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DIVERSITY OF THE SYSTEMIC INFLAMMATORY RESPONSE IN NEONATAL SEPSIS

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Summary

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Key words: *SIRS (systemic inflammatory response syndrome), "hypoergic", "hyperergic" variants of neonatal sepsis.*

A survey of 94 infants of the first week of life was made. The "A" group was presented by newborns who had hypoergic variant of sepsis (17 preterm newborns with the gestational age >32 weeks and 11 term newborns). The "B" group was presented by newborns who had hyperergic sepsis (16 preterm infants with the gestational age >32 weeks and 27 term infants). The group of comparison was comprised by 23 newborns with acute pneumonia. The following lab–tests were made: level of 12 acute-phase proteins, IgG, IgM, IgA; levels of STG, TTG, T3, the analyses of leukocyte formula, four leukocyte indexes of reactivity.

On the bases of obtained data patterns of 2 lab-clinical variants of the SIRS were suggested. Pattern SIRS in hypoergic variant of sepsis is a deficient condition with prevalence of proteases in the spectrum of mediators against hypothyroidism of septic genesis. Pattern SIRS in hyperergic variant of sepsis – is a "cytokine storm" with maintained hormonal provision of protein-synthetic processes and immunity.

Резюме

К ВОПРОСУ О СИСТЕМНОМ ВОСПАЛИТЕЛЬНОМ ОТВЕТЕ ПРИ НЕОНАТАЛЬНОМ СЕПСИСЕ

Обследовано 94 ребенка первой недели жизни. Группу «А» составили новорожденные с гипоэргическим вариантом сепсиса (17 недоношенных со сроком гестации >32 недель и 11 доношенных). Группа «В» - новорожденные с гиперэргическим вариантом сепсиса (16 недоношенных со сроком гестации > 32 недель и 27 доношенных). Группа сравнения представлена 23 новорожденными с острой пневмонией.

Лабораторное обследование включало определение уровней 12 белков острой фазы, IgG, IgM, IgA, уровней СТГ, ТТГ, Т3, анализ лейкоцитарной формулы с определением 4 лейкоцитарных индексов реактивности.

На основании полученных данных было выделено 2 клинико-лабораторных варианта SIRS.

Характер SIRS при гипоэргическом варианте сепсиса — дефицитное состояние с преобладанием протеаз в спектре медиаторов и гипотиреоидизм септического генеза.

SIRS при гиперэргическом варианте сепсиса — это «цитокиновый шторм» с сохранением гормонального обеспечения процессов белкового синтеза и иммунитета.

Introduction. Systemic inflammatory response syndrome-(SIRS) is the pathogenetic basis of sepsis [1]. The neonatal SIRS developd in particular immunological status of newborn, birth stress and more often in premature i.e. initially immunodeficiency organism.

Years of research in the field of neonatal sepsis led us to the conclusion that there are at least 2 variants of sepsis. Initially by complex survey of children on 27 hemostatic parameters we were able to identify objective criteria to differentiate two patterns of DIC - "decompensated" and "overcompensate" for neonatal sepsis [2]. Comparison of these data with the full range of clinical and laboratory data made it possible to formulate the concept of 2 clinical-laboratory variants of neonatal sepsis, "hypoergic" and "hyperergic" [3-5].

The **aim** of this study was to formulate a pattern of 2 clinical-laboratory variants of SIRS in neonatal sepsis on the basis of acute phase proteins spectrum, immunological parameters, hormonal profile, indixes of cellular reactivity. This fact would help to create an

appropriate "patterns of blood" in combination with the previously formulated pattern of DIC- syndrome.

Methods. We examined 71 newborns with sepsis occurred in the first week of life in the dynamics of pathological process (from 2 to 14 times). There were 28 children with hypoergic variant "A" (17 of them were preterm with gestational age > 32 weeks) and 43 with hyperergic variant «B" - (including 16 preterm newborns with gestational age > 32 weeks). Mortality rate in variant "A" was 63,1% and in variant «B» – 13,7%. A comparison group was comprised by infants with neonatal pneumonia - 23 children. Normative data for all hemostatic parameters were obtained and published previously [6].

