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INTRAOPERATIVE CORRECTION OF IMMUNE RESPONSE AS A PART OF COMPREHENSIVE TREATMENT FOR CONGENITAL HYDRONEPHROSIS IN CHILDREN

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ИНТРАОПЕРАЦИОННАЯ ИММУНОКОРРЕКЦИЯ В КОМПЛЕКСНОМ ЛЕЧЕНИИ ВРОЖДЕННОГО ГИДРОНЕФРОЗА У ДЕТЕЙ

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The study revealed several changes in the immunological parameters in 70 children aged 5–12 years with CH complicated by SP. A decrease in the number of CD3-, CD4-, CD16-lymphocytes and indicators of phagocytosis was noted with an increase in the number of CD19-lymphocytes and serum immunoglobulins. To correct the above disorders in 35 children, the method of the intraoperative correction of immune response was used, which consisted of a single injection of a bolus of Imunofan (Bionoks, Russian Federation) under the capsule at the final stage of laparoscopic intervention under the capsule in the region of the lower pole of the kidney. All patients were discharged from the hospital in a satisfactory condition in the stage of partial clinical and laboratory remission of SP. Patients were examined three months after treatment. Compared with the indicators at admission, the examination showed a significant normalization of the absolute number of NK-cells ($p<0.0001$) and B-lymphocytes ($p=0.0229$); absolute ($p=0.0227$) and relative number ($p=0.0192$) of T-lymphocytes; cells with helper functions ($p=0.0026$; $p=0.0132$) and T-suppressors ($p=0.0996$). High levels of serum immunoglobulins decreased with a simultaneous increase in the phagocytic activity of neutrophils ($p=0.0001$). Thus, the intraoperative correction of immune response by Imunofan in the complex treatment of children with CH complicated by SP provides an improvement in the immediate and long-term results of treatment.

Keywords: congenital hydronephrosis, secondary pyelonephritis, surgical treatment, immune response, children

В исследовании выявлены сдвиги иммунологических показателей у 70 детей 5–12 лет с врожденным гидронефрозом (ВГ), осложненным вторичным пиелонефритом (ВП). Отмечено снижение количества CD3-, CD4-, CD16-лимфоцитов и показателей фагоцитоза при повышении количества CD19-лимфоцитов и сывороточных иммуноглобулинов. Для коррекции вышеназванных нарушений у 35 детей использован метод интраоперационной иммунокоррекции, заключающийся в однократном введении на завершающем этапе лапароскопического вмешательства под капсулу в районе нижнего полюса почки болюса препарата Имунофан (Бионокс, Российская Федерация). Все больные были выписаны из стационара в удовлетворительном состоянии в стадии частичной клинико-лабораторной ремиссии ВП. Через 3 месяца после лечения больные были обследованы. По сравнению с показателями при поступлении у пациентов отмечалась достоверная нормализация абсолютного количества NK-клеток ($p<0,0001$) и В-лимфоцитов ($p=0,0229$); абсолютного ($p=0,0227$) и относительного числа ($p=0,0192$) Т-лимфоцитов; клеток с хелперными функциями ($p=0,0026$; $p=0,0132$) и Т-супрессоров ($p=0,0996$). Снижались высокие показатели сывороточных иммуноглобулинов с одновременным повышением фагоцитарной активности нейтрофилов ($p=0,0001$). Таким образом, проведение интраоперационной иммунокоррекции Имунофаном в комплексном лечении детей с ВГ, осложненным ВП, обеспечивает улучшение непосредственных и отдаленных результатов лечения.

Ключевые слова: врожденный гидронефроз, оперативное лечение, вторичный пиелонефрит, иммунокоррекция, дети

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CD – cluster of differentiation
CH – congenital hydronephrosis
IRI – immunoregulatory index
NK – natural killers
PAN – phagocytic activity of neutrophils
SP – secondary pyelonephritis

Congenital hydronephrosis (CH) is the most common pediatric urinary system pathology [1–3], which is often complicated by secondary pyelonephritis (SP) [4–7]. The severity of congenital obstructive uropathy is influenced by many factors, some of which are dilation of the collecting ducts and distal tubules and local ischemia [8–11], as well as immunopathological processes [12, 13]. The latter occurs primarily against the background of high virulence of uropathogens [14, 15]. Several immunocorrection methods have been proposed by researchers, and some of them have appeared to be quite effective [16]. However, we consider intraoperative correction of immune response the most advantageous method for its higher selectivity [17–19] and the ability to enhance antibacterial and other treatments administered [20–24].

