ASSESSMENT OF THE LEVEL OF NEUROSPECIFIC AUTOANTIBODIES IN BLOOD SERUM IN CHILDREN BORN WITH LOW BODY WEIGHT

[1]Akramova Kh.A., [2]Akhmedova D.I., [3]Djalilov A.A.
Tashkent Pediatric Medical Institute, Uzbekistan
https://doi.org/10.5281/zenodo.10275610

Abstract. *According to WHO, every year about 30 million babies are born premature, low birth weight or sick and require specialized care to survive. Perinatal damage to the central nervous system unites a large group of brain lesions of different causes and origins that occur during pregnancy, childbirth and in the first days of a child's life. Severe forms of perinatal CNS lesions are observed in 1.5–10% of full-term and 60–70% of premature infants. Purpose of the study: to identify a predisposition to pathology of the central nervous system and internal organs in low-birth-weight newborns by conducting immunochemical screening. Methods. 64 newborns were examined, born at a gestational age of 32-37 weeks with low body weight - 1500.0-2499.0 g. Newborns were divided into 2 groups: those born with a body weight of 1500.0-1999.0 g at a gestational age of 32-34 weeks and those born at a gestational age of 35-37 weeks with a body weight of 2000.0-2499.0 g. The comparison group consisted of healthy full-term newborns weighing more than 2500.0 g. All children underwent a standard clinical examination, the levels of 12 types of IgG autoantibodies to 12 types of antigenic components of brain cells and receptors were assessed, and the immunoreactivity index was calculated. Results: deviations from the conventional norm were present in almost all 12 positions of neurospecific autoantibodies. In newborns with low body weight, the level of autoantibodies to myelin basic protein, NF -200, S 100, GFAP was significantly increased, and the levels were statistically significantly higher in children 1- group, which indicates structural changes in the central nervous system, disruption of myelination processes, formation of astroglia, neutrotrophic functions, more pronounced in newborns with a gestation period of 32-34 weeks. Objective signs of cerebral ischemia of the 1st and 2nd degrees with the same frequency (61 .5% and 63.2%) were observed in newborns weighing 1500.0-1999.0 and 2000.0-2499.0 g. In newborns with low body weight (1500.0-2499.0 g), regardless of gestational age after 32 weeks, there was an increase in the level of autoantibodies to the receptor structures of the brain responsible for cognitive, emotional-volitional and behavioral reactions, as well as those involved in the implementation autism.*

Keywords: *low body weight, children, gestational age, autoantibodies, neurological status, assessment, receptors, prognosis.*

Actuality. According to the WHO, every year about 30 million babies are born premature, low birth weight or sick and require specialized care to survive [15]. The incidence of low-birth-weight preterm newborns is 5-16%, with the greatest attention paid to extremely low and very low birth weight infants, in whom perinatal mortality is up to 90% [7]. Among the causes of disability, damage to the central nervous system accounts for 98.6%, among them neurosensory anomalies - 29%, impaired rates of mental development - 42%; bronchopulmonary dysplasia is about 53%, damage to the cardiovascular system is 30% [2, 6, 13]. The severity of cerebral ischemia is closely related to gestational age and birth weight, and the initial premorbid background of the newborn

child [3,10]. The percentage of practically healthy children born with very low body weight (VLBW) and extremely low body weight (ELBW) does not exceed 10 - 25.0%, but they constitute the main percentage of mortality and disability in young children [11].

