, which are specific markers of this parasitic invasion [24]. E. granulosus infection elicits a humoral and cellular response, showing an increase in serum antibodies and pro-inflammatory cytokines. The data obtained by us and the results of the analysis of some studies in this area show the etiopathogenetic conditionality of the development of liver echinococcosis with the state of the immune status of the human body, in particular, with immunodeficiency, which manifests itself in depression of all parts of the immune system [25, 26].

When studying the cytokine profile in the patients examined by us, a significant increase in relation to the control values of the level of TNF-α and IL-6 in the blood serum, which is directly dependent on the severity of the pathological process and the functional state of the liver and suppresses the secretion of anti-inflammatory cytokines, which was confirmed by the data of foreign authors [27, 28].

Both previously published works and our research data show that Echinococcus granulosus cysts induce a strong antibody response in most patients, causing, at the same time, a reaction of antigen-specific antibodies of various classes with different intensity and specificity against the background of their synthesis and increased secretion. The increase in quantitative and qualitative indicators of the level of IgG, IgM and IgA in the blood serum of patients with liver echinococcosis, with a predominance of IgG should be noted [29, 30, 31].

Thus, the initial level of cytokines and immunoglobulins in the examined group of patients indicates a pronounced suppressive effect of the parasitic disease on the body. The biochemical studies performed and the data obtained showed that a significant decrease in the cytokines IL-1, IL-6, and IL-10 in patients after surgery and ongoing maintenance therapy can serve as a potential immunological marker for evaluating its effectiveness [32, 33]. Thus, in the process of using the drug imunofan, normalization of the cellular and humoral immunity took place, against the background of a consistent decrease in the concentration of cytokines and immunoglobulins in various postoperative periods, which ultimately had a positive

effect on the outcome of therapeutic and preventive measures.

Conclusion. A comprehensive study of inflammatory mediators and the dynamics of cytokine levels makes it possible to diagnose complications in time and prevent possible relapses of the disease.

Perspectives of further research. The data obtained made it possible to substantiate the further use of imunofan and develop recommendations for the management of patients with liver echinococcosis in the postoperative period.

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ВДОСКОНАЛЕННЯ МЕТОДІВ ЛІКУВАННЯ ТА ПРОФІЛАКТИКИ ЕХІНОКОКОЗУ ПЕЧІНКИ

Аббасалієва Парвін Махір кизи

Резюме. *Мета.* Визначення оптимальних патогенетично обґрунтованих методів та засобів для покращення результатів діагностики та лікування ехінококозу печінки.

Методи. У ході лікування в 1, 3, 5, 10 добу післяопераційного періоду хворим проводили дослідження функціонального стану печінки з аналізу крові на кількість прозапальних цитокінів TNFa, IL-6, IL-4 та IL-10, IL-1. Активність гуморального імунітету оцінювалась на підставі рівня імуноглобулінів IgA, IgG та IgM.

Результати. На 1 добу після операції рівень Ig A підвищився, і становив 5,56±0,1 q/L. Поліпшення динаміки показників спостерігалося на 5 добу спостережень, причому ця тенденція зберігалася до 10 діб після хірургічного лікування. На 5 добу виявлено достовірне порівняно з показниками до лікування та на першу добу після лікування зниження концентрації основних прозапальних цитокінів TNFa, IL-6 та IL-4 - 12,5±0,6 pg/mL; 11,7±0,3 pg/mL та 4,0±0,2 pg/mL, відповідно. Дана схема лікування призводила до

вираженого зниження рівня TNFa, IL-6 та IL-10 на 10 добу. Значне зниження цитокінів IL-1, IL-6 та IL-10 у пацієнтів після оперативного втручання та зниження показників після проведеної підтримуючої терапії може бути потенційним імунологічним маркером для оцінки її ефективності. При вивченні цитокінового профілю у обстежуваних хворих відмічалось значне підвищення по відношенню до контрольних значень рівня TNF-α та ІЛ-6 у сироватці крові, який знаходиться у прямій залежності від тяжкості перебігу патологічного процесу та функціонального стану печінки, та пригнічує секрецію протизапальних цитокінів. Кісти Echinococcus granulosus викликають індукування сильної відповіді антитіл у більшості пацієнтів, викликаючи при цьому реакцію антиген-специфічних антитіл різних класів з різною інтенсивністю та специфічністю на тлі їх синтезу та підвищеної секреції.

Висновки. Комплексне вивчення медіаторів запалення та динаміки рівнів цитокінів дозволяє вчасно діагностувати ускладнення та запобігати можливим рецидивам ехінококозу печінки. Отримані дані дозволили обґрунтувати подальше застосування імунофана та розробити рекомендації щодо ведення хворих з ехінококозом печінки у післяопераційному періоді.

Ключові слова: ехінококоз печінки, імунофан, біохімічний аналіз крові, цитокіни, імуноглобуліни.

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