Artículo de investigación

Peripheral blood parameters as a marker of nonspecific adaptive response of the body in acute infectious diseases with tonsillitis syndrome

Параметры периферической крови как маркеры неспецифического адаптационного ответа при острых инфекционных заболеваниях с синдромом тонзиллита

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Abstract

Evaluation of nonspecific adaptive response of the body in children with acute infectious diseases associated with tonsillitis syndrome was the aim of this research. This prospective study included clinical, anamnestic and laboratory examination of children with acute infectious diseases with tonsillitis syndrome. A systemic multiple factor analysis was conducted (significance level $p<0.05$). The evaluation of peripheral blood parameters (specific gravity of lymphocytes and indices of reactive protective potential (RPP) - specific immune lymphocytic-monocytic parameter (SILMP) and coefficient of phagocytic defense (CPD)) gives the possibility to determine the condition of nonspecific adaptation in children with acute infectious diseases associated with tonsillitis syndrome. Children with tonsillitis syndrome show significant increase of integral RPP parameters, i.e. decrease of RPP, which is more pronounced

Абстрак

Целью настоящего исследования явилась оценка неспецифической адаптационной реакции организма у детей с острыми инфекционными заболеваниями, ассоциированными с синдромом тонзиллита. Данное проспективное исследование включало клинико-анамнестическое и лабораторное обследование детей с острыми инфекционными заболеваниями с синдромом тонзиллита. Проведен системный многофакторный анализ (уровень значимости p<0,05). Оценка показателей периферической крови (удельного веса лимфоцитов и показателей реактивно-протективный потенциал (РПП) - специфического иммунного лимфоцитарно-моноцитарного параметра (ИЛМП) и коэффициента фагоцитарной защиты (КФЗ) дает возможность определить состояние неспецифической адаптации у детей с

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on discharge (on admission - in 57% of children, on discharge - in 87%). The most unfavourable initial nonspecific adaptative body response (NABR) (according to the percentage of lymphocytes) is the reaction of increased activation, as it is associated with the transition to the overactivation by the time of discharge (37% of children). Systemic multiple factor analysis determined which peripheral blood parameters have more influence on children's adaptation during the course of infectious disease: RPP indices showed high influence coefficients in all diseases (CPD was the highest in bacterial infection - Pi 198.3; SILMP was the highest in viral infection - Pi 147.81; in mixed infection CPD and SILMP were roughly the same - Pi – 107.25 and Pi - 78.11, respectively), which proves the feasibility of RPP evaluation for prognostic purposes in the treatment of this category of patients.

Key words: Reactive-protective potential, lymphocytes, nonspecific adaptation, acute infectious diseases, tonsillitis.

острыми инфекционными заболеваниями, ассоциированными с синдромом тонзиллита. У детей с синдромом тонзиллита отмечается достоверное повышение интегральных показателей РПП, т. е. снижение РПП, которое более выражено при выписке (при поступлении - у 57% детей, при выписке - у 87%). Наиболее неблагоприятной исходной неспецифической адаптационной реакцией организма (по проценту лимфоцитов) является реакция повышенной активации, так как она связана с переходом к гиперактивации к моменту выписки (37% детей). Системный многофакторный анализ определил, какие показатели периферической крови оказывают большее влияние на адаптацию детей в течение инфекционного заболевания: показатели РПП показали высокие коэффициенты влияния при всех заболеваниях, что доказывает целесообразность оценки РПП в прогностических целях при лечении данной категории больных.

Ключевые слова: реактивно-протективный потенциал, лимфоциты, неспецифическая адаптация, острые инфекционные заболевания, тонзиллит.

Introduction

Stress factors, which include acute infectious processes, activate compensatory mechanism aimed at temporary maintenance of homeostasis and formation of continuous adaptation [1]. Adaptation is considered as a complex of body reactions that maintain its functional stability in case of environmental changes (Jones et al., 2001; Gorban et al., 2016). The essence of adaptation is the ability of the body to change the intensity, rhythm and mode of all its processes the way that all the main parameters of internal environment are maintained within the physiological limits despite of the influence of external factors (Procaccini et al., 2014).