Children born with low body weight (1500.0-2499.0 g) have a more favorable early and long-term prognosis in terms of their development and physical health, however, underweight is a risk factor for functional disorders of the central and autonomic nervous systems [7, 2, 14]. The immediate consequences of the birth of children with low body weight have been sufficiently studied and include: the development of respiratory distress syndrome, persistence of fetal circulation, infections, impaired thermocoagulation, necrotizing enterocolitis [2,16] Less is known about the risk of pathological conditions associated with low body weight, which the implementation time frame goes beyond the neonatal period. According to various authors, prematurity and low birth weight cause functional failure of neuropsychic development in the motor, emotional, motivational, and cognitive spheres; In some premature newborns, persistent disorders are observed in the first years of life, manifested in cognitive impairment, learning difficulties, and socialization in society [1,7,16]. Low birth weight newborns are characterized by biological immaturity, limited stomach volumes, and small reserves of iron, calcium, vitamins, fat, and glycogen, which creates the preconditions for a decrease in adaptive capabilities [10]. However, criteria for predicting disorders of the central nervous system, autonomic nervous system and somatic pathology have not been developed. A promising modern direction is the determination of autoantibodies to organs and tissues for preclinical diagnosis of functional and a number of organic changes in them. The pathogenetic role and diagnostic significance of autoantibodies to brain proteins and neurotransmitter receptors has prospects in prognostic terms in children born with low birth weight. Studying the level of autoantibodies to gliospecific proteins is important for understanding the mechanisms of damage to astrocytic glia and the blood-brain barrier (BBB) in low-birth-weight children, as well as for improving methods for early diagnosis of disorders of higher nervous activity and their prevention. Autoantibodies to components of nervous tissue in newborns are of maternal origin, because they belong to class G immunoglobulins - IgG , embryotropic antibodies and freely penetrate trans placentally to the developing fetus. With a persistent abnormal increase in the production of certain biologically active autoantibodies (auto-ATs) in the mother, they, reaching the fetus in excess quantities, cause tissue-specific damage [5]. Suboptimal conditions of intrauterine development, caused by persistent changes in the production of maternal embryotropic antibodies, are not in all cases accompanied by the death of the embryo or fetus, or the birth of a child with developmental defects, but almost always lead to noticeable negative changes in the child’s health and a delay in intrauterine development. Somatic pathology of the mother is in 2nd place among the causes of fetal growth retardation and the birth of children with low body weight. When the level of autoantibodies increases in a child, pathological changes in organs can form both due to direct aggression caused by antibodies, and due to prenatal programming of his immune system for increased production of the same antibodies as his mother (the phenomenon of maternal epigenetic immune imprinting) [4.9].

The level of antibodies reflects the structural and functional state of the central nervous system, including a number of receptors. Persistent changes in the production of auto-ATs to the following antigens may reflect the presence or formation of various forms of CNS pathology, cognitive and behavioral disorders [1,8].

In this regard, the goal of our work was to identify a predisposition to pathology of the central nervous system and internal organs in low-birth-weight newborns by conducting immunochemical screening in order to

Materials and methods. We examined 64 newborns who were born at a gestational age of 32-37 weeks with a low body weight of 1500.0-2499.0 g. Newborns were divided into 2 groups: those born with a body weight of 1500.0-1999.0 g at a gestational age of 32-34 weeks (n =26) and those born at a gestational age of 35-37 weeks with a body weight of 2000.0-2499.0 g (n =38). The comparison group consisted of healthy full-term newborns weighing more than 2500.0 g, born at 38-40 weeks of gestation (n = 12). All children underwent a standard clinical examination, and the levels of 12 types of IgG autoantibodies to 12 types of antigenic components of brain cells and receptors were assessed, and an immunoreactivity index was calculated. Autoantibodies were determined by solid-phase ELISA on a Rayto analyzer (China), using ELI-Nero-12-Test test systems (Immunculus, Russia). To conduct the entire panel of tests, 0.5 ml of the child's blood serum was required; blood was drawn on days 5-7 of life.

Results obtained. Research results showed that low birth weight babies were born to mothers aged 25-34 years. At the same time, the parity of pregnancy draws attention - low birth weight children of the 1st group (32-34 weeks of gestation) were born mainly from the first pregnancy (n = 21; 80.7%), while in the second group (35-37 weeks of gestation) from the first Only 13 (34.2%) children were born during pregnancy, and 25 (65.8%) were born from the 2nd, 3rd and 4th pregnancies. A study of the anamnesis and the presence of somatic diseases in mothers showed that IDA was observed in 8 (30.8%) and 12 (31.6%) women - in groups 1 and 2, respectively ($p > 0.05$); gestosis was significantly more common in mothers of the second group: 24 (63.1%) versus 10 (38.5%) ($p < 0.05$); somatic diseases were detected in 8 (30.8%) and 14 (36.8%) women of the first and second groups, which was not statistically significant ($p > 0.05$). The mothers of low-birth-weight children had no history of organic diseases of the nervous system, but 6 (23.1%) and 8 (21.1%) women complained of frequent mood swings and nervousness - in groups 1 and 2, respectively. Only 5 (7.8%) women had higher education, of which 2 were from the first and 3 from the second group.

