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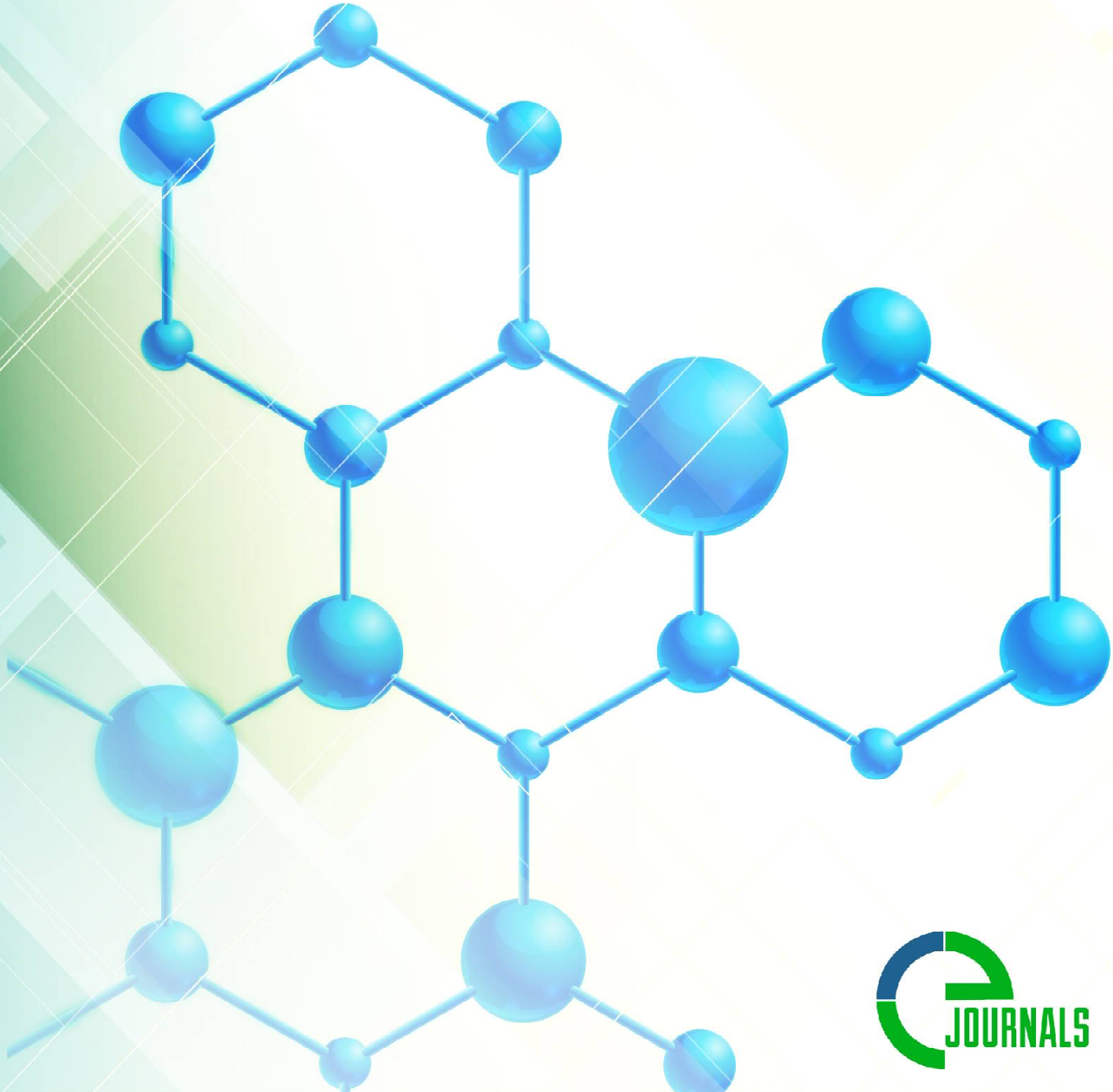

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PATHOGENETIC SIGNIFICANCE OF BIOCHEMICALLY ASSOCIATED WITH HEMOSTASIS OF PHALATE CYCLE FII AND FV GENES IN DIAGNOSIS OF PERIVENTRICULAR LEUKOMALATION IN CHILDREN.

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Abstract.A number of studies are being carried out in the world aimed at improving the efficiency of diagnosis and treatment of clinical and pathogenetic parallels of periventricular leukomalacia in children. In this regard, the issues of determining the frequency and nature of neurological disorders, the structure of complications in children with periventricular leukomalacia, studying the role of the condition, the course of individual clinical signs and determining the prognosis in periventricular leukomalacia complicated by periventricular hemorrhage are relevant. Also of particular importance is the identification of the presence of an association between polymorphic variants of candidate genes in PVL: factor V Leiden, prothrombin G20210A factor II, study of the frequency and structure of complications in children with PVL and periventricular hemorrhage (PVH), depending on the nature of the "gene-gene interactions" and genotypic combinations, development of a methodology and study of information content for the diagnosis and prediction of the course of vascular disorders of hemorrhagic and ischemic nature in PVL using available neurophysiological research methods.