The aim of this study was to provide evidence for the use of the intraoperative correction of immune response as a part of comprehensive treatment for CH with SP in children.

Material and Methods. An open-label controlled prospective comparative single-center study was carried out at Kirov Region Children's Hospital and the Department of Pediatric Surgery of the Kirov State Medical University. Immunology research was carried out in the immunohematology laboratory of the Kirov Research Institute of Hematology and Blood Transfusion. We studied 70 children aged 5–12 years (Me=6.9) with CH and SP (the observation group), 39 boys (55.7 %), and 31 girls. All the children underwent clinical, biochemical, bacteriological, instrumental and immunological examinations. To reveal changes in the patients' immunological profile, the ratio of CD3-, CD4-, CD8-, CD16-, and CD19-lymphocytes was determined both upon admission to the hospital and three months after inpatient treatment. The immunoregulatory index (IRI) was estimated using the formula: IRI=CD4/CD8. The concentrations of serum immunoglobulins IgG, IgA and IgM were determined by radial immunodiffusion. The phagocytic activity of neutrophils (PAN) was assessed by the absorption of 0.1-μm latex particles (%). The patients' immunological indicators were compared with those of 300 children of the same age belonging to health status groups I and II (the control group). In the observation group, 35 patients (Group 1) received comprehensive conventional treatment; the other 35 patients (Group 2) received complete traditional therapy combined with Imunofan (Arginyl-Alpha-Aspartyl-Lysyl-Valyl-Thyrosyl-Argininum) bolus injection (Bionoks, Russian Federation). After the main stage of surgical treatment of CH (Anderson-Hines type video laparoscopic surgery [17]), a daily dose of 0.005 % Imunofan solution at a dosage of 0.1 ml per year of life was injected under the kidney capsule using a special technique [14] (Fig. 1). No further immunotropic treatment was carried out.

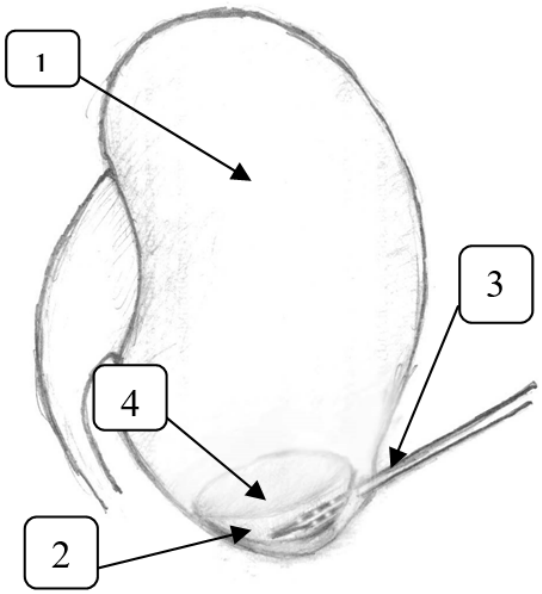

Fig. 1. The scheme of intraoperative injection of an immunotropic drug in kidney surgery: 1 – the kidney, 2 – the lower pole of the kidney, 3 – the needle, 4 – the bolus of the injected medication

Statistical data analysis includes descriptive analysis and inferential statistics. Immunogram values are represented quantitatively and qualitatively. The number of cells per 1 μl (cells/μl) or the number of cells x 10^9 per 1 liter are examples of absolute quantity values. We used the Shapiro – Wilk test as our numerical means of assessing the normality of the quantitative data.