Table 1.

Assessment of the condition of newborns using the Apgar scale

Observation groups	Gestational age, weeks	Body weight at birth, g	Grade Apgar scale	
			1st minute, point	5th minute point
Control group, n=12	39.0±0.1	2932±112	7.1±0.3	8.9±0.2
Group 1 (1500-1999), n=26, p1	32.91±0.33	1823±141	5.5±0.3	6.5±0.3
Group 2 (2000-2500) , n=38, p2	36.21±0.27	2329±93	6.3±0.2	7.5±0.2
P1:2	<0.05	<0.05	<0.05	<0.05

Assessment of the condition of newborns using the Apgar scale showed that there was a significant difference in parameters at 1 and 5 minutes of life in children of the 1st and 2nd groups. Newborns of group 2 had a higher Apgar score (Table 1).

Analysis of transient conditions of newborns showed that a protracted course of neonatal jaundice occurred in 16 (61.5%) and 24 (63.2%) low birth weight newborns - in groups 1 and 2, respectively (p > 0.05) , whereas in the control group - only 3 (25%) children.

A study of the neurological status showed that more than half of low-birth-weight newborns had cerebral ischemia (CI) of grades 1 and 2; grade 3 ischemia was not detected in our studies. As can be seen from Table 2, signs of cerebral ischemia were equally common in both groups. Damage to the central nervous system most often manifested itself as depression syndrome, which was diagnosed in 16 (61.5%) children of the 1st group and 13 (34.2%) children of the 2nd group; agitation syndrome was observed in 8 (30.7%) children of the 1st group and in 16 (42.1%) children of the 2nd group.

Table 2.

Incidence of central ischemia in low birth weight newborns

Observation groups	Newborns without CI		Newborns with CI 1st degree		Newborns with CI 2nd degree	
	n	%	n	%	n	%
Control group, n=12	12	100	0	0	0	0
1 subgroup (1500-1999), n=26	10	38.5	6	23.0	10	38.5
2 subgroup (2000-2500) , n=38	14	36.8	eleven	28.9	13	34.3
R	> 0.05		> 0.05		p>0.05	

Note: P – statistical significance of differences between 1 and 2 subgroups

The next stage of the work was to assess the level of neurospecific autoantibodies. To understand changes in the level of neurospecific autoantibodies, it is necessary to clarify their physiological and pathogenetic significance [9] (Table 2).

Considering the lack of data in the literature on the level of autoantibodies to nervous tissue determined in newborns, we also selected a comparison group. Note that the deviation of the level of autoantibodies from the average level in standard serum, expressed in %, is taken as the conditional norm; the conditional norm lies in the range from (- 20%) to + 10% (green zone). If the level of autoantibodies in the subject exceeds that in the standard by 10-20% (+10 - +19%), then this is interpreted as a relative deviation (yellow zone), if the level of autoantibodies exceeds the standard by 20% or more (+20% or more) – then this is a reliable deviation (red zone) [9].

Pathogenetic significance of autoantibodies to nervous tissue [8,9]

Autoantibodies, type	Physiological significance	Pathogenetic significance
OBM	Basic protein of myelin sheaths of axons	Demyelinating marker processes
S100β	A highly specific member of the family of Ca2+-binding proteins for nervous tissue	Regulator of apoptosis, trophic factor of serotonergic neurons, an increase in autoantibodies to it is accompanied by disturbances in the emotional-volitional sphere, in some cases this increase is initiated by the human papillomavirus
NF-200	Axon specific protein	Accompanies the process of degeneration of nerve fibers
GFAP	Brain-specific glial fibrillary acidic protein, which forms intermediate filaments of the astrocyte cytoskeletal system,	The growth of autoantibodies to it accompanies the proliferation of astroglia - gliosis, including reactive astrogliosis
VGCC	Voltage-dependent Ca^{++} channel, membrane protein	Is a specific antigen for cerebellar ataxia, amyotrophic sclerosis, autism
Cholinergic receptors	Reception of neurotransmitters	Marker of cognitive impairment, learning, memory
Glutamate receptors, GABA receptors	Reception of neurotransmitters	Markers of disturbances in the regulation of excitation/inhibition processes
Dopamine receptors	Reception of neurotransmitters	Marker of cognitive impairment and shifts in the emotional-volitional sphere, motivation
Serotonin, opiate and beta-endorphin receptors	Reception of neurotransmitters	As a marker of disorders in the emotional-volitional sphere, autism, bipolar disorders