Key words: gene polymorphism, periventricucular leukomalacia, hypoxia, asphyxia.

A prominent place among periventricular brain lesions in premature infants is periventricular leukomalacia (PVL). Brain lesions in infants occupy a leading place in the structure of perinatal pathology of the nervous system and are the main cause of maladjustment and disability at later stages of child development. The development of the medical field in our country on the basis of international standards, effective diagnosis and treatment of periventricular leukomalacia, various genetic hereditary diseases and diseases of various degrees of disability in children resulting from this, are one of the problems that need to be solved. In this regard, in comprehensive measures to radically improve the health care system of the Republic of Uzbekistan, such priority tasks have been identified as "improving the efficiency, quality and availability of medical care for children, as well as creating a system of medical standardization, introducing high-tech methods of diagnosis and treatment, supporting a healthy lifestyle by creating effective models of patronage services and clinical examination and disease prevention ... ". Based on these tasks, it is of particular importance to identify the clinical, pathogenetic and immunological parallels of periventricular leukomalacia in children, the provision of modern medical services at a high level and the improvement of the use of modern technologies in the treatment and optimization of the disease.

As a result of the clinical-genetic assessment of the clinical-pathogenetic and immunological parallels of periventricular leukomalacia in children, the following scientific results were obtained:it was substantiated a comprehensive systematic analysis of factors, diseases and their prevalence associated with the clinical-pathogenetic and immunological parallels of periventricular leukomalacia (StrokePreventionResearchUnit, UniversityDepartmentofClinicalNeurology, JohnRadcliffeHospital, Oxford (Great Britain), Voronezh State Medical Academy named after N.N.Burdenko (Russia), Kazan State Medical University, Tatarstan); the system of clinical-genetic assessment of

clinical-pathogenetic and immunological parallels of periventricular leukomalacia in children has been substantiated (Tashkent Institute for Advanced Medical Studies).

In recent years, the molecular genetic basis of the development of periventricular leukomalacia complicated by periventricular hemorrhage and the search for opportunities to control the expression of genes involved in the implementation of cell death under conditions of hypoxia, asphyxia, and trauma have attracted special attention of researchers. However, to date, it has not been possible to identify specific polymorphic variants of genes or gene mutations that determine the development of hypoxic-ischemic or hemorrhagic PVL.

Purpose of the study: a comprehensive assessment of the complications of clinical, pathogenetic and immunogenetic parallels of periventricular leukomalacia in children.

Research materials and methods:

2005 to 2009 in stationary conditions, a comprehensive examination was carried out of 150 children aged from 1 day to 1 year of life, who underwent periventricular leukomalacia complicated by periventricular hemorrhages, and 50 apparently healthy children. The studies were carried out in the Republican Specialized Scientific and Practical Medical Center for Obstetrics and Gynecology and in the Department of Pathology of Premature Children's Hospital No. 5 in Tashkent. In the follow-up, the children were observed in the microneurology department of the City Children's Clinical Hospital (CCCH).

The surveyed were divided into three groups. Group 1 consisted of 102 (51.0%) children with periventricular leukomalacia complicated by periventricular hemorrhage. Group 2 included 48 (24.0%) children with periventricular hemorrhage. Group 3 included 50 (25.0%) apparently healthy children with unexpressed cerebral pathology.

The degree of prematurity was determined taking into account the gestational age, body weight and height, morphological and functional signs of prematurity. In the 1st group there were 39 full-term (38.2%), in the 2nd - 30 (62.5%), in the 3rd - 49 (98.0%); prematurity, respectively 63 (61.8%), 18 (37.5%) and 1 (2.0%).

The nature of the transferred hypoxia was determined according to the schemes developed by G.M. Savelyeva, M.V. Fedorova, N.P. Shabalov et al. (2009), on the basis of a set of anamnestic and documentary data on the features of the course of pregnancy and childbirth, the results of histological examination of placental tissue, clinical examination of children with the isolation of signs characteristic of newborns who underwent chronic oxygen starvation during pregnancy (intrauterine malnutrition, morphofunctional immaturity, trophic disorders, etc.), neurological status, as well as based on the results of the analysis of the course of the adaptation period.

All children underwent clinical, neurological and paraclinical studies, which included the assessment of the following parameters: anthropometric parameters (length, body weight, chest circumference, head, shoulder girdle perimeter) were obtained using a horizontal rostometer, medical (electronic) scales and a centimeter tape. The accuracy of measuring body length, chest circumference, head, shoulder girdle perimeter was 0.1 cm, body weight 10 g; for the clinical-anamnestic method, a card of complex examination of women in labor and newborns was used. During the neurological examination of newborns, they were based on the data of L.O.Badalyan and Zhurba-Mastyukova.