The test showed that most quantitative data were distributed close to normal. At the same time, part of the quantitative data had a distribution other than normal, making it possible to use the median (Me) and quartiles [Q1; Q3], and for data analysis – non-parametric methods. Qualitative data are presented as relative values (P, %) and 95 % confidence intervals for relative values (95 % CI). 95 % confidence intervals were calculated using the Wilson method. The assessment of the statistical significance of differences in related (dependent) quantitative data was performed using the Wilcoxon test. The evaluation of the statistical significance of differences in independent sample quantitative data was performed using the Mann – Whitney test. Characterization of the statistical significance of differences in quantitative data is presented depending on the selected criterion: the value of the Wilcoxon test (T), the value of the

Mann – Whitney test (U), and the level of statistical significance (p).

The assessment of the statistical significance of differences in independent qualitative data (indicators of the immunogram, represented by relative values three months after the treatment in the observation group and the control group) was performed using the Chi-square test (χ^2) adjusted for Yates continuity. The frequencies in the cells of four-field tables when calculating these criteria were represented by the number of cells per 1 ml. The value $p<0.05$ was chosen as the critical level of statistical significance of differences (p). Statistical processing was performed in MS Excel 10.0 (Microsoft, USA) and SPSS Statistics 22 (IBM, USA)

Results and Discussion. All patients with CH and SP admitted to the clinic for inpatient treatment were examined, including immunological examination. An analysis of the results of their immunograms showed that various shifts in immunological parameters characterize children of this category: a decrease in the absolute and relative number of CD4-lymphocytes and, as a result, IRI; reduction in the number of natural killers; excess of B-lymphocytes and immunoglobulins in blood serum; decrease in phagocytosis rates (Table 1) compared with healthy children.

Table 1

Immunological indicators in healthy children and in patients with CH and SP upon admission to the hospital

Indicators	Healthy children, n=300 (M±m)	Patients upon their admission to the hospital, n=70 (M±m)
CD3 cells, 10^9/l	1.04±0.07	1.24±0.04*
CD3 cells, %	64.1±1.25	62. 48 ±0.44
CD4 cells, 10^9/l	0.59±0.02	0.52±0.02*
CD4 cells, %	49.20±1.32	43.61±0.29*
CD8 cells, 10^9/l	0.30±0.023	0.29±0.03
CD8 cells, %	25.1±0.9	25.55±0.32
IRI	2.0±0.09	1.81±0.04*
CD16 cells, 10^9/l	0.37±0.05	0.14±0.02
CD16 cells, %	18.2±1.95	5.69±0.94*
CD19 cells, 10^9/l	0.17±0.02	0.43±0.02*
CD19 cells, %	9.90±0.77	17.30±0.37*
Ig G, g/l	9.44±0.18	12.03±0.20*
Ig A, g/l	1.10±0.05	1.51±0.05*
Ig M, g/l	1.17±0.05	1.85±0.10*
PAN, %	69.17±1.24	52.86±0.65*

* p<0,05 – compared with healthy children.

A comparative analysis of the observation and control groups by age and sex characteristics did not reveal any statistically significant differences between the two groups (U=1955.0, p=0.84; χ^2=0.11: df=1, p=0.75). To minimize the severity of CH clinical manifestations and reduce the recurrence risk of the disease, intraoperative correction of immune response by Imunofan was used as a part of the comprehensive treatment of group 2 patients (35 patients). The Imunofan was used according to a special permit protocol of local ethics committee. Parental consent was obtained in each case. A medical institution purchased the medication by decision of medical consultation. Group 1 was formed in parallel; treated without the use of intraoperative immunocorrection (also 35 patients).

In all the cases, no postoperative complications were noted. All the patients were discharged from the hospital in satisfactory condition with partial clinical and laboratory remission of SP. After that, the patients were under the supervision of both a pediatric surgeon and a pediatrician (a pediatric nephrologist). Three months later, at the stage of complete clinical and laboratory remission of CH, the children's immunogram was retaken. The immunogram showed (Table 2) that the values of the absolute number of NK-cells ($p<0.0001$) and B-lymphocytes (p=0.0229), the absolute (p=0 .0227) and relative number (p=0.0192) of T-lymphocytes, T-helpers (p=0.0026; p=0.0132) and T-suppressors (absolute number, p=0.0996) became close to the normal range. Elevated serum immunoglobulin levels were observed to decrease; phagocytic activity of neutrophils was found to increase (p=0.0001).