As our observations showed, deviations from the conventional norm were present in almost all 12 positions of neurospecific autoantibodies. It is noteworthy that the level of autoantibodies to myelin basic protein (MBP) was significantly higher in children born at 32-34 weeks of gestation, relative to the indicators of children of group 2, which indicates a high level of demyelinating processes in them and is confirmed by the presence of periventricular leukomalacia. Thus, MBP was increased on average to 50.3±5.4% in children of the 1st group, while in more mature newborns of the 2nd group it was increased to 39.7±2.3%, and in children in the control group, this indicator was at the level of reference values recommended by the authors of the method [9], amounting to 5.2±0.6% (Table 3).

Table 3.

Level of autoantibodies to nervous tissue in low birth weight newborns

Autoantibodies, type	1st group, n=26	2nd group, n=38	Control group, n=12
OBM	50.3±5.4	39.7±2.3*	5.2±0.6
S100β	54.7±2.6	48.6±1.8*	7.4±1.0
NF-200	23.0± 3.0	31.5±3.5*	4.6±0.6
GFAP	45.9± 9.4	62.8±8.8*	5.7±0.3
VGCC	-13.0± 1.2	- 2.6±1.1	- 3.0± 1.0
Cholinergic receptors	20.6± 1.4	24.4±4.0	11.0±2.0
Glutamate receptors	17.3±5.8	23.6±11.0	16.5±1.0
GABA receptors	35.2± 2.0	45.0±6.0	6.7±2.6
Dopamine receptors	22.3± 2.0	25.8±5.6	4.6±1.1
Serotonin receptors	37.0 ±7.0	36.5±7.1	13.8±2.5
opiate receptors	24.6± 6.3	30.4±4.8	14.7±3.7
beta-endorphin receptors	52.7±2.6	52.8±3.5	16.3±6.1

Note: *-differences are statistically significant between the average indicators of the 1st and 2nd subgroups

The level of autoantibodies to GFAP was significantly higher in children of group 2, which indicates intensive proliferation of astroglial cells and gliosis in children, which is more typical for newborns born at 35-37 weeks of gestation. An increase in the levels of auto-ATs to GFAP can accompany proliferative processes in astrocytic glia, activation of astrocytes (in response to damage), cell hypertrophy, and in some cases, cause dystrophic processes and irreversible formation of a glial scar and changes in tissue structures.

At the same time, these children also had an increased level of autoantibodies to protein S 100, which indicates, on the one hand, increased binding of this protein and the prevention of apoptosis, and on the other, a decrease in its trophic effects on serotonergic neurons. The level of autoantibodies to serotonin, opiate and beta-endorphin receptors was significantly increased in all low-birth-weight newborns, which indicates the potential destruction of these receptors, or their blockade, as a prerequisite for disorders in the cognitive, emotional-volitional sphere and learning abilities. Long-term elevated levels of autoantibodies indicate a poor prognosis.

Note that when interpreting the results of a multiplex study of autoantibodies, it is advisable to present not the average values of these indicators, but the number of patients with deviations in the compared groups, and also indicate the direction of the deviation [1,9]. In this light, our results are presented in Table 4.

A decrease in the level of autoantibodies is more typical for long-term deep disorders, and an increase is more typical for reactive processes. The definition of a panel of autoantibodies is fully consistent with new views on the importance of the immune system in maintaining the constancy of the molecular composition of the body and the homeostatic regulation of a wide variety of processes in changing conditions of the external and internal environment.

Table 4.