All children in the acute period from the 1st to the 6th day of life underwent neurosonographic examination on a Siemens apparatus using sensors with a frequency of 7.5 and 3.5 MHz, as well as with the transfer to the second stage of nursing from the 3rd to the 7th a day and then in the follow-up up to the 1st year of life using the Sonoscope-300 (Kransbuhler firm) sensors with a frequency of 7.5 and 3.5 MHz. The

technical parameters and capabilities were the same. Multiplicity scan - on average 2-3 fold.

The anatomical structures of the brain were examined according to the standard technique in the coronary and sagittal planes in 10 standard sections. No special preparation of patients was required, the severity of the condition was not a contraindication to neurosonography (NSG).

Standard NSG of the infant's brain includes a modified transgranular examination, supplemented by transcranial scanning in the TH0-TH2 (3.5 S) mode. In addition, unlike the techniques proposed by S.M. Voevodin, O.E. Ozerov, when examining a child's head are used both sector and linear sensors. This combination eliminates the disadvantages inherent in traditional transgenic scanning. The use of the F (5L) - scanning mode expands the diagnostic capabilities. In this mode, one can more clearly assess the pulsation of the cerebral vessels, determine the area of the germinal matrix and the state of the brain in the area of frequent occurrence of periventricular leukomalacia - the anterior "favorite" PVL area.

All children underwent a Doppler sonography study using the SonolyerVersaPro apparatus (Siemens, Germany) with a convexital probe 5.5-7.5 MHz with a Doppler frequency of 2.0 MHz in the mode of color and beat-pulse mapping, in the acute period from 1 to 6th day of life, as well as after the course of treatment. The frequency of scanning is on average 2-3.

Clinical and electroencephalographic examination was carried out in patients with PVL during physiological daytime sleep. During the registration of the EEG, the mother was with the child. EEG study was carried out on an 8-channel electroencephalograph Bioscript, registration of EEG signals - according to the international system in an electroencephalographic camerain 8 standard leads (frontal, central, occipital, temporal both hemispheres) by mono- and bipolar methods. In addition to the background recording, a functional test was performed - light rhythmic photostimulation. When identifying the spectral EEG pattern, we used a system of visual qualitative assessment, which makes it possible to reveal the relationship between the formation of brain bioelectrical activity and its morphological and functional characteristics at different stages of a child's development.

In the study of periventricular leukomalacia in children, one of the main directions is molecular genetic research to identify the so-called candidate genes.

Molecular genetic polymorphism of the genes of factor Leiden V, mutation of prothrombin G20210A factor II were studied in 200 young children of Uzbek nationality in the laboratory of functional genomics of the Institute of Genetics and Experimental Biology of Plants of the Academy of Sciences of the Republic of Uzbekistan. The control group consisted of 50 conditionally healthy children who were not family related to each other.

The data obtained in the study were subjected to statistical processing on a Pentium-IV personal computer using the Microsoft Office Excel-2003 software package, including the use of built-in statistical processing functions and Biostatistics for Windows (version 4.03). Methods of variational parametric and nonparametric statistics were used with the calculation of the arithmetic mean of the studied indicator (M), standard deviation ( ), standard error of the mean (m), relative values (frequency,%); The statistical significance of the obtained measurements when comparing the mean quantitative values was determined by the Student's test (t) with the calculation of the error probability (P) when checking the normal distribution (by the kurtosis test) and the equality of general variances (F is the Fisher test). Statistical significance for qualitative values was calculated using the ?2 test (chi-square).

Results and Discussions:

Clinical assessment of periventricular leukomalacia complicated by periventricular hemorrhage, based on the results of physical examination and obstetric history data. The literature data of recent years indicate that the risk of PVL is correlated with the incidence of PVL. In our studies, among patients of the 2nd group with periventricular hemorrhage, there were 31 boys (64.6%), and 17 girls (35.4%). In 17 children, at birth, the condition was assessed as moderately severe, in 28 - as severe. There were 18 premature babies (37.5%), of whom 9 were born within 34 weeks (18.8%); full-term - 31 (64.6%). Hypoxia among children of the 2nd group was in 15 (31.3%), asphyxia - in 13 (27.1%), trauma during childbirth - in 11 (22.9%).

The age of the majority of mothers of children in the 1st group was in the range of 19-30 years, but in contrast to the 2nd group, there were more women under the age of 19 and from 31 to 40 years. In 46 (45.1%) women in this group it was the 1st pregnancy, in 63 (61.8%) - the 1st birth. When analyzing the health status of mothers of this group, it was revealed that all 102 women by the beginning of pregnancy suffered from various chronic somatic and gynecological diseases (cardiovascular system, respiratory system, gastrointestinal tract, endocrine). During pregnancy, 6 (5.9%) examined mothers were diagnosed with toxoplasmosis, 29 (28.4%) - CMV, 10 (9.8%) - chlamydia, 21 (20.6%) - herpes. Anemia of II degree during the 2nd half of pregnancy was in 84 (82.4%), ARVI - in 19 (18.6%), toxicosis - in 10 (9.8%), the threat of termination of pregnancy - in 55 (53 , 9%) women.