Research methods included the determination of platelet hemostasis: platelet count and assessment of their functional activity, studied by two methods: microscopic and using aggregometer. Microscopic identification was performed by the method of aggregation O'Brein JR (1963) modified by Chumakova GN, et al. (1987). As agregants were used ADP (Calbiochem Behring Corp.), epinephrine (Calbiochem Behring Corp.), ristocetin. To evaluate the dynamic properties of the platelet aggregometer "THROMLITE 1006" was also used. Platelet counts were determined by two methods: phase-contrast microscopy and in some cases with an automatic counter.

All parameters of coagulation hemostasis were determined using reagents of Behring company (Germany). Tests of overall coagulation: activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT) batroxobin time (BT) were measured by enzymatic method. The contents of fibrinogen (FG), fibronectin (FN), antithrombin III (AT-III), C1-inhibitor (C1-IN), a1-antitrypsin (a1-AT), a2-macroglobulin (a2-MG), a-fetoprotein (a-FP), plasminogen (PG) were investigated by direct radial immunodiffusion. The level of von Willebrand factor (vWF) was determined by agglutination of standard lyophilized platelets. The concentrations of FG, II, V, VII, VIII, IX, X, XI, XII coagulation factors and protein C (Prot. C) and high molecular kininogen (CMC) were determined by enzymatic method. Determination of factor XIII was assessed by stability of the clot in the monochloroacetic acid. The content of degradation products of fibrin and fibrinogen (FDP) were examined by semiquantitative agglutination of staphylococci.

Determination of immunoglobulin in the serum was performed by radial immunodiffusion (Mancini G. et al., 1965). Circulating immune complexes (CIC) were determined by two methods: by precipitation in polyethylene glycol-6000 (PEG), and in some children by method of Kositskaya AS , et al. (1986) using 0.025% acetic acid.

Determination of hormone levels (somatotropin-growth hormone (GH), thyrotropin- thyroid-stimulating hormone (TSH), triiodothyronine (T3)) in blood plasma were made using reagents of Hema company (Moscow), on the basis of technology from Fitzgerald International Industries, Inc. (USA).

Determination of circulating blood volume (CBV) was produced using circulating blood deficiency indicator (CBDI) of "REC" company. The work of device is based on the low-frequency conductometry and does not require the introduction of substances into the blood, reducing research to 15 minutes.

The measurement of osmolarity was carried out on osmometer OMKA 1C-01, on measuring the temperature of bioliquid freezing.

Absolute and relative content of all white blood cell forms was assessed by the standard method. Leukocyte reactivity indixes were calculated: the index of the nuclear shift (NSI), leukocytic intoxication index (LII), lymphocyte index (LI), as well as proposed by us index of immunoreactivity (IIR).

$$\mathbf{NSI} = \frac{\textit{myelocytes} + \textit{metamyelocytes} + \textit{stab neutrophils}}{\textit{segmented neutrophils (seg)}}$$

$$\mathbf{IIR} = \frac{\textit{lymphocytes} + \textit{eosinophils lymphocytes}}{\textit{monocytes neutrophils}} \qquad \mathbf{LI} = \frac{\textit{lymphocytes} + \textit{eosinophils lymphocytes}}{\textit{monocytes neutrophils}}$$

$$\mathbf{LII} = \frac{\textit{[5 promyelocytes + 4 myelocytes + 3 metamyelocytes + 2 stab neutrophils + segmented neutrophils] + [}\text{plasmocytes} + \textit{1]}}{\textit{[lymphocytes + monocytes] x [eosinophils +1]}}$$

LII proposed by JJ Kalf-Caliph in 1941 is used nowadays to evaluate the toxicity of pneumonia and infectious diseases. Since it was not designed to analyze septic condition and there was no promyelocyte in the formula, we have modified this formula including promyelocytes with coefficient 5.

In total were made: -3195 studies of the functional activity of platelets;

-21 340 definitions of the parameters of coagulation hemostasis and proteins of "acute phase";

-2952 determinations of CIC and the three classes of immunoglobulin, 539 determinations of the functional activity of macrophages (NBT-test);

-280 of certain hormones;

-4725 definitions of CBV and the osmolarity of blood plasma;

-17,040 calculated indices of cell reactivity;

The results of all above mentioned studies were matched with the whole spectrum of clinical and "routine" laboratory data, including life history and diseases of parents, condition of the mother during pregnancy and childbirth, clinical and laboratory dynamics of the present condition in newborn.