The nature of autoantibody abnormalities in low-birth-weight newborns

Autoantibodies, type	Nature of deviations	1st group, n=26		2nd group, n=38		Control group, n=12	
		n	%	n	%	n	%
NF-200	Conventional norm (-20 - +10)	0	0	0	0	12	100
	Relates. deviation	0	0	0	0	0	0
	Ven. deviation	26	100	0	80	0	0
GFAP	Conventional norm (-20 - +10)	0	0	0	0	12	100
	Relates. deviation	0	0	0	0	0	0
	Ven. Deviation	26	100	38	100	0	0
S100β	Conditional normal (-20 - +10)	0	0	0	0	12	100
	Relates. deviation	0	0	0	0	0	0
	Ven. Deviation	26	100	38	100	0	0
OBM	Conditional normal (-20 - +10)	0	0	0	0	12	100
	Relates. deviation	0	0	0	0	0	0
	Ven. Deviation	26	100	38	100	0	0
VGCC	Conditional normal (-20 - +10)	26	100	thirty *	78.9*	12	100
	Relates. deviation	0	0	8*	21.1	0	0
	Ven. Deviation	0	0	0	0	0	0
Cholinergic receptors	Conditional normal (-20 - +10)	0	0	7*	18.4	6	50
	Relates. deviation	8	30.7	1*	2.6	6	50
	Ven. Deviation	18	69.3	thirty	78.9	0	0
Glutamate receptors	Conditional normal (-20 - +10)	0	0	0	0	0	0
	Relates. deviation	16	61.5	23	60.5	4	33
	Ven. Deviation	10	38.5	15	39.5	8	67
GABA receptors	Conditional normal (-20 - +10)	4	15.4	3*	7.9	12	100
	Relates. deviation	2	7.6	0	0	0	0
	Ven. Deviation	20	76.9	35*	92.1	0	0
Dopamine receptors	Conditional normal (-20 - +10)	0	0	0	0	12	100
	Relates. deviation	0	0	24*	63.1	0	0
	Ven. Deviation	26	100	14	36.9	0	0

Serotonin receptors	Conditional normal (-20 - +10)	26	100	38	100	4	33
	Relates. deviation	0	0	0	0	8	67
	Ven. Deviation	26	100	38	100		
opiate receptors	Conditional normal (-20 - +10)	0	0	0	0	5	41.7
	Relates. deviation	0	0	0	0	7	58.3
	Ven. Deviation	26	100	38	100	0	0
beta-endorphin receptors	Conditional normal (-20 - +10)	0	0	0	0	5	41.7
	Relates. deviation	0	0	0	0	7	58.3
	Ven. Deviation	26	100	38	100	0	0

Note: *-differences are statistically significant between the average indicators of the 1st and 2nd groups

The complex functions of the immune system under consideration are based on a pervasive multicomponent system of natural autoantibodies, which rapidly responds with quantitative changes to a variety of functional and metabolic changes in isolated cell populations, organs and the body as a whole.

A number of studies have confirmed that the determination of antibodies to various membrane, cytoplasmic and nuclear antigens of the body's cells and intercellular matrix, as well as secretory products of cells, like a mirror, reflects the antigenic structure of the body and forms a dynamic "Immunological homunculus" [8,9]. Multicomponent assessment of the content of auto-AT allows for a systemic analysis and clarification of the role and participation of pathoimmune mechanisms in the development of low-birth-weight newborns.

Conclusions:

1. Low birth weight newborns with a weight of 1500.0-1999.0 g and a gestation period of 32-34 weeks are born from the first pregnancy in 80.7% of cases, which indicates the need for close attention to this cohort of women.

2.NF -200, S 100, GFAP is significantly increased, and it is statistically significantly higher in children with a weight of 1500.0-1999.0 than in children with a weight of 2000.0 -2499.0 g, which indicates structural changes in the central nervous system, disruption of myelination processes, formation of astroglia, neutrotrophic functions, more pronounced in newborns with a gestation period of 32-34 weeks.

3. Objective signs of cerebral ischemia of the 1st and 2nd degrees with the same frequency (61.5% and 63.2%) occur in newborns weighing 1500.0-1999.0 and 2000.0-2499.0g.

4. In newborns with low body weight (1500.0-2499.0 g), regardless of gestational age after 32 weeks, there is an increase in the level of autoantibodies to the receptor structures of the brain responsible for cognitive, emotional-volitional and behavioral reactions, as well as those involved in the implementation of autism.

REFERENCES

1. Девятых Д.В., Гергет О.М., Михаленко И.В. Применение искусственных нейронных сетей для прогнозирования развития перинатального поражения нервной системы //

Известия Волгоградского государственного технического университета. - 2013. - № 8(111) -С. 77-81.