Table 2

Immunological indicators in group 2 patients 3 months after the surgery

Indicators	Me	Min	Max	Q_1–Q_3	P-value in normal distribution
CD16 cells, %	10.000	2.000	18.700	7.500–11.000	0.3514
CD16 cells, abs.	0.323	0.0500	0.530	0.130–0.470	<0.0001
CD19 cells, %	12.650	7.000	16.000	10.000–14.300	0.2483
CD19 cells, abs.	0.375	0.0900	0.620	0.160–0.500	0.0229
CD3 cells, %	77.500	64.700	84.000	75.200–81.000	0.0227
CD3 cells, abs.	1.625	0.600	3.570	1.230–3.090	0.0192
CD4 cells, %	50.400	38.700	57.000	42.400–54.000	0.0026
CD4 cells, abs.	1.180	0.390	1.880	0.720–1.600	0.0132
CD8 cells, %	25.950	18.500	36.000	21.000–27.400	0.5032
CD8 cells, abs.	0.545	0.220	1.250	0.370–0.710	0.0996
IgM, g/l	1.685	0.680	2.350	0.860–1.800	0.2443
IgA, g/l	1.315	0.500	3.320	0.900–1.800	0.1063
IgG, g/l	10.665	4.410	24.300	8.800–13.080	0.0774
Lymphocytes, %	33.050	12.000	57.600	22.000–40.000	0.7401
Lymphocytes, abs.	2.670	0.800	4.780	1.900–3.960	0.0061
Leucocytes, abs.	9.250	4.020	13.200	5.700–10.300	0.3645
IRI	2.100	1.100	3.000	1.600–2.620	0.1415
PAN, %	68.500	33.000	75.000	62.000–72.000	0.0001

Comparison of independent samples according to the Mann – Whitney test for a part of quantitative data with a distribution other than usual when using non-parametric methods showed (Table 3) that the above trends are primarily characteristic of a decrease in the excess number of B-lymphocytes when using intraoperative correction of immune response by Imunofan, an increase of the reduced number of T-lymphocytes (absolute and relative numbers) and cells with helper functions (relative number).

Table 3

Comparison of group 2 patients' samples upon their admission to the hospital and 3 months after the treatment (according to the Mann – Whitney U-test)

Indicators	Upon admission to the hospital		After the immuno-correction		P
	Me	Average rank	Me	Average rank	
CD19 cells, %	17.0000	78.6893	12.6500	56.9512	**0.0047**
CD19 cells, abs.	0.4100	76.8010	0.3750	57.5000	**0.0126**
CD3 cells, %	61.7000	65.2864	77.5000	89.2875	**0.0019**
CD3 cells, abs.	1.2700	62.6553	1.6250	88.2206	**0.0011**
CD4 cells, %	50.4000	65.0825	48.0000	80.8676	**0.0440**
CD8 cells, %	25.9500	68.4029	25.0000	70.8088	0.7591
IgM, g/l	1.7000	70.0583	1.7000	75.3077	0.4970
IgA, g/l	1.3000	71.9417	1.3000	72.1500	0.9785
IgG, g/l	11.0000	70.9461	11.0000	72.9125	0.7977
IRI	1.8000	69.7767	1.7000	79.3415	0.2135
PAN, %	49.0000	38.9863	55.0000	52.3333	0.1707

Calculations have shown that changes in the mentioned above immunological indicators are the most sensitive and specific ones in laboratory investigation for CH and SP in children (Fig. 2).