Results. In hypoergic variant "A" gram-negative flora dominated: Pseudomonas aeruginosa – in 40%, K. pneumoniae - in 33%, Acinetobacter – in 34%, E. Coli – in 20%. Only in 6% of patients S. epidermidis was allocated. In 73% of children Candida was seeded. In hyperergic variant «B» S.aureus and S.epidermidis were found in 77% of newborns, in 35,3% - there was a combination with E Coli and Kliebsiella. Candida was found 3 times less than in variant «A» (22%). Pseudomonas aeruginosa was revealed only in one child (3% of patients) with a «B» variant of sepsis.

Contents of 12th acute phase proteins, including members of the coagulation cascade and anticoagulants during the height period are shown in the Table 1. There were differences in the concentration of investigated proteins: FG, FN, CMC, α2-MG, AT-III, VIIIf, PG. Variant «A» had hypocoagulation with significantly lower levels of the above proteins, thrombocytopenia with low aggregation activity. Variant «B» in spite of the current active DIC had high levels of these proteins and tendency to a reduce but higher level of platelets than variant «A».

A common factor, regardless of sepsis variant, was increasing of α1-AT, C1-IN, and von Willebrand factor (vWF) in 100% of the patients. However, the values of α1-AT (2.9g/l) and C1-IN (0.62 g/l) at hypoergic variant compared to hyperergic variant (2.1 g/l and 0.3 g/l, respectively) were significantly higher. Low levels of total plasma protein (M±m = 29.2±2.7 g/l), its hyperosmolarity (in "A" variant - 309-312 mOsm/l and in "B" variant- 298-303 mOsm/l), deficit in blood volume (CBV in group "A» -76.5-78.5 ml/kg and in «B» -79.7 - 91.5 ml/kg) - also support the abovementioned theory. This correlates with a higher and more prolonged hypotension (up to 2 weeks) in variant «A» which required constant inotropic support. Systolic blood pressure in the form «A» was in average 35±4 mm Hg and in variant "B" – 50.0±7.0 and the hypotension period was short (2 - 3 days).

Elevated levels of C-reactive protein (CRP) and Alpha-1-acid glycoprotein (AGP) or orosomucoid (ORM) occurred in both groups but not in all patients (ORM - in 91% of children and CRP - in 66% of patients regardless of the sepsis variant) (see Table 1).

The levels of the IgM and IgA are presented in Table 1 and levels of circulating immune complexes (CIC) and the NBT-test - in Fig. 1.

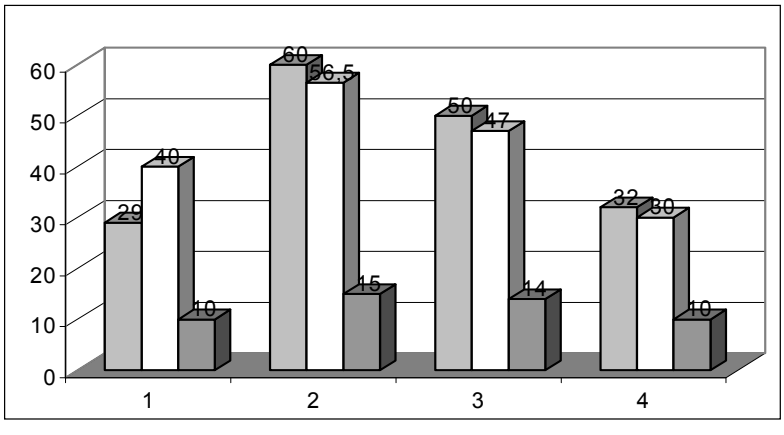

Figure 1. *Blood levels of circulating immune complexes (CIC - left column) and the phagocytic activity of leucocytes test with nitro blue tetrazolium (NBT stimulated and basal – respectively central and the right column) in healthy newborns (1), in patients with neonatal pneumonia (2), with hyperergic variant B (3) and hypoergic variant A (4) of neonatal sepsis. CIC and the NST test data are presented in conventional units.*