Reaction to stress has an important influence on the nature of its outcomes. The body is searching for reaction mechanism that can help reach stable balance. If it is not possible, the resistance phase of adaptation syndrome turns into the exhaustion phase, which in severe cases can lead to death (Jones et al., 2001; Gorban et al., 2016). During the adaptation period, the immune system and all its protective forces are activated, the immune sensitivity threshold lowers, and the child actively starts to form natural immunity (Lebedev et al., 2017). Child's body has powerful compensatory mechanisms that are responsible for his/her health condition, but their capabilities are limited. If the development of adaptation does not begin within a certain period of time, disadaptation forms, which can trigger the development of a disease (Lebedev et al., 2017). Infectious diseases as a stress factor can be the cause of disadaptation (Santalova et al., 2017). It has been reported that severe cases can lead to immunodepression and even tumor development (Santalova et al., 2017).

In this regard, it is important to evaluate both specific and nonspecific adaptative reactions of the body in children as a response to acute infectious process, including the one with tonsillitis syndrome. Evaluation of the adaptive body responses can be performed considering the parameters of nonspecific adaptative body response (NABR), markers of which are specific immune lymphocytic-monocytic potential (SILMP), which reveals the ability of the body to respond to the nonshared antigens by producing antibodies, and coefficient of cellular phagocytic defense (CPD), which shows the possible risk of breaking the resisting barrier by some infection.

Materials and methods

This prospective study included clinical, anamnestic and laboratory examination of children with acute infectious diseases associated with tonsillitis syndrome. The research was carried out in the 2nd Children's infectious department of the Samara City Hospital №5.

The main group included 100 children aged from 3 to 7 years (48 girls and 52 boys) treated for the above-mentioned diseases. The mean age of children was 58.70±1.61 months. All the children suffered from the moderate form of the disease. The children of the main group were examined according to the treatment guidelines for the children's infectious hospital (Group 2 – on admission, Group 3 - on discharge).

Reference values of hemograms of healthy children from the National Guidelines for Pediatrics ed. by Baranov A.A., 2015 were taken as control parameters for the evaluation of NABR in children. The percentage of lymphocytes and reactive-protective potential (specific immune lymphocytic-monocytic potential (SILMP) and coefficient of cellular phagocytic defense (CPD)) were determined. The types of adaptive responses according to the percentage of lymphocytes were evaluated in correspondence with the reference values (Garkavi et al., 2012) (Table 1).

Table 1: Age-specific rate of adaptive responses according to the percentage of lymphocytes

Age, years	Stress reaction	Training reaction	Reaction of moderate activation	Reaction of increased activation	Overactivation
3-5	<29,5	29,5-37,5	38-45	45,5-57	>57
6-9	<25	25-32	32,5-40	40,5-51	>51

Stress reaction and training reaction are nonspecific anti-stress body responses that are necessary for the maintenance of homeostasis under the influence of stress factors. Reaction of activation is divided into two types: reaction of moderate activation under the influence of stress, which is formed in the beginning, and then the reaction of increased activation. Both reactions lead to rapid and significant increase of active nonspecific body resistance by means of genuine increase of activity of its defense systems. Reaction of overactivation is characterized by the above normal elevation of the percentage of lymphocytes in the differential WBC, and excessive activity of the nervous and endocrine systems. This reaction is dangerous for the risk of adaptation failure and is considered as nonspecific basis for pathological processes resulting from desynchronization of regulating systems (Garkavi et al., 2012).

Specific immune lymphocytic-monocytic potential was counted according to the following formula:

<u>Specific gravity of lymphocytes + Specific gravity of monocytes</u>
SILMP =
x 100;

Total leukocyte count where 100 is the value revealing the studied function.