Intranatal factors play an equally important role in the occurrence of periventricular leukomalacia complicated by periventricular hemorrhage, among which, according to anamnestic data, early rupture of amniotic fluid was in 41 (40.2%), polluted water - in 42 (41.2%); 9 (8.8%) newborns were born with an umbilical cord entwined around the neck, rapid delivery took place in 28 (35.4%), breech presentation - in 14 (13.7%), foot presentation - in 7 (6.9%).

The data obtained show that in children of the 1st group the risk of developing periventricular leukomalacia complicated by periventricular hemorrhage is significantly higher than in children of the 2nd group (with periventricular hemorrhage), which is mainly associated with birth asphyxia and trauma. Delivery in these women was carried out using obstetric aids: caesarean section was performed in 24 (23.5%), obstetric forceps were used in 5 (4.9%), vacuum - in 5 (4.9%), manual examination - in 5 (4.9%).

The peculiarities of the clinical course of periventricular leukomalacia complicated by periventricular hemorrhage include a more severe condition than in patients of group 1 (without periventricular hemorrhage). The severity of the condition, assessed on the Apgar scale at the 1st minute of life, was 6-7 points in 24 (23.6%) children, 5-6 points - in 33 (32.4%), 4-5 points - in 25 (24.5%), 3-4 points - in 13 (12.7%), 1-2 points - in 5 (4.9%). In 77 (75.5%) newborns, the condition at birth was assessed as severe, which was expressed in an increase in lethargy, a decrease in spontaneous motor activity, inhibition of congenital reflexes - in 84 (82.4%), muscular dystonia - in 65 (63.7 %). 100% had symptoms characteristic of PVL. During the general examination, attention was paid to the posture of the newborn: the head was slightly tilted back, spastic synkinesia was expressed, the legs were in the extension position, the protective reflex was absent or was sharply reduced. When the stepping reflex was evoked, its perversion was noted: the reflex was lateralized (the child walked to the sides) - the Wolp reflex.

The results of neurological examination indicate that in patients of the 1st group, clinical symptoms, especially changes in the cranial innervation and motor sphere, were more pronounced than in the 2nd. So, converging strabismus was more on the left noted in 31 (30.4%), diverging on the left - in 14 (13.7%) children of the 1st group,

while in the 2nd group - respectively, in 12 (25.0%) and 41 (85.4%).

In the 1st group, the reaction of the pupils to light was weakened in 84 (82.4%) patients, in the 2nd - in 34 (70.8%). On the part of muscle tone, more pronounced changes were also observed in the 1st group. If in the 1st group a decrease in tone was noted in 16 (15.7%) patients, and in the 2nd - in 22.9%, then in the 1st group there was more often a tendency to dystonia (63.7%), spasticity tone - in 1.0%, anisotonia - in 2.0%; in group 2, these phenomena were recorded, respectively, in 37.5; 0 and 2.1% of children. In the reflex sphere, clear dissociation was found in the severity of reflexes of both oral and spinal automatism; the reflex sphere tended to be depressed. In the postpartum period, the syndrome of CNS depression was expressed in hypodynamia, hypotension, hyporeflexia, decreased sucking reflex in 97 (95.1%), swallowing in 94 (92.2%). Suppression of spinal reflexes was observed (support - in 92.2%, automatic walking - in 72.5%, protective - in 75.5%, cervical ACTR - in 90.2%).

In the early recovery period, symptoms of depression persisted in 30.4% of children. Thus, a weak quadruple symptom (in 87.3%), weak support (in 92.2%), weak swallowing (in 92.2%) were replaced by signs of neuro-reflex excitability: muscle hypertonicity, large-spreading tremor of the limbs, startle, horizontal or vertical nystagmus. Along with this, 22.5% of children showed signs of intracranial hypertension, which were manifested by paroxysms of piercing screaming (in 5.8%), tension (in 88.2%), swelling (in 64.7%) and pulsation (in 53, 9%) of a large fontanel, a combination of Greffe's symptoms, pronounced tension (in 45.1%), a weakened reaction of the pupils (in 82.4%), hemisyndrome (in 7.8%).

Both in the acute period (7-10th day) and in the early recovery period (after 10 days of life), were observed symptoms of vegetative stability: cyanosis at rest (in 79.4%), blue skin color (in 79.4%) , a symptom of "Harlequin", a violation of thermoregulation, dyskinesia of the gastrointestinal tract - regurgitation.

Convulsive reactions in patients of the 1st group manifested themselves polymorphically with a predominance of opercular (in 15.7%), ocular (in 14.7%), generalized-clonic (in 9.8%), tonic (in 10.8%), which indicated a more diffuse reaction of the cerebral cortex.