Table 1

Levels of acute phase proteins and immunoglobulins in the blood plasma at the height of different variants septic process (M ± m)

Variant	FG g/l	FN g/l	AT-III g/l	a1-AT g/l	a2-MG g/l	C1-IN g/l	VIIIf %	PG ug/l	vWF %	OM g/l	CMC %	IgA g/l	IgM g/l
Healthy newborns	2,0 ±0,3	0,16 ±0,01	0,17 ±0,002	1,8 ±0,02	2,4 ±0,1	0,18 ±0,01	81,0 ±1,1	45,0 ±3,0	121,8 ±15,2	0,42 ±0,01	100,8 ±1,1	34% had +	0,34 ±0,03
Sepsis «A»	1,0* 0,2±	0,12* ± 0,01	0,08* ± 0,02	2,94* ± 0,19	0,5* ± 0,17	0,62* ±0,12	63,5* ±5,4	32,0* ±5,5	309,0 ±27,5	1,31* ±0,2	53,0* ±4,0	0,46* ±0,07	0,66* ± 0,05
Sepsis «Б»	3,0 * ± 0,2	0,26* ±0,02	0,24* ± 0,01	2,3* ± 0,26	2,32* ± 0,29	0,31* ±0,09	137,1* ±15,1	67,9* ±4,8	336,1 ±27,2	1,63* ±0,05	65,1* ±5,4	0,28* ±0,1	1,34* ± 0,06
Pneumonia N =23	2,3 ±0,8	0,23 ±0,03	0,19 ±0,01	2,1 ±0,1	1,6 ±0,2	0,24 ±0,02	109,9 ±10,2	78,0 ±11,0	221,1 ±30,5	0,7 ±0,09	101, ±12,2	0,17 ±0,05	0,5 ± 0,17

∗ P < 0,05 (differences between the variants of sepsis)

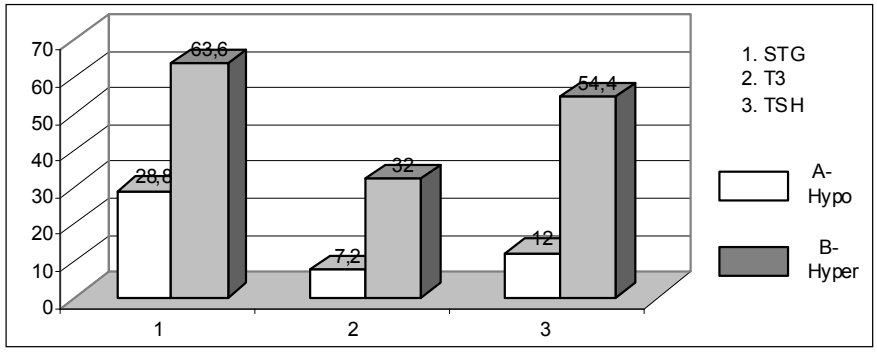

Figure 2. *Blood levels of hormones: somatotropin (STG), thyrotropin (TSH) and triiodothyronine (T3) for 2 variants of neonatal sepsis. Vatiant «A» - hypoergic and variant «B» - hyperergic. TSH and T3 are given in comparable units (mIU/L x 10 and ng/ml x 10)*

In the first examination conducted on the 1st-3d days of life low levels of IgG were revealed (in group "A" in average = 3.7 g/l while in group «B» in average = 4.4 g/l) that indicates a low level of passive immunity in all children with neonatal sepsis. The lower figures in the group «A» probably are associated with a greater proportion of preterm infants (60.7%).

If variant «A» (hypoergic) at the height stage there was lower IgM, CIC as well as indicators of NBT - test both stimulated and basal production of levels of reactive oxygen species. The difference between stimulated and basal activity characterizes the low «reserve» of functional activity. This is consistent with lymphopenia observed for a long time (up to 1 month), shift of leukocyte formula to the promyelocytes in the absence of metamyelocytes and myelocytes, presence of toxic granulation of neutrophils in the absence of neutrophilia, often full absence of eosinophils. At the same time, the IgA levels were higher and correlated with the concentration of α1-AT and vWF.