Cellular phagocytic defense was counted according to the following formula:

<u>Specific gravity of band neutrophils + segmented neutrophils + monocytes</u>
CPD =
x 100;

Total leukocyte count where 100 is a coefficient revealing the required function.

The less is CPD, the more pronounced is the risk of breaking the defense barrier by the infection.
Statistical and mathematical processing of the observed measurements was conducted using SPSS Statistics 21.0 software (license № 20130626-3), Microsoft Office Word – 2010, and Microsoft Office Excel – 2010 on AMD Athlon II PC with Windows XP. A systemic

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multiple factor analysis of the studied parameters was carried out. The differences between the compared figures, irrespectively of the method of analysis, were considered statistically significant at the critical level $p<0.05$.

Results and discussion

Infectious diseases associated with the development of tonsillitis syndrome are presented in Table 2.

Table 2: Nosological forms of infectious process

Etiology	Number of children
Bacterial infection	40 (40%)
Viral infection	25 (25%)
Viral-bacterial association	35(35%)

Acute infectious diseases were classified according to their etiology: bacterial (a case of streptococcal tonsillitis), viral (a case of infectious mononucleosis) and viral-bacterial association (e.g. comorbid causative agent). The diagnosis was verified in all the cases. The main symptoms of infectious diseases associated with tonsillitis syndrome are shown in Table 3.

Table 3: General symptoms of infectious diseases with tonsillitis syndrome

Symptoms	Bacterial infection	Viral infection	Viral-bacterial association
Fever > 38^0C	73%	90%	80%
Fever duration	2-3 days	4-5 days	3-4 days
Sore throat	10%	90%	100%
Edema of tonsils and exudate	80%	60%	20%
Catarrhal symptoms (rhinorrhea, cough, microvesiculation on faucial pillars)	100%	65%	100%
Streptococci in smear culture	100%	0%	75%
Enlargement of local lymphatic nodes	30%	95%	15%
Hepato- and/or splenomegaly	0%	95%	0%
Lymphocytic leucocytosis of peripheral blood	5%	95%	30%
Atypical lymphocytes in peripheral blood	0%	95%	0%

Comparative analysis of the investigated parameters of children’s hemograms at different stages of acute respiratory diseases vs. reference values showed significant difference between them (Table 4).

Table 4: Comparative analysis of hemogram parameters of healthy and diseased children at different stages of acute infectious process

Parameter	Reference values (1)	Values on admission (2)	Values on discharge (3)	p 1-2	p 1-3	p 2-3
Total leucocyte count	6,8±0,80	13,65±0,75	7,69±0,20	0,007	0,725	<0,001
Specific gravity of band neutrophils	2,15±0,60	4,03±0,69	2,05±0,56	0,325	0,958	<0,001
Specific gravity of segmented neutrophils	48,3±6,30	56,11±2,02	44,82±1,26	0,695	0,861	<0,001
Specific gravity of lymphocytes	36,2±1,20	27,22±1,28	45,98±1,17	0,019	0,010	<0,001
Specific gravity of monocytes	5,1±0,20	6,16±0,31	4,13±0,21	0,098	0,128	<0,001
Erythrocyte sedimentation rate	8,0±0,60	21,34±1,41	10,90±0,70	0,001	0,129	<0,001

The table shows the mean values and their standard errors; statistical significance of differences (p) in accordance with Mann–Whitney–Wilcoxon criterion is reliable for $p<0.05$.

Comparison study of the blood count parameters in healthy and diseased children at different stages of acute respiratory process revealed the increased markers of inflammation both on admission and on discharge, which was manifested in the high specific gravity (SG) of lymphocytes. The initial condition of NABR influenced the adaptation during the infectious process (Table 5, 6).