The severity of the condition in children of this group was aggravated by the presence of concomitant diseases such as anemia (in 27.5%), conjugational jaundice (in 13.7%), sepsis (in 2.9%), hypotrophy (in 82.4%), which significantly worsened the somatic status. This was manifested by symptoms of intoxication: an increase in temperature to subfebrile and febrile numbers, a stop of weight gain, the appearance of regurgitation, bloating due to intestinal paresis, an enlarged liver. Among children who underwent periventricular leukomalacia complicated by periventricular hemorrhage with signs of infectious toxicosis, signs of disseminated intravascular coagulation were observed, which was manifested by increased bleeding from the injection sites, the presence of small punctate skin hemorrhages.

It should be noted that periventricular leukomalacia, complicated by periventricular hemorrhage, proceeds more unfavorably than periventricular hemorrhage, and tends to transform into an organic defect. The frequency, duration, nature and type of caused neurological disorders are characterized by a causal relationship, the timeliness and reliability of detection of which provide a solution to the problems of early diagnosis and therapy, effective prevention and further prognosis of periventricular leukomalacia in young children.

Most of the mothers of the children of the 2nd group were at the age of 20-35 years. The pathological course of the gestation period was more typical for the first-pregnant women - in 25 (52.1%), among women with the 2nd and 3rd pregnancies, the pathological

course was observed, respectively, in 16.7 and 10.4% of the examined.

In 24 (50.0%) mothers of the 2nd group, pregnancy proceeded with preeclampsia of I - III degree, in 38 (79.2%) - with polyhydramnios, anemia of II degree in the 2nd half of pregnancy. Rapid labor in 17 (35.4%) mothers was complicated by weakness of labor, 14 (29.2%) had dry anhydrous labor, 6 (12.5%) had breech presentation, 7 (14.6%)) - early discharge of amniotic fluid, in 14 (29.2%) - double entanglement of the umbilical cord around the neck. 11 (22.9%) women had CMV, 5 (10.4%) had herpes (Fig. 1).

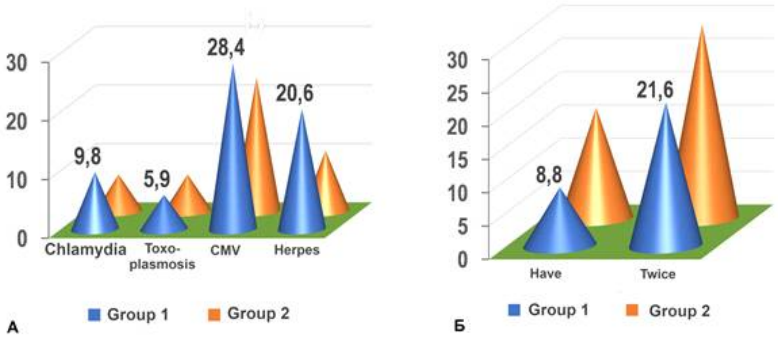

Fig. 1. Complications of the course of pregnancy: A - infections during pregnancy; B - entanglement with the umbilical cord

In 53.8% of children in this group, the condition at birth was severe: the Apgar score at the 1st and 5th minutes was 6-7 points in 17 (35.4%), 5-6 points - in 15 (31, 3%), 4-5 points - in 12 (25.0%).

Upon admission to the neonatal pathology department, 48 children with PVL of traumatic genesis (with PVL) had a pale skin, with a marble pattern in 34 (70.8%), cyanosis at rest in 34 (70.8%). In 34 (29.2%) children, clinical signs of dystrophic changes in the skin were observed: dryness, maceration of the feet and palms, inguinal folds, peeling.

Neurological examination of children revealed a variety of neurological abnormalities in children with PVL with PVH. Thus, in group 2, 7 (14.6%) had a syndrome of CNS depression, 12 (25.0%) had convulsive syndrome, 14 (29.2%) had hypertensive syndrome, 17 (35.4 %) - syndrome of movement disorders. Immediately in the postpartum period, the syndrome of CNS depression in 79.2% of children was expressed by hypodynamia, hypotension, hyporeflexia, and decreased sucking reflex. Suppression of spinal reflexes was observed (support - 85.4%, automatic walking - 62.5%, protective - 50.0%, cervical ACTR - 83.3%).

Along with this, there was a suppression of the reflexes of Moro (37.5%), Babkin (14.6%), Rossolimo, Babinsky, a decrease and dystonic tone (22.9-37.5%), a decrease in tendon reflexes (60.4%) , lethargy, regurgitation, pallor of the skin, cyanosis of the nasolabial triangle at rest (70.8%), acrocyanosis, bradycardia, muffling of heart sounds, weakening of breathing, bloating.

On the 3-4th day from the moment of admission to acute renal failure, the depression syndrome was replaced by the syndrome of increased neuro-reflex excitability, which, like in 27.9% of children initially admitted with clinical semiotics of this syndrome, was mainly manifested by an increase in spontaneous motor activity, anxiety , superficial sleep, lengthening of the period of active wakefulness, difficulty falling asleep, paroxysms of unmotivated crying, increased congenital reflexes, muscular dystonia, the presence of a shallow tremor of the chin and limbs.