In hyperergic variant CIC, IgM levels and functional activity of phagocytes (NBT-test) were initially higher and increased over time in a 3-3.5 times correlating with increased levels of monocytes, lymphocytes, eosinophils, LI and IIR index.

All 100% of septic patients had hormonal dysfunction (Figure 2), but its character was different. The first determination of hormone levels (1-3 days of life) in the group «A» found low values of TSH or T3 in 97% of newborns. In group «B» such newborns accounted for only 7.8 %.

Hormonal profile in the height stage of the process in hypoergic and hyperergic variants of neonatal sepsis were significantly different. None of the patients with hyperergic variant had low content of T3. While in the hypoergic variant there were registered: 1) the syndrome of «low T3» (T3 <1.0 ng/ml, range 0.5-1.0, TSH is not changed) – in 31.3% of children; 2) the central suppression of TSH production (TSH 0.06-0.47 mIU /l, T3 0.58-0.81 ng/ml) occurred in 47.2% and 3) low levels of all three hormones (GH,TSH, T3) – in 18.7% of children. So in hypoergic variant of sepsis in the majority of children took place as a dysfunction of the pituitary-thyroid system at birth and hypothyroidism of septic origin in the height of SIRS. Reduced secretion of TSH may be related with the effect of dopamine due to prolonged inotropic support.

Children with hyperergic variant of SIRS were characterized by more maturity of the axis hypothalamus - pituitary - thyroid gland. Episodes of decreased TSH levels (<1.7 mIU/L) without decreasing of T3 were observed in 34.6% of children in this group. In

Table 2

Leukocyte indexes of blood reactivity at the height of different variants septic process (M ± m)

Indexes		LI M (range)	LII (M (range)	NSI M (range)	IIR M (range)
Variant «A» N=28	Beginning process	0,3** (0,1-0,7)	4,4** (0,3-10,0)	0,17 (0,02-0,4)	2,6 (1,1-4,1)
	Height process	0,71** (0,02-2,3) *	8,8** (1,1-19,7) *	3,1 (0,4-3,8)	1,76 (0,5-3,5) *
Variant «Б» N=43	Beginning process	0,42** (0,1-1,0)	2,7** (0,1-7,8)	0,54 (0,01-4,3)	2,3** (1,0-4,2)
	Height process	1,8** (0,6-4,2) *	4,2** (1,3-7,8) *	1,9 (0,3-11,2)	8,8** (3,5-19,0) *
Pneumonia N=23	Beginning process	0,3** (0,16-0,6)	1,6 (1,6-4,8)	0,53 (0,02-1,9)	2,65** (0,4-5,4)
	Height process	0,9** (0,3-1,2)	1,3 (0,6-3,2	0,18 (04-o,4)	3,8** (2,1-6,8)

∗ P < 0,05 (differences between the variants of sepsis) ∗∗ P < 0,05 (differences between stages of the process)

Table 3

Standard values for leukocyte index of reactivity

Age	NSI	LII	IIR	LI
1 day of life	0,01-0,37	0,27--3,56	2,14-8,59	0,17-0,63
2 day of life	0,02-0,40	0,17- 2,85	2,20-8,47	0,21-0,73
3 day of life	0,01-0,28	0,12- 1,27	1,65-7,80	0,29-0,95
4 day of life	0,02-0,25	0,09- 1,02	1,85-9,52	0,38-1,27
5 day of life	0,03-0,34	0,08- 0,84	2,26-8,73	0,48-1,48
6 day of life	0,03-0,23	0,09- 0,89	2,32-8,82	0,50-1,29
7 day of life	0,03-0,33	0,07- 0,65	2,56-9,97	0,64-1,81
8 day of life	0,03-0,33	0,07- 0,71	2,71-10,18	0,64-1,80
9-15 day of life	0,02-0,33	0,05- 0,57	2,70-10,34	0,68-2,13
1 month	0,02-0,18	0,03- 0,34	4,05-18,14	1,09-3,91

hyperergic variant 15.4% of children had elevated levels of T3 (more than 2.8 ng/ml). The main feature of this variant was a high incidence of resistance to growth hormone (GH> 50 ng/ml, range 51 - 135 ng/ml). It was noted in 65.3% of children with variant «B» and only 25.5% in the variant «A». According to our data, high content of growth hormone in the early stages of sepsis and its progressive reduction over time and the increase in T3 level are favorable signs. Poor outcome was associated with low levels of all the abovementioned hormones.