Table 5: Distribution of children according to NABR type on admission and on discharge

NABR type (according to the percentage of lymphocytes)	Group 2 %	Group 3 %
Stress reaction	56%	8%
Training reaction	19%	10%
Reaction of moderate activation	16%	23%
Reaction of increased activation	8%	48%
Overactivation	1%	11%
Total	100	100

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Table 6: The nature of changes in the NABR indices (according to the percentage of lymphocytes) in children with different baseline levels

		Reaction prior to discharge					
		Stress reaction	Training reaction	Reaction of moderate activation	Reaction of increased activation	Over-activation	Total
Reaction on admission	Stress reaction	5	5	18	24	4	56
	Training reaction	2	3	4	8	2	19
	Reaction of moderate activation	1	2	0	12	1	16
	Reaction of increased activation	0	0	1	4	3	8
	Overactivation	0	0	0	0	1	1
Total		8	10	23	48	11	100

*(p<0,001).

Thus, only 8 % of children with initial stress or training reaction had overactivation on discharge; 6% of children showed overactivation on discharge after initial reaction of moderate activation; meanwhile, initial reaction of increased activation led to overactivation in 37% of children. This type of reaction is considered as nonspecific basis for some diseases and poses a threat of adaptation failure. Comparison method based on the Wilcoxon test for paired samples was used to study the dynamics of NABR levels. Significant increase of integral indices of total body reactivity (SILMP, CPD) denoted its decrease, especially pronounced on discharge (Table 7).

Table 7: Values of RPP coefficients in children with acute infectious diseases

Parameter	RPP coefficients values		p
	Group 2	Group 3	
CPD	6,54±0,51	7,01±0,32	<0,001
SILMP	3,50±0,29	7,08±0,26	<0,001

While distributing the children of Group 2 and Group 3 according to the RPP indices at different stages of acute respiratory disease, RPP decrease was noted in 57% of children at the acute stage of the disease and in 87% of children on discharge (Table 8).

Table 8: Distribution of children according to the indices of reactive-protective potential at the beginning of the disease and on discharge

RPP values	Group 2 %	Group 3 %
Reference value	43%	13%
Decrease	57%	87%
Total	100%	100%

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Next, we used systemic multiple factor analysis (SMFA) to determine the influence of studied parameters of the immune system on the adaptation process in children with acute infectious diseases associated with tonsillitis syndrome depending on the etiology of the infection. The weighting factor (influence coefficient) was calculated during mathematical modeling (Table 9).

Table 9: Results of systemic multiple factor analysis of adaptation process in children with tonsillitis of different etiology (1 - relative difference of parameters; 2 – weighting factor)

Parameter	Bacterial infection		Viral infection		Viral-bacterial association	
	admission	discharge	admission	discharge	admission	discharge
Leucocytes, cell/ml	1,29±0,4 2 – 113,1	0,16±0,39 2 – 39,4	1,13±1,54 2 – 65,6	0,18±0,35 2 – 34,9	0,59±0,09 2 – 77,8	0,07±0,06 2 – 47,8
Band neutrophils, %	1,64±0,7 2 – 122,4	-0,45±0,14 2 – 128,1	0,54±0,11 2 – 27,3	-0,42±0,07 2 – 20,0	0,24±0,06 2 – 46,8	0,69±0,15 2 – 77,1
Segmented neutrophils, %	0,37±0,04 2 – 71,8	-0,01±0,001 2 – 24,5	-0,34±0,04 2 – 3,8	-0,27±0,06 2 – 4,6	0,28±0,03 2 – 102,4	0,0±0,01 2 – 42,6
Lymphocytes, %	-0,43±0,04 2 – 66,5	0,28±0,01 2 – 24,6	0,0±0,02 2 – 96,4	0,33±0,02 2 – 119,7	-0,22±0,00 2 – 9,1	0,22±0,02 2 – 31,9
Monocytes, %	0,31±0,07 2 – 11,3	-0,14±0,03 2 – 16,2	0,27±0,05 2 – 58,8	-0,09±0,02 2 – 22,2	0,05±0,01 2 – 17,3	-0,32±0,08 2 – 19,4
Eosinophils, %	2,65±0,6 2 – 80,0	3,6±0,8 2 – 94,2	0,6±0,04 2 – 56,5	1,0±0,07 10,3	0,0±0,05 2– 18,3	1,45±0,3 2 – 66,2
ESR, mm/hour	1,87±0,03 2 – 90,8	0,49±0,02 2 – 30,5	1,65±0,04 2 – 16,9	0,52±0,02 2 – 7,38	1,5±0,06 2– 99,3	0,11±0,06 2 – 22,0
CPD, c.u.	-0,02±0,00 2 – 198,3	0,14±0,03 2 – 80,9	-0,49±0,07 2 – 65,6	-0,17±0,03 2 – 28,8	0,39±0,07 2 – 107,3	0,18±0,05 2 – 82,4
SILMP, c.u.	-0,58±0,12 2 – 88,2	1,08±0,05 2 – 68,2	-0,46±0,06 2 – 147,8	1,08±0,11 2 – 84,5	-0,27±0,05 2 – 79,1	0,17±0,05 2 – 83,8
MB of immune component, c.u	**0,8**	**0,66**	**0,32**	**0,24**	**0,29**	**0,29**

