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Estimation Of The Efficiency Of Pathogenetic Treatment Of Children Moving Perinatal Hypoxia.

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ABSTRACT

The aim of the study was to assess the effectiveness of pathogenetically substantiated therapy for developmental disorders in children of the first year of life who had perinatal hypoxia, based on an analysis of neurobio chemical blood markers. Research materials: 419 patients aged from 0 to 6 months were examined, 2 age groups of 1-3 and 4-6 months were allocated, the physical and psychomotor development of each patient was analyzed. To separate the patients of the main group of studies according to the severity (mild, moderate and severe) of the nervous system, an integrated approach was used based on the analysis of the reproductive and gynecological history of the patients' mothers, their somatic health and the characteristics of the optimal course of pregnancy and childbirth; ballroom assessment of the neuropsychic development of children; analysis of Z-scores for individual physical development of patients (body weight, height, body mass index) according to WHO-approved standard program WHO AnthroPlus. Developed groups of children for pathogenetic and standard treatment of the effects of perinatal CNS damage. As a result of the study, the dependence of the changes in neurobio chemical markers on the chosen treatment tactics taking into account the pathogenesis of the development of CNS damage was established. So, earlier (1-3 months after birth) the use of vasoactive drugs in combination with vitamin therapy and syndromic therapy led to the normalization of the levels of markers of vascular metabolism, which, in turn, led to the restoration of metabolic processes in the nervous tissue (decrease in the level of neurometabolic markers - S100A1B and NGF. In late (4-6 months after birth) treatment of patients with neuroprotectors and vasoactive drugs in combination with vitamin therapy, neurometabolism markers did not react in any way; and angiotensin II remained at the level of baseline prior to treatment, and the use of only symptomatic therapy did not affect the variability of the studied markers. Thus, the pathogenetically sound approach to the choice of therapy for the effects of perinatal CNS damage, reduced the risk of consequences in the age dynamics and severity of the CNS.

Keywords: nerve growth factor, neurological deficit, homocysteine, central nervous system.

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RELEVANCE

Despite the modern improvement of perinatal care, with the introduction into clinical practice of various innovative treatment regulations, revealed pathology in children of the first year of life, there is no tendency to reduce the frequency of effects of perinatal CNS lesions [2, 6, 6]. According to statistics from the Ministry of Health of Russia, since 2000, there has been a more than twofold increase in encephalopathy in newborns, with perinatal hypoxia being the dominant factor in the formation of pathology [1.6]. According to the Federal State Statistics Service of the Russian Federation over the past five years, in the Central Federal District, the proportion of children of the first year of life with an officially registered diagnosis of "consequences of perinatal damage" increases annually by an average of 0.6%, which in absolute terms amounts to several thousand new patients who require specialized diagnosis , observation and appropriate treatment, as in the conditions of medical organization, and at home [6].

At present, the concept of choosing the optimal treatment of children who have undergone perinatal hypoxia based on an effective system for early diagnosis of CNS damage, based on a comprehensive analysis of neurovascular markers of brain damage in the newborn [4,8], has been formed. Reliable and easy to use, easy to interpret at any level of medical care for the population, the decision support system for choosing a therapy will more effectively carry out therapeutic and preventive measures aimed at preventing developmental disorders of children who have undergone perinatal hypoxia [5,7].

Modern standards of treatment of the effects of CNS damage in children of the first year of life are based on the syndromic approach, which is established during neurological examination of the patient and, basically, does not take into account the pathogenetic component of the development of a particular set of neurological disorders [9,12,13].

The failure of the microcirculation of the nervous system in childbirth and the antenatal period is the dominant pathogenesis, affecting the dystrophic processes of the brain nerve tissue of newborn children, which allows us to develop an approach to pathogenetically substantiated therapy by analyzing the variability of neurovascular markers reflecting the formation of adaptation processes [4,11]. The capillary endothelium of the brain is extremely sensitive to ischemic-hypoxic effects, which leads the pathology of this factor to the leading position [6,7].