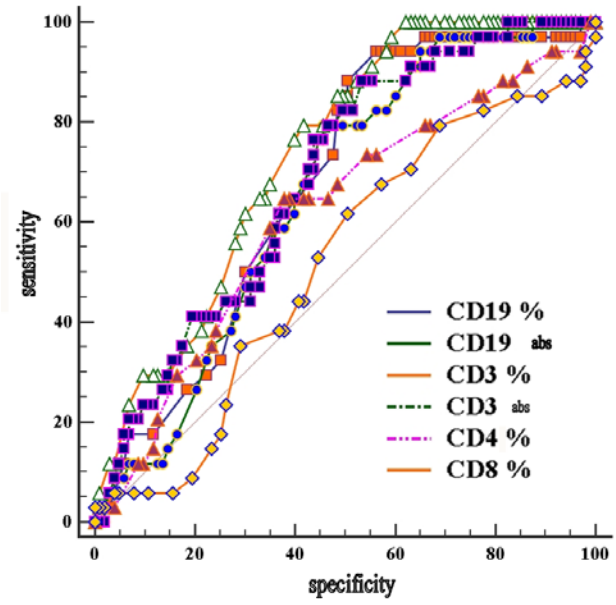

Fig. 2. Sensitivity and specificity of detection of the most important immunological markers in CH and SP in children

Comparative studies of the immunological parameters of group 1 and group 2 after treatment (three months after hospital discharge) showed that in patients with CH and SP, with intraoperative correction of immune response by Imunofan included in complex treatment, almost all initially impaired indicators of the body's immunological resistance returned to normal, which cannot be said about patients treated without the use of this immunotropic method (Table 4).

A slight interest decrease in immunological and immunotherapeutic issues, which was outlined in the professional community by the end of the pre-pandemic period, did a disservice to domestic medicine. The coronavirus pandemic has turned the world's attention to the immune system showing that immune responses contribute to the development of many common disorders not traditionally viewed as immunologic. Applying knowledge of our body's immune responses in our everyday practice is essential to future diagnosis and successful management of various diseases, including child diseases [3, 9]. The following changes in immunologic reactivity generally accompany CH and SP: decrease in cellular immune response and phagocytosis, increase in humoral immune response and nonspecific resistance, and an abnormal helper/suppressor ratio. These are the problems requiring comprehensive treatment in cases of CH and SP.

Table 4

Immunological indicators of group 1 and group 2 (3 months after hospital discharge)

Indicators	Group 1 (M±m)	Group 2 (M±m)
CD3 cells, 10^9/l	1.33±0.04	3.54±0.07*
CD3 cells, %	73.94±0.49	72.4±2.92
CD4 cells, 10^9/l	0.70±0.03	0.88±0.08
CD4 cells, %	45.75±0.62	46.6±2.0*
CD8 cells, 10^9/l	0.50±0.03	0.36±0.085
CD8 cells, %	27.57±0.62	34.8±1.76
CD4/CD8 (IRI)	1.92±0.17	2.18±0.135*
CD16 cells, 10^9/l	0.39±0.03	0.41±0.07
CD16 cells, %	15.43±0.86	15±1.7
CD19 cells, 10^9/l	0.40±0.02	0.25±0.03
CD19 cells, %	15.34±0.45	0.89±0.77
IgG, g/l	18.87±0.27	11.4±3.7*
IgA, g/l	1.53±0.09	1.1±0.06
IgM, g/l	1.85±0.20	1.36±0.07
PAN, %	54.40±1.24	64.6±4.38*

* $p<0,05$ – compared with Group 1.

In addition, we conducted a catamnesis study in all patients within one year after inpatient treatment. Group 1 – 3 patients had CH exacerbations (1, 2, and 8 months after the surgery). Group 2 patients had no disease exacerbations. Thus, the results of the catamnesis show encouraging findings for intraoperative immunocorrection in children with CH.

Conclusions. The inclusion of intraoperative correction of immune response by Imunofan in the complex treatment of CH and SP in sick children led to the most significant following results: normalization of the absolute number of natural killer and B-lymphocytes, the absolute and relative number of T-lymphocytes, cells with helper functions and T-suppressors (total quantity), a decrease (without expressed reliability) in excess levels of serum immunoglobulins, an increase in reduced indicators of the phagocytic link of nonspecific resistance, which is partly confirmed by studies by other authors [8, 22–24]. The uncertainties of this study may be related to the relatively small size of the observation group, the lack of randomization, and the lack of preliminary calculation of the number of observations in the formation of samples.

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