Hypoxia in group 2 was in 15 (31.3%), asphyxia - in 13 (27.1%), trauma during childbirth - in 11 (22.9%). The results of the examination made it possible to establish the features of the course of PVL with PVH, which develops in chronic intrauterine hypoxia of ischemic genesis and in combination with asphyxia and trauma during childbirth, aggravating the clinical condition. Due to the weak activity of the compensatory and defense mechanisms of the body, hypoxic-ischemic brain lesions with periventricular hemorrhage can occur with aggravated premorbid conditions: anemia, chronic infections, intoxication, hypotrophy, etc., which lead to insufficiency of compensatory-adaptive mechanisms.

As a control (3rd) group, were examined 50 healthy newborns: 20 (40.0%) girls and 30 (60.0%) boys. In terms of gestation less than 33 weeks, 1 (2.0%) was born, 37 weeks - 2 (4.0%), i.e., were premature, 38 weeks - 1 (22.0%), 39 weeks - 23 (46 , 0%), 40 weeks - 13 (26.0%). The mothers of the children in the control group were healthy. There were 14 (28.0%) women aged 17 to 19, 36 (72.0%) women aged 20-30. During pregnancy, they were all under regular supervision. Pregnancy, childbirth and the postpartum period were uneventful in all women.

When analyzing the health status of mothers in this group, it was revealed that 19 (93.3%) of them did not suffer from chronic somatic and gynecological diseases by the beginning of pregnancy. Childbirth proceeded without stimulation in 11 (68.8%), spontaneous - in 50 (100.0%). At birth, the condition was assessed on the Apgar scale in the range of 7-10 points in 49 (98.0%) children. There was no umbilical cord entanglement and birth trauma, all the children screamed at once. Clinical manifestations in children of the control group: pupils in young children were round, symmetrical, 2-3 mm in diameter. A healthy newborn is characterized by a loud, well-modulated, emotional cry. In a healthy full-term baby, the so-called embryonic posture was noted due to a flexor increase in the tone of the arm.

When assessing reflex activity, the normal amplitude of the reflex during the first test and its subsequent decrease indicated general exhaustion.

In the control group, among the premature infants were newborns with gestational ages of 33 and 37 weeks. With a body weight of 2500–3000 g, 21 (42.0%) children were born, 3000–3500 g - 29 (58.0%). Body length averaged 49.2±0.43, head circumference corresponded to gestational age. The adaptation period in all newborns of this group proceeded without complications.

We studied clinical and molecular genetic parameters in Uzbek children with PVL and with its complications, depending on the polymorphism of the FII, FV genes and their combinations.

To confirm preliminary studies of genetic links with cerebrovascular disorders, we studied the effect of genetic variants biochemically associated with hemostasis (Leiden factor V, factor FII prothrombin G20210A) in a large number of children. In addition, we analyzed the impact of these genotypes on other parameters.

Molecular genetic polymorphism of genes factor V Leiden, mutation prothrombin G20210A factor FII was studied in 200 young children in the laboratory of functional genomics of the Research Institute of Genetics and Experimental Biology. There were 150 sick children, and the control group consisted of 50 conditionally healthy children who did not have family relationships with each other (Table 1).

Table 1

Frequency of distribution of genotypes of polymorphisms of FII and FV genes in the general and control groups

Polymorphism	Genotype	Genotype frequency of occurrence				Statistical data
		sick, n=150		healthy, n=50		
		абс	%	абс	%	
FII 20210A	G/A	26	17,3	5	10,0	χ^2=1,54; P=0,2; OR=1,9; 95%CI 0,6832–5,212
	A/A	4	2,7	–	–	χ^2=1,4; P=0,2;
	G/ G	120	80,0	45	90,0	χ^2=2,3; P=0,1;
FV G169A	G/A	24	16,0	10	20,0	χ^2=0,4; P=0,5; OR=0,8; 95%CI 0,335–1,728
	A/A	11	7,3	-	-	χ^2=3,9; P=0,05;

Note: Frequency of FII alleles (266/34 versus 90/10) = χ2 = 0.1; P = 0.7; OR = 1.15; 95% CI 0.5464-2.422. Frequency of FV alleles (254/46 versus 80/20) = χ2 = 1.2; P = 0.2; OR = 0.7; 95% CI 0.404-1.296. Total frequency FII (G / A + A / A) = χ2 = 2.3; P = 0.1; OR = 2.25; 95% CI 0.822-6.158. Total frequency FV (G / A + A / A) = χ2 = 0.2; P = 0.6; OR = 1.2; 95% CI 0.552-2.681

The distribution frequencies of the normal genotype A / A in the studied groups of patients and controls were 2.7% (4/150) and 0 (0/50), respectively. Such differences in the distribution of the normal genotype in the studied groups also turned out to be statistically insignificant (χ2 = 0.4; P = 0.5). The distribution of the mutant heterozygous G / A genotype of this genetic marker in the studied study group of patients was 17.3% (26/150). As expected, a rare homozygous G / G mutation of this marker in both groups studied was found in 80% (120/150) χ2 = 2.3; P = 0.1. According to the odds ratio (OR), the risk of developing in the presence of the A / G genotype is increased by more than 1.9 times compared with non-carriers of this mutation. However, despite such an increase in the frequency distribution of the heterozygous G / A genotype, no statistically significant differences were found (χ2 = 1.54; P = 0.2; OR = 1.9; 95% CI 0.6832–5.212).