The developed mathematical model was used for calculating influence coefficients. On the part of the immune system, all nosological forms showed high influence coefficients of RPP indices (Fig. 1, 2, 3).

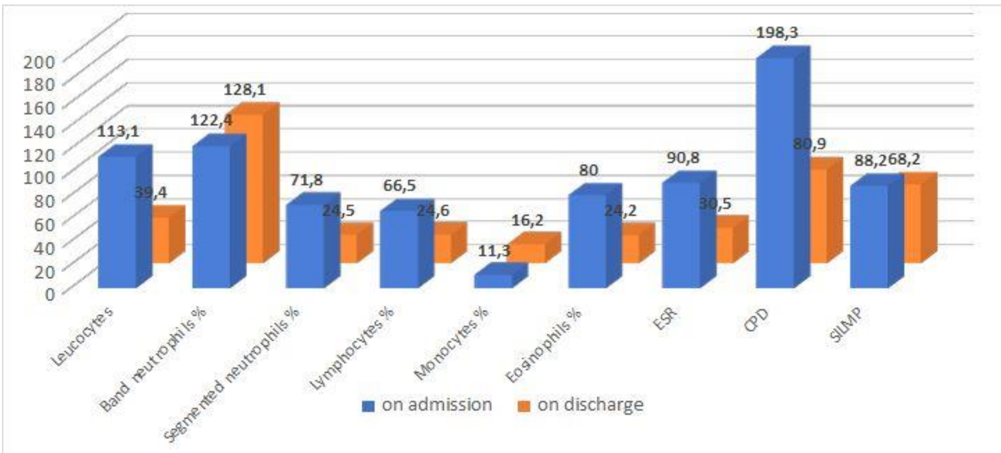

Fig. 1. Influence coefficients of immune parameters of adaptation in diseases of bacterial etiology.