2. Дегтярева Е.Г., Куфа М.А., Кантемирова М.Г. Новые подходы к оценке риска повреждения сердечно-сосудистой и центральной нервных систем у детей с задержкой внутриутробного развития // Детские болезни сердца и сосудов.- 2015. - №4.- С 23-29. 309.
3. Ивахнишина Н.М.,Супрун С.В.,Дудукалов С.Г., Каргин В.П. .Результаты диагностики внутриутробных и перинатальных инфекций у недоношенных маловесных детей //Журнал «Бюллетень » - 2014. - № 54. – С. 88-97.
4. Лучанинова В.Н., Погодаева Т.В. Иммунохимический скрининг с целью определения предрасположенности к патологии почек у новорождённых// Нефрология. 2012. Том 16. №1.-С.82-88.
5. Мальцева ЛИ, Замалеева РС, Полетаев АБ и др. Клиническое значение регуляторных аутоантител в развитии плацентарной недостаточности у женщин с отягощённым акушерским анамнезом // Гинекология 2005; (11): 5-27.
6. Михаленко И.В., Михалев Е.В. Ермоленко С.П. Клинико-биохимическая характеристика недоношенных новорожденных с экстремально низкой массой тела при рождении // Педиатрическая фармакология. - 2013. - Том 10.- № 4. - С. 113-118.
7. «О глобальных действиях в отношении преждевременных родов. Рожденные слишком рано» // Доклад ВОЗ. -2014. - С. 8-16.
8. Орлова В.А., Михайлова И.И., Минутко В.Л., Симонова А.В. Аномалии уровней сывороточных аутоантител к антигенам нервной ткани у больных шизофренией: мультипараметрическая иммунологическая оценка // Социальная и клиническая психиатрия 2016, т. 26 № 1.-С.12-19.
9. Полетаев АБ, Алиева Ф, Мальцева ЛИ. Иммунопатология беременности и здоровье ребенка // Русский медицинский журнал: независимое издание для практикующих врачей 2010; (4): 162-167.
10. Трифонова А.С., Перцева В.А. , Г.В. Тамазян, Л.В. Малютина Особенности профилактических мероприятий по снижению заболеваемости и смертности недоношенных с очень низкой и экстримально низкой массой // Вестник РУДН, сер. Медицина. Акушерство и гинекология. – 2011. - № 6. – С. 176-185
11. Щербатюк Е.С., Хмилевская С.А., Зрячкин Н.И. Особенности состояния здоровья и проблемы реабилитации детей раннего возраста, родившихся С экстремально низкой и очень низкой массой тела (обзор) // Saratov Journal of Medical Scientific Research. 2017. Vol. 13, № 2.-С.246-251.
12. Акрамова Х., Джалилов А., Ахмедова Д. Особенности развития и состояния здоровья детей, рожденных смалым весом, до достижения годовалого возраста //in Library. – 2020. – Т. 20. – №. 2. – С. 423-429.
13. Турдиева Д. Э., Алиева Н. Р., Табибова М. В. внебольничная пневмония у детеЙ раннего возраСта //Медицина: теория и практика. – 2019. – Т. 4. – №. S. – С. 550-550.
14. Akramova Kh.A., Akhmedova D.I., Khaybullina ZR Diagnostic significance of oxidative stress markers in underweight new-born babies on the initial days of life in the prognosis of adaptation disorders (experimental study) // European science review.- 2015.-№ 7-8.-P.28-30

15. Khursandoy Akramova, Dilorom Akhmedova, Dilfuza Turdieva, Comparative Analysis Of Peculiarities Of Adaptation Of Babies // Jour of Adv Research in Dynamical & Control Systems, Vol. 12, 2020, P. 2735-2740
16. The report of Global coalition of organizations “Survive and Thrive: Transforming care for every small and sick newborn”. 13 December 2018.
17. Zhelev V.A., Mikhalenko I.V., Mikhalev E.V., Ermolenko S.P. Neurometabolic predictors in outcomes of perinatal brain injury // J. Perinat.Med. - 2013.-№41-P.708. DOI 10.1515/jpm-2013-2003.