The most significant differences between the groups of patients and controls were revealed when analyzing the polymorphism in the FV factor gene. Table 1 shows the results of the analysis of the distribution of genotypes of the polymorphic marker G1691A of the FV gene in the main and control groups G / A 16% –20% (χ2 = 0.4; P = 0.5; OR = 0.8; 95% CI 0.335–1.728) , the frequency of occurrence of the FV1691A allele in patients significantly exceeded that in the group of healthy people. The difference in the frequency of carriage of the healthy G / G genotype among the studied groups also turned out to be statistically insignificant (76.7 versus 80% χ2 = 0.2; P = 0.6).

Heterozygous carriage of polymorphism G1691A of the FV gene was observed A / A in 7.3% $\chi 2 = 3.9$; $P = 0.05$, more than 3.9 times significantly more often among patients in comparison with the control group, while homozygotes for this option were not found among the examined healthy people.

Studies have shown that 69 out of 150 full-term patients, 81 premature patients, the examined subgroups and the control group were characterized by the highest statistical significance of FII 20210A. Genotype G / G52 - 75.4% - 45 - 90.0%, $\chi 2 = 4.1$; $P = 0.04$, i.e. highly significantly differed among themselves in the distribution of the frequencies of alleles and genotypes in general for a given DNA locus.

In the first examined group, the frequency of occurrence of the mutant allele "1691A" of the FV gene was A / A6 genotype - 7.4% $\chi 2 = 3.9$; $P = 0.05$; in the full-term and control group, a positive association was also found for the carriage of the FV Leiden mutation; the revealed difference has reached the limits of statistical significance.

Frequencies of distribution of genotypes G / G and G / A of the FV gene in the studied groups were 72.5–80.0% $\chi 2 = 0.9$; $P = 0.3$, as well as 20.3% –20.0% $\chi 2 = 0.001$ ($P = 0.9$); OR = 1.0; 95% CI 0.411–2.52 and did not differ significantly from those in the general group and among themselves. As can be seen from the data obtained, there was a tendency to a significant increase in the frequency of the homozygous genotype FII 20210AG / G 52–75.4% –45–90.0% $\chi 2 = 4.1$ ($P = 0.04$) compared to the control; according to the odds ratio, the risk of development in the presence of a homozygous genotype increases by more than 4.1 times compared with non-carriers of this genotype FVG1691A 72.5% –80.0% $\chi 2 = 0.9$ ($P = 0.3$). Thus, our findings prove the high significance of the FII 20210A marker: genotype G / G52–75.4% –45–90.0% $\chi 2 = 4.1$ ($P = 0.04$) of premature infants and FV-Leiden were A / A 6-7.4% $\chi 2 = 3.9$ ($P = 0.05$); PVL also developed in the group of term infants. The presence of the molecular marker FII 20210A and FV 1691A in the genotype is associated with an increased risk of PVL development more in premature infants than in term infants.

According to a study conducted on 150 patients, in 121 sick children of only Uzbek nationality, the FII gene mutation is more common in the heterozygous and homozygous variant, FII 20210A (G / A) - in 19.0%, FII 20210A (A / A) - in 3.3% ($\chi 2 = 0.575$, $P > 0.05$); in control 20210A (G / A) - in 112.2%, 20210A (A / A) - in 0 ($\chi 2 = 0.356$, $P > 0.05$).

The mutation of the FVG1691A genes was also significantly more often found in the heterozygous and homozygous variant in children of Uzbek nationality: G1691A (G / A) was found in 15.7%, G169A (A / A) - in 7.4% ($\chi 2 = 0.456$, $P > 0$, 05) children, in control G169A (G / A) - in 22.0%, G169A (A / A) - in 0 ($\chi 2 = 1.967$, $P > 0.05$). A homozygous variant of the FII and FV genes was not found in the control group of Uzbek children.

Among PVL patients (n = 60) with G / A genotype (6.7 and 15.0%, respectively) and A / A genotype (1.7 and 15.0%) with a polymorphic marker of the FII gene, differences in A values / A were found in 1.7% with some predominance of the average values of the parameters with the carriage of the A / A genotypes of the FV factor - in 15.0%.

Among patients with PVH (n = 47) with the G / A genotype in 14.9 and 23.4% and A / A genotypes of 0 and 4.3% of the polymorphic marker of the FII gene, differences in the A / A values of 0% with some predominance of the average values of the parameters with the carriage of the A / A genotypes of the FV factor in 4.3%. Thus, the homozygous variant was less common in the group with PVL than in the group with PVL.