Homocysteine and angiotensin are the leading markers in diagnosing the pathological state and endothelial function of the microcirculatory bed, which are released in high concentrations when capillary filtration structures are damaged, causing impaired impulses between the brain neurons and myelinization of axonal structures of the white matter, which, in turn, affects the metabolism of the nerve cells and the regenerative potential of astrocytal glia, manifested by the variability of the S-100 protein and NGF markers in the bioch blood imii [10]. The increase in homocysteine levels is directly related to the activity of the cystathionine beta-synthase enzyme, which is involved in the metabolism of white matter myelin structures, therefore hyperhomocysteinemia is a direct evidence of impaired conduction and synergy of nerve impulses between neurons in brain structures [5,6]. The growth of angiotensin is a direct consequence of hyperhomocysteinemia, provoking a cytotoxic effect on the vascular endothelium, which in turn potentiates the increase in the group of prostacyclins derivatives, leading to an even greater spasm of vascular microcirculation of the CNS [6].

Such a variety of pathogenetic response and metabolic reception of neurobiochemical markers, of course, must be taken into account when choosing the optimal treatment regimen for hypoxic-ischemic CNS damage, thus avoiding microcirculatory metabolism disorders in the CNS in young children and significantly reducing the risk of cognitive impairment of the brain as a consequence of this condition.

MATERIALS AND METHODS

To accomplish the task, a study was conducted, approved by the Ethics Committee of the State Budgetary Educational Institution of Higher Professional Education of the Voronezh State Medical Academy named after N.N. Burdenko Ministry of Health of the Russian Federation (Protocol No. 6 dated October 19, 2013) on the basis of the Department of Early Age "Voronezh City Children's Clinical Hospital No. 1", Scientific Research Institute of Industrial Library of the Voronezh State Medical Academy named after N.N. Burdenko

and BUZ IN "Voronezh City Polyclinic № 2" in the framework of the basic State assignment on research activities of the Voronezh State Medical Academy. N.N. Burdenko for the period 2013-2015. (approved by order of the Ministry of Health of the Russian Federation dated April 30, 2013 No. 281): Patterns of morpho- and immunogenesis in clinical and experimental practice. All subjects confirmed their participation in the study by signing Voluntary Informed Consent. During the study, 419 patients aged from 1 to 6 months were examined (of them, boys accounted for 52%, girls - 48%), divided later on into the main group - 336 patients who were hospitalized for the effects of perinatal nervous system damage varying degrees of severity (the first age group (1-3 months) - 164 (48%) patients and the second age group (4-6 months) - 172 (52%) children) and the control ("apparently healthy children") group - 83 a child who has been examined by a pediatrician as part of a standard examination in the regulated periods of observation at the stage of outpatient services. A prerequisite for the inclusion of patients in the control group was the absence of abnormalities in the physical and neuropsychological development of the child (CPD), registration with a neurologist and receiving medical therapy for neurological abnormalities in the first year of life. This approach to the allocation of two subgroups is due to the fact that the first age period (1-3 months) is characterized by the increasing role of the glial component of the nervous system, aimed at reducing pathological processes in neurons and reducing the severity of neurological disorders, which is especially important for the timely diagnosis of neurological deficit (ND a child; and the second age period (4-6 months), which is characterized by neurodystrophic processes with a decrease in glial reactivity, rupture of synaptic connections, impaired interaction of various brain areas, which determines a wider clinical picture of neurological symptoms at this stage, both in the absence of adequate therapy earlier and when evaluating the result after the treatment.

To separate the patients of the main group of studies according to the severity (mild, moderate and severe) of the nervous system, an integrated approach was used based on the analysis of the reproductive and gynecological history of the patients' mothers, their somatic health and the characteristics of the optimal course of pregnancy (SPD) and childbirth (SHOTR) [14,15,16]; a point estimate for the neuropsychic development of children [9]; analysis of Z-scores for the individual physical development of patients (body weight, height, BMI) according to the WHO-approved standard WHO AnthroPlus program [15] (Table 1).

Table 1: Differential criteria for assessing the degree of damage to the nervous system in patients

Criterion	Degreeofmanifestation	Equivalentofmanifestation
SOTB	optimal (%)	77±3
	suboptimal (%)	≤73
SOTB	optimal (%)	67±4
	suboptimal (%)	≤62
Z-score	normalvalues	0,671≤0,678
	below / aboveaverage	-1,28≤0,670 / 0,679≤1,28
	low / high	-1,89≤-1,29 / 1,29≤1,89
	verylow / veryhigh	≤-1,9 / 1,9≤
The severity of neurological deficit	rate (point)	27≤30
	easy (point)	22≤26
	average (point)	14≤21
	heavy (point)	**≤**13

The analysis of biochemical markers in the study was carried out by taking venous blood (3-5 ml), carried out under the conditions of the treatment room in Vacuette and Greiner bio-one tubes (manufactured in Austria) once: at the time of the child's admission to the hospital and during the routine examination district pediatrician for a group of "conditionally healthy" children. Then a standard centrifugation procedure was carried out (Himac CT 6E / CT 6EL apparatus) to obtain serum (determination of biochemical parameters).