Blood analysis and leukocyte indexes of reactivity are presented in Tables 2 and 3.

Two variants of neonatal sepsis were significantly different for quantitative and qualitative composition of leukocytes at the beginning of the process. Initially, in variant «A» total number of leukocytes was an average of 7.3 x 10^9, nuclear shift (increased NSI) was absent in 70% of newborns, 91% of children had lymphopenia (mean 0.69 x 10^9). In variant "B" the number of leukocytes at baseline was 23.0 x 10^9, 67% of children had an increased NSI, being regenerative in nature.

At the beginning of the process children in both groups were characterized by high LII and low LI and IIR, reflecting lower immune reactivity in which developed sepsis. In variant «A» initially high was LII in 75% of children, LI in 47% of children was below norm and IIR was in 46% below norm.

At the height stage in 100% of children in group «A» was marked aneosinophilia (in the form of episodes from 3 to 11 times and in 21% with lethal outcome - throughout the disease). Nuclear shift to promyelocytes was detected in 81% of children in variant «A» in the background of normal or decreased content of neutrophils. Myelocytes and metamyelocytes were absent in the blood (ie, there was a «failure» resembling acute myeloid leukemia). Simultaneously there was observed toxic granularity in neutrophils. This character of NSI was observed for a long time (up to 38 days of life or death). We decided it was a sign of depletion of bone marrow pool reserve of neutrophils. A similar shift was observed in the form of a single episode in 12.3% of children in group «B». In hypoergic variant NSI is not regenerative. Episodes of neutropenia were observed in 59% of the children. Monocytopenia was observed in 60% of patients (mean minimum value was 0.2 x 10^9). The maximum absolute value of the monocytes content was 3.9 x 10^9.

In hyperergic variant increased or normal level of neutrophils was in 81% of children and only 32% of children had a single episode of eosinopenia. The absolute content of lymphocytes significantly varied between episodes of lymphopenia to lymphocytosis (minimum values were 1.7 x 10^9 and the maximum 10.6 x 10^9) that is significantly higher than in the group "A".

The most informative criterion characterizing the different variants of SIRS was a combination of cell reactivity indices each of which reflects only a part of the process. High levels of LII correlate with the severity of endotoxemia but in different variants of SIRS it seems to reflect a different qualitative characteristic of the inflammatory mediator spectrum. So in sepsis «A» high LII was combined with low IIR and in sepsis «B» high LII was combined with a high IIR that allowed us to use this feature as a differential. LII has revealed differences between the variants in absolute values - the value of the index > 3.4 is a characteristic feature of hypoergic variant «A».

Increasing of indixes LI and IIR in favorable dynamics of clinical status is a good sign and indicates the increase in the relative content of lymphocytes. However, LI reflects only the proportion of their content in relation to the neutrophils. IIR reflects imbalance of basic cells that produce cytokines and imbalance in the cytokine profile in the presence of lymphopenia. Deficit of eosinophils means a lack of inflammation antimediators hence the lack of detoxification component in the spectrum of mediators.

Thus, the main hallmark of 2 SIRS variants by analyzing criteria is the dynamics of the complex index LII, IIR and LI. Each index individually and one-time assessment does not allow differentiating the variant of SIRS and predicting of trend. NSI in «A» variant usually masks low bone marrow reserve.

Pneumonia in the initial stage of the development has a number of common features with variant «B», however all indexes were within normal limits.

Discussion. Clinical-laboratory variants of SIRS in neonatal sepsis are not identified either in Russian or foreign literature. However, there were attempts to detect differences in the spectrum of cytokines IL1b, IL6, IL8, CSF (colony-stimulating factors) for gram-positive and gram-negative sepsis, but their results were contradictory [7-11]. There is a common opinion about the "imbalance" of inflammation mediators, including cytokines in sepsis [10, 12-14]. In our opinion, the contradictory of literature data indicates the existence of heterogeneity of SIRS and the presence of variants associated with both the features of the original reactivity and the type of pathogen.