Evaluating the PVL group with PVH with the G / A genotype in 11.6 and 9.3% and A / A genotypes in 7.0 and 0% of the polymorphic marker of the FII gene, differences in the A / A values of 0% were revealed with some predominance mean values of parameters with carriage of G / A genotypes of factor FII in 11.6%. Thus, in the PVL group with PVR, the heterozygous variant was recorded less frequently than in the PVL group.

Of the etiological factors that led to PVL in children of Uzbek nationality, hypoxia is most common: in the FII gene polymorphism (G / A) - in 15.4%, (A / A) - in 5.8% ($\chi 2 = 1.627$ and $P > 0.05$). Mutation of FV G1691A genes was also studied in heterozygous and homozygous variants in children of Uzbek nationality: G1691A (G / A) - in 19.2%, G1691A (A / A) - in 5.8% ($\chi 2$ 3.165 and $P > 0.05$); the etiological factor asphyxia (n = 53) occurs in the FII gene polymorphism (G / A) - in 17.0%, (A / A) - in 1.9% ($\chi 2$ 5.410 and $P < 0.05$). Also, the mutation of the FV G1691A genes was studied in the heterozygous and homozygous variant in children of Uzbek nationality, G1691A (G / A) - in 15.1%, G1691A (A / A) - in 7.5% ($\chi 2$ 0.846 and $P > 0.05$); the etiological factor as trauma (n = 104) occurs in the FII gene polymorphism (G / A) in 16.3%, (A / A) in 2.9% ($\chi 2$ 9.616 and $P < 0.01$). The mutation of the FV G1691A genes was also studied in the heterozygous and homozygous variant in children of Uzbek nationality, G1691A (G / A) - in 15.4%, G1691A (A / A) - in 4.8% ($\chi 2$ 5.297 and $P < 0.05$); etiological factor infection (n = 62) occurs in the FII gene polymorphism (G / A) - in 14.5%, (A / A) - in 4.8% ($\chi 2$ 2.307 and $P > 0.05$), also gene mutation FVG1691A was studied in heterozygous and homozygous variants in children of Uzbek nationality: G1691A (G / A) in 16.1%, G1691A (A / A) in 6.5% ($\chi 2$ 2.013 and $P > 0.05$).

Taking into account the heterogeneous nature of the clinical manifestations of periventricular leukomalacia and its complications, we analyzed the distribution of the studied polymorphisms, as well as the "gene-gene interactions" between them. Most often, such combinations were determined with a combination of genotype polymorphisms (FII + FV), in groups with PVL G / A - in 24.5%; with PVC G / A - in 15.8%; with PVL in combination with PVH G / A - in 14.7%. But the homozygous mutant is also found in patients with PVL, PVH, with a reduced A / A carrier in 14.3 and 5.3%, and only in the FV genotype.

To assess the neurological status and the degree of functional activity, patients with periventricular leukomalacia complicated by PVH were divided according to lesion syndromes, which included depression syndrome, motor disorders syndrome, hypertensive and convulsive syndromes.

The most common syndrome in periventricular leukomalacia was the syndrome of motor disorders (n = 55): it occurs in the FII gene polymorphism (G / A) - in 12.7%, (A / A) - in 1.8% ($\chi 2$ 3.370 and $P > 0, 05$), the mutation of the FV G1691A genes was also studied in the heterozygous and homozygous variant in children of Uzbek nationality, G1691A (G / A) - in 10.9%, G1691A (A / A) - in 9.1% ($\chi 2$ 0.000 and $P > 0.05$); with depression syndrome (n = 38) occurs in the FII gene polymorphism (G / A) - in 18.4%, (A / A) - in 2.6% ($\chi 2$ 3.493 and $P > 0.05$), also gene mutation FV G1691A was studied in a heterozygous and homozygous variant in children of Uzbek nationality, G1691A (G / A) - in 15.8%, G1691A (A / A) - in 2.6% ($\chi 2$ 2.518 and $P > 0.105$); in hypertensive syndrome (n = 37) occurs in the FII gene polymorphism (G / A) - in 13.5%, (A / A) - in 2.7% ($\chi 2$ 1.632 and $P > 0.05$), also gene mutation FV G1691A was studied in heterozygous and homozygous variants in children of Uzbek nationality, G1691A (G / A) - in 16.2%, G1691A (A / A) - in 5.4% ($\chi 2$ 1.261 and $P > 0.05$); with convulsive syndrome (n = 18) occurs in the FII gene polymorphism (G / A) - in 22.2%, (A / A) - in 5.6% ($\chi 2$ 0.929 and $P > 0.05$), also gene mutation FV G1691A was studied in heterozygous and homozygous variants in children of Uzbek nationality, G1691A (G / A) - in 11.1%, G1691A (A / A) - in 0% ($\chi 2$ 0.529 and $P > 0.05$).

To identify a causal relationship between the existence of PVL complications or diseases complicating PVL and PVH in the study and control groups (case – control), the chance and risk of PVL in young children were calculated (Fig. 2).