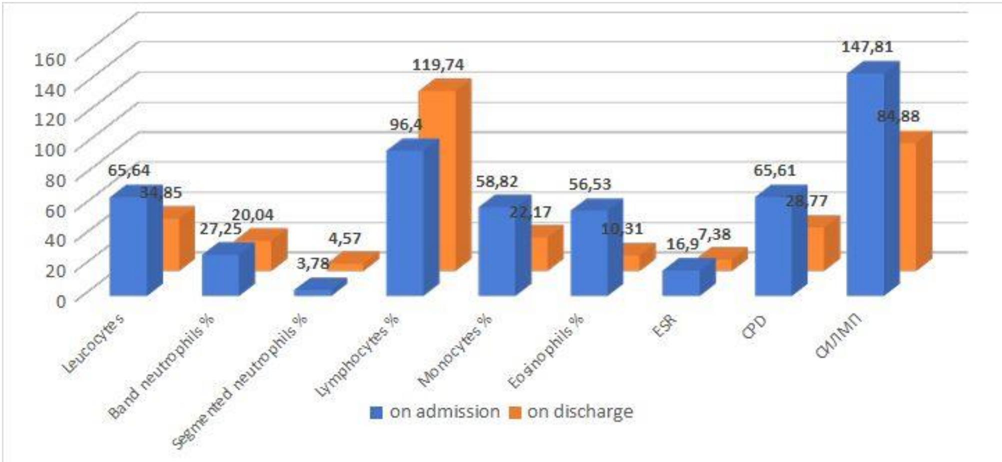

Fig. 2. Influence coefficients of immune parameters of adaptation in infectious diseases of viral etiology.

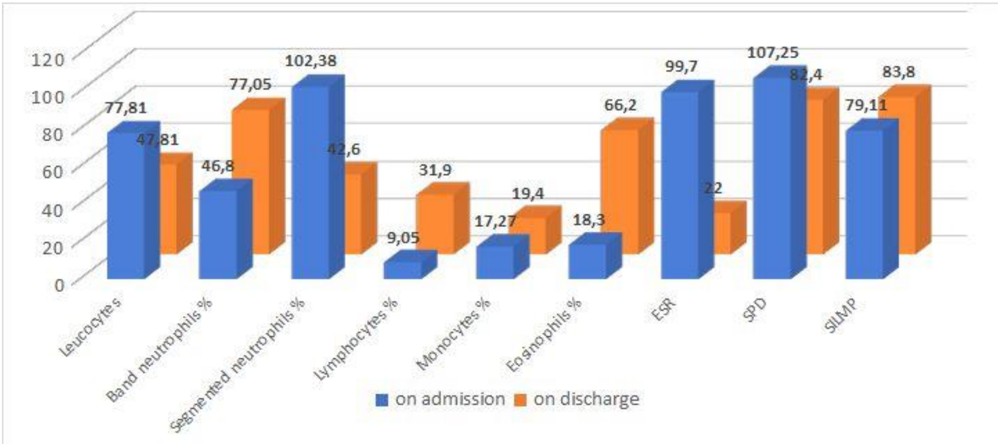

Fig. 3. Influence coefficients of immune parameters of adaptation in infectious diseases of mixed etiology.

Presented figures testify that CPD level was the highest in bacterial infection - Pi 198.3; SILMP was the highest in viral infection – Pi 147.81; in mixed infection the levels of CPD and SILMP were roughly the same - Pi – 107.25 and Pi - 78.11, respectively. The revealed tendency of RPP influence maintained on discharge.

Conclusion

The evaluation of peripheral blood parameters (specific gravity of lymphocytes and RPP indices – SILMP and CPD) provide a means to determine the state of nonspecific adaptation in children with acute infectious diseases with tonsillitis syndrome. Children with tonsillitis syndrome show significant increase of integral indices of systemic reactivity (RPP), i.e. its decrease, which is more prominent on discharge (on admission – in 57% of children, on discharge – in 87%). The initial NABR condition (according to the percentage of lymphocytes) influences adaptation during the infectious process: initial reaction of increased activation is the most unfavourable one as it was associated with transition to overactivation by the time of discharge (37% children).

Systemic multiple factor analysis revealed the most influential parameters of the immune system on the adaptation of children in the course of acute infectious disease with tonsillitis syndrome: all nosological forms showed high levels of RPP influence (CPD level was the highest in bacterial infection - Pi 198.3; SILMP was the highest in viral infection – Pi 147.81; in mixed infection the levels of CPD and SILMP were roughly the same - Pi – 107.25 and Pi - 78.11, respectively), which proves the advisability of RPP evaluation in treatment of this category of patients for prognostic reasons.

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