Our data on the initial low concentrations of TSH and T3, low content of total protein, IgG in hypoergic variant «A» indicate the immaturity of the system hypothalamus - pituitary - thyroid gland at birth and suggest the failure mechanisms of immunological protection and hormonal support.

The predominance of gram-negative bacteria as the causative agents of sepsis in the group «A» requires a higher level of endotoxemia. ET leading to a reduction of marginalized pool of leukocytes, exposure of vascular endothelium triggers the activation of proteolytic cascade systems of the plasma [15]. Our data on the high content of α1-AT providing 88% of anti-protease activity of plasma and C1-IN suppressing contact activation of thrombin and kallikrein-kinin system confirmed the fact of «proteolytic explosion» in sepsis [15-18]. Obviously in variant «A» there is no appropriate level of antimediators in particular due to lack of eosinophils and low protein synthetic capacity of the organism.

In hypoergic variant «A» we revealed more pronounced violation of ability of phagocytes to a full answer in the NBT-test due to neutropenia. We associate this fact with higher levels of ET able to activate neutrophils with elastase releasing [19], damage cells and stimulate apoptosis of neutrophils [19-21] and low T3 level [22-24].

Hypothyroidism of septic origin, noted by us only in hypoergic variant, consistent with the idea of ET damaging effect especially for TSH receptor on thyroid follicular cells. Damage of the entire hypothalamic-pituitary - thyroid axis in patients who died indicated Leon Sans et al [22,25,26]. In general, this variant of SIRS can be described as «deficient». It is necessary to keep in mind not only the shortage of protein, energy deficit and deficit of lymphokines due to lymphopenia and the possible shortage of cytokines of monocytic origin. There are reports on the limitation of monocytes response of preterm children to ET («endotoxin tolerance») [27], decreased IL8 production in sepsis [28].

Thus, endotoxicosis in hypoergic sepsis "A" has a distinguishing quality characteristic from variant "B". This is evidenced not only by differences in the spectrum of acute phase proteins, but also analysis of the complex indixes of cell reactivity we used.

Children with hyperergic variant did not have marked signs of thyroid function depression either at baseline or during the septic process. Among the causative agents gram-positive flora dominated so we could expect a stimulating influence of the staphylococcal enterotoxin as superantigen on the proliferation of lymphocytes and their contribution to the corresponding hypercytokinemia and toxemia. However, we believe that in this variant of SIRS ET of gram-negative bacteria is involved which is received through the intestinal mucosa. Increased intestinal permeability in sepsis, serious injury, shock is regarded as a trigger of multiple organ failure [8]. The concentration of ET, probably, is different in hypo-and hyperergic variant of SIRS.

ET, depending on the concentration may have different effects on the axis hypothalamus - pituitary - adrenal and pituitary glands - the thyroid gland [29-31]. Increase production of T3 (15 4% of children), we observed only in hyperergic variant. In the same group distinguishing feature of the hormonal profile was the high basal level of growth hormone. The body's resistance of septic patient to endogenous (and exogenous) growth factor is associated with two factors: 1) reduction of the receptor expression for the growth hormone in the liver cells under the influence of cytokines and as a result reduction of the production of insulin-like growth factor - IFR1; 2) the presence of common signaling way of the growth hormone and IL-1β in the liver cells which prevents the realization of anabolic effects of GH [32, 33].

High levels of acute phase proteins (not only in comparison with the variant "A" but higher than the norm) in variant "B" and total plasma protein, we associate with the conservation of energy and plastic resources in this variant of sepsis and their hormonal support. This is confirmed by the absence of low T3 in all children of this group, absence of neutropenia and lymphopenia, aneosinophilia, higher basal NBT-test and IgM and higher values of LI and IIR. We attribute this as with the peculiarities of the reactivity and with the type of pathogen contributing to a different cytokine profile. The presence of antimediators by eosinophilic origin ensures detoxification and allows maintaining a «balance» in the protease/ antiprotease coagulation link. However, despite this fact there is no balance in the cytokine network in accordance with clinical data. We tend to agree with the characteristic of this SIRS as a «cytokine storm» [34].

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