To determine the level of homocysteine, a test system was used for the quantitative determination of total L-homocysteine in human serum or plasma (catalog number 414-8880– 96 definitions, manufacturer Axis-Shield, supplier company — BioHimMak, Russia). The test system is designed to determine homocysteine in the blood by ELISA.

To determine the beta subunit of the human nerve growth factor, an enzyme immunoassay kit (Beta-NGF; catalog number ELH-BNGF-001 - 96 definitions, manufactured by RayBio, the supplier company - BioHimMak, Russia) was used. The protein marker S100A1B was determined by quantitative enzyme immunoassay in the COBAS system (the supplier company is BioHimMac, Russia). The determination of the level of angiotensin II was carried out using the enzyme immunoassay system test BCM Diagnostics (catalog number S-1188, the supplier company - BioHimMac, Russia).

The obtained quantitative data were processed using the methods of variation statistics, single-factor analysis of variance and pairwise correlation analysis. Statistical processing of the research results was carried out using the Excel 2010, IBM SPSS Statistics 17.0 for Windows software packages using parametric criteria. The Shapiro-Wilk test was used to check the distribution form. Results are presented as mean values and their standard error (M ± m). Comparison of quantitative variables in multiple comparisons was performed using the Wilcoxon test, pair-wise comparison was performed using Student's t-test. Differences were considered statistically significant at a level of p≤0.05. Correlation analysis was performed using the Spearman criterion. Relationships of r> 0.7 were considered strong, with a level of p <0.05.Treatment methods. Patients of all groups received traditional course rehabilitation therapy, providing for medication and non-drug treatment. In order to pathogenetic substantiate the use of drug therapy depending on the level and type of marker, as well as assessing its effectiveness, patients of the main group were divided into two subgroups: the “standard therapy” subgroup — patients treated in accordance with clinical manifestations and the “ pathogenetic therapy ”- patients who received treatment in accordance with the currently leading clinical syndrome and marker-type variability. Drug therapy was presented: drugs have a neurotrophic and nootropic effect; drugs improving general cerebral hemodynamics and microcirculation; drugs reducing intracranial hypertension; drugs that normalize muscle tone; drugs that reduce hyperkinesis, vitamins of group B. Non-drug treatment methods in all treatment regimens included massage, physical therapy, physiotherapy (medicinal electrophoresis, magnetic therapy, ozokerite-paraffin-therapy, etc.) (Table 2).

Table 2: The distribution of prescribed treatment regimens in the study

Groups	I (n)		II (n)		III (n)	
Age (month)	Pathogentictherapy	Standardtherapy	Pathogentictherapy	Standardtherapy	Pathogentictherapy	Standardtherapy
1-3	scheme B (n = 29)	scheme D (n = 31)	scheme A (n = 29)	scheme D (n = 30)	scheme C (n = 21)	scheme D (n = 24)
4-6	scheme B (n = 32)	scheme D (n = 31)	scheme A (n = 29)	scheme D (n = 31)	scheme C (n = 26)	scheme D (n = 24)

Scheme A: neuroprotectors + drug, depending on the leading syndrome;
Scheme B: vasoactive drugs + vitamin therapy (folic acid + vitamins of group B) + drug, depending on the leading syndrome;
Scheme C: neuroprotectors + vasoactive drugs (folic acid + vitamins of group B) + drug, depending on the leading syndrome;
Scheme D: standard drug treatment without regard to the level of neurobiochemical markers.

RESULTS AND THEIR DISCUSSION

The optimal levels of pregnancy and childbirth affected the severity of the nervous system lesions: the control group patients were found to have optimal levels of SROTB and SCOTR, and in the main group children - suboptimal course variants, at which social factors dominated (61%) and current pregnancy criteria (28%) mother. At the same time, the level of SCOTB and SCOTB was 2 times significantly (p≤0.05) higher with mild severity of CNS damage than with severe.

A comparative analysis of the physical development of patients in the study indicates that the number of patients with a normal value of physical development according to the Z-score was minimal (19.8%), and they all corresponded to the control group of the study; and in the main group, 136 (32.4%) patients with physical development were found to be above or below average; 143 (34.1%) patients with low and high

developmental disabilities and 57 (13.7%) patients with very low and very high developmental disabilities. Evaluation of patients' NPR by severity revealed the following pattern: from 30 to 27 points, 83 patients received - all of them belonged to the group of “conditionally healthy children”. Patients (112 children) who scored from 26 to 22 points were assigned to the group with a mild severity of NDP. With a score of 21 to 14 points, the average severity of NDP was established in 118 patients, and children who scored 13 or less (96 people) were assigned to the group with severe NDP.

It should be noted that the division by age in the group of conditionally healthy children was not of practical importance. Thus, in the course of the analysis of patients, mild severity of CNS damage was determined in 122 (36%) children (1-3 months - 60 patients, 4-6 months - 62 patients), the average severity of CNS damage in 118 (35%) children (1-3 months - 58 patients, 4-6 months - 60 patients) and severe CNS damage - in 96 (29%) children (1-3 months - 45 patients, 4-6 months - 51 patients).

The correlation analysis found that the severity of the central nervous system lesion reliably ($p \leq 0.05$) correlated ($r \geq 0.8$) with the severity of neurological deficit, markers of the optimal course of pregnancy and childbirth, and the physical development of children reliably ($p \leq 0, 05$) reflected the established severity of damage to the central nervous system.

Analysis of clinical syndromes in patients of the main group revealed that, regardless of the age of patients, the incidence of neurological syndromes increased with the degree of severity of CNS damage: in the group of patients 1-3 months the syndrome of movement disorders dominated regardless of the severity (incidence 58.4%) in combination with the syndrome of increased neuro-reflex excitability (PNRV) (incidence of 47.6%); in severe cases of CNS damage, post-hypoxic ventricular dilatation syndrome is described in 26.3% of cases; The leading neurological syndrome of the age group 4-6 months was the syndrome of movement disorders (incidence 34.7%) and psychomotor retardation (occurrence 31.9%), regardless of the severity of the CNS damage.

Thus, on the basis of the obtained results of the evaluation of differential criteria for examining children, it can be concluded that the severity of the central nervous system damage is due to a complex combination of reliable ($p \leq 0.05$) changes in the parameters of the study. Minor damage to the central nervous system was formed by combining the severity of ND - 23 ± 2 points ($p \leq 0.05$), the dynamics of the course of pregnancy and childbirth - 62 ± 4% and 57 ± 2%, respectively ($p \leq 0.05$). The average degree of damage combined in itself the severity of ND - 18 ± 3 points ($p \leq 0.05$), SHOTB and SCOTR - 51 ± 3% and 42 ± 2%, respectively ($p \leq 0.05$). For the severe form of the central nervous system lesion was characterized by a ND of 11 ± 3 points ($p \leq 0.05$), SHOTB - 32 ± 3% ($p \leq 0.05$) and SHOTR - 31 ± 2% ($p \leq 0.05$). At the same time, the assessment of the physical development of children in the study by age groups fully corresponded to the identified severity of CNS damage: mild - 1.1 ± 0.2 cu (74 ± 4 ‰, $p \leq 0.05$); average - 1.5 ± 0.3 cu (86 ± 3 ‰, $p \leq 0.05$) and heavy - 1.9 ± 0.3 cu (93 ± 2, $p \leq 0.05$).

Analysis of the clinical diagnosis at birth in patients in the survey allowed us to determine the proportion distribution by type of lesion of the nervous system (or its absence): the vast majority (289 patients / 69%) had hypoxic-ischemic damage to the nervous system, 83 (19%) patients had no data a history of brain damage. The incidence of neurological syndromes in patients 1–3 months increased with an increase in the severity level of the CNS lesion: in the first age group, PNRV syndrome prevailed (incidence 0.68–0.76) in combination with benign intracranial hypertension (incidence 0.62–0, 68), and a severe degree of CNS damage was associated with a disorder of the autonomic nervous system and impaired motor development (occurrence 0.42 - 0.51). In the second age group (4-6 months), in addition to the set of symptoms established earlier, the syndrome of motor development disorder was noted, which ranked second after PnRV in frequency of occurrence (0.48 - 0.52).

Further, in table 3, presents a general comparative description of the values of biochemical parameters in the study.

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Table 3: Indicators of neurobiochemical markers in the study

Agegroups (month)	Biochemicalindicators	Group of "conditionally healthy" ("norm")	Groupofmild CNS	Group of moderate degree of CNS damage	Severe CNS group
1-3	S-100 (pg / ml)	175,7±19,6	263,7±34,1	348,8±41,2	351,7±36,4#
	NGF (pg / ml)	19,1±2,24	21,36±1,72	15,3±1,83	10,7±1,22#
	HZ (µmol / ml)	5,23±0,89	7,14±0,52	8,14±0,32	12,1±1,21#
	AT II (ng / ml)	0,128±0,041	0,136±0,024	0,148±0,019	0,136±0,091
4-6	S-100 (pg / ml)	175,7±19,6	328,9±27,6*	297,6±19,1*	179,3±21,6*
	NGF (pg / ml)	19,1±2,24	16,53±2,67*	10,5±1,17*	8,1±1,44
	HZ (µmol / ml)	5,23±0,89	8,19±0,24*	10,7±0,86*	16,8±1,9*#
	AT II (ng / ml)	0,128±0,041	0,137±0,018	0,131±0,021*	0,095±0,027*

Note: * - p≤0.05 according to Student's t-test between age groups, # - p≤0.05 according to Wilcoxon between groups according to severity of CNS damage

In patients aged 1-3 months, S-100 protein values significantly increased compared with the control indicators with mild and moderate severity of CNS damage by 48% and 86%, respectively. At the age of 4-6 months, the studied marker had a reliable, consistently high level compared with the norm values, regardless of the severity of the CNS damage: an average of 42-48%. It is worth noting that in the case of severe damage to the central nervous system in the first age group, there was a decrease in the marker by one third, but this data was unreliable.

The dynamics of the nerve growth factor in the study looked as follows: while mild severity in the first age group showed a significant increase in the level by 14%, then later, with the degree of damage weighted, the values of the indicator decreased relative to the control data by 10% and 25%, respectively. At the age of 4-6 months, the studied marker significantly decreased by 12% only with moderate severity of the lesion; in the case of mild and severe, a decrease in this indicator was below the norm, but these results were not of a reliable nature.

A study of homocysteine revealed that at all ages, this marker was significantly increased relative to the norm and severity of CNS damage. The maximum digestion level of homocysteine reached in severe lesions in the second age group - significantly higher than the norm almost 3 times. The level of angiotensin II in the study was higher than the controls in the first age group, regardless of severity. In the second group of the study, the values of angiotensin II decreased inversely with the severity.

Thus, on the basis of the obtained biochemical markers, it can be concluded that systemic hypoxia led to disruption of the metabolism in the neurovascular complex, causing destruction of capillary endotheliocytes due to increasing hyperhomocysteinemia, which, through exposure to alternative metabolic pathways of angiotensin II, decreases the secretion of the latter and leads to local vascular disease. distorphic processes in the central nervous system.

Brain neurons at an early age (1-3 months) try to compensate for the dysfunction of the microvasculature by increasing metabolism in the glial environment, which is characterized by an increase in S100A1B. In the late age range (4-6 months), the protective role of the glial environment dies away and metabolic disturbances in the synthetic apparatus of the neuron itself take the first place, which is manifested by an increase in the NGF factor.

All of the above leads to the fact that the first age period (1-3 months) is characterized by a decrease in neuronal loss and a decrease in the severity of neurological disorders, which is especially important for the timely diagnosis of a child's neurological deficit, and the second age period (4-6 months) is due to neurocytodystophy, rupture of synaptic connections, violation of the interaction of various areas of the brain, which determines a broader clinical picture of neurological symptoms in these age groups the results of changes in neurobiochemical markers and the degree of neurological deficit in children in the study after therapy are presented in Table 4 (standard therapy - therapy 1, pathogenetic - therapy 2).

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Table 4: Changes in the state of neurological deficit and values of neurobiochemical markers in children in the study after treatment

Groups byage (month)	biochemical markers and ND	groupofmild CNS		group of moderate degree of CNS damage		severe CNS group	
		Therapy 1	Therapy2	Therapy 1	Therapy2	Therapy 1	Therapy2
1-3	ND(point)	25±1	27±1*	20±1	23±1*	13±1	17±1*
	S-100A1B (pg /ml)	213,3±27,6	165,1±21,4*	312,8±36,9	273,4±32,3*	331,3±34,2	306,6±31,7
	NGF (pg /ml)	24,5±1,97	27,8±2,22*	16,2±1,94	18,3±2,19	11,3±1,28	11,9±1,23
	HZ(µmol/m)	7,82±0,57	5,81±0,42*	9,19±0,76	6,11±0,43*	10,7±0,99	7,96±0,98
	AT II(ng / ml)	0,116±0,017	0,101±0,019*	0,134±0,012	0,122±0,014	0,134±0,09	0,12±0,076
4-6	ND(point)	21±1	24±1*	16±1	19±1*	11±1	14±1*
	S-100A1B (pg / ml)	299,6±25,1	267,1±22,4*	281,5±18,1	260,6±16,7*	178,1±20,7	165,7±19,8
	NGF(pg / ml)	17,9±2,9	19,8±3,19*	11,1±1,23	11,4±1,27*	8,1±1,37	8,6±1,49
	HZ(µmol/ml)	10,9±1,12	7,13±0,19*	15,1±1,82	8,59±1,11	22,9±2,6	14,9±1,71*
	AT II(ng/ml)	0,132±0,016	0,125±0,012*	0,139±0,021	0,114±0,017*	0,11±0,03	0,086±0,021*

Note: * - p≤0,05 by t-student test between groups according to severity depending on the received therapy

The increase in the average scores in assessing neurological deficit, expressed in the reduction of neurological symptoms, with pathogenetic therapy was in the range of 4-5 points, and with standard therapy - 2-3 points, regardless of the severity of the central nervous system lesion and age of the patient.

Pathogenetic therapy led to a significant (p≤0.05) decrease in neurovascular markers in all age groups and in all forms of CNS damage, in contrast to standard therapy, to which neurovascular markers practically did not respond.

Drug correction of neurotrophic markers led in all age groups to activate the protective function of glia (decrease protein level S100A1B) and enhance neurometabolism in the white matter of the brain (increase the NGF marker), reducing the severity of CNS damage. Standard therapy did not cause such significant and reliable positive dynamics of neurotrophic markers.

Thus, a pathogenetically substantiated approach to the choice of treatment of perinatal CNS lesions based on differential analysis of biochemical markers reduces the risks of development of consequences in the age dynamics and severity of the lesion: earlier (1-3 months after birth) use of vasoactive drugs combined with vitamin therapy therapy led to the normalization of the levels of vascular metabolism markers (homocysteine and AT II), which, in turn, led to the restoration of metabolic processes in nerves active tissue (multiple decrease in the level of neurometabolism markers).

CONCLUSION

Based on the study, it can be concluded that the severity of the central nervous system lesion reliably (p≤0.05) correlated (r≥0.8) with the form of the clinical syndrome and the level of the optimal course of pregnancy and childbirth. The severity of the central nervous system lesion reliably (p≤0.05) reflected the physical development of children, established on the basis of the WHO Z-score (from 0.9 to 2.4 cu), the incidence of neurological syndromes PNRV (0.68 - 0 , 76), benign intracranial hypertension (0.62 - 0.68) and impaired motor development (0.42 - 0.51). Significant (p≤0.001) differences in the levels of markers of neuroplasticity and endothelial dysfunction in patients with varying severity of the effects of perinatal lesions had a pronounced specificity for each age group: for 1-3 months there was an increase in endothelial dysfunction and a decrease in trophism of neurons of the brain proportional to the increased severity The central nervous system against the background of an increase in the compensatory function of the surrounding neuroglia and a decrease in the risk of neuronal loss; for 4-6 months was characterized by an increase in the concentration of neurovascular and neurodystrophic markers of the nervous system. The greatest positive results in the treatment associated with a reduction in the severity of neurological deficit

were manifested in pathogenetic treatment based on a differential approach to the assessment of biochemical markers in the age dynamics. So, earlier (1-3 months after birth) the use of vasoactive drugs in combination with vitamin therapy and syndromic therapy led to the normalization of the levels of markers of vascular metabolism (HZ and AT II), which, in turn, led to the restoration of metabolic processes in the nervous tissue (a decrease in the level of neurometabolism markers - S100A1B and NGF). During late (4-6 months after birth) treatment of patients with neuroprotectors and vasoactive drugs in combination with vitamin therapy, the neurometabolic markers (S100A1B and NGF) did not significantly ($p \leq 0.05$); homocysteine and angiotensin II remained at the level of baseline indicators before the start of therapy, and the use of only symptomatic therapy was not reflected in any way in the variability of the studied markers. Thus, a pathogenetically substantiated approach to the choice of treatment for the effects of perinatal CNS damage based on differential analysis of biochemical markers reduced the risk of development of consequences in the age dynamics and severity of damage to the central nervous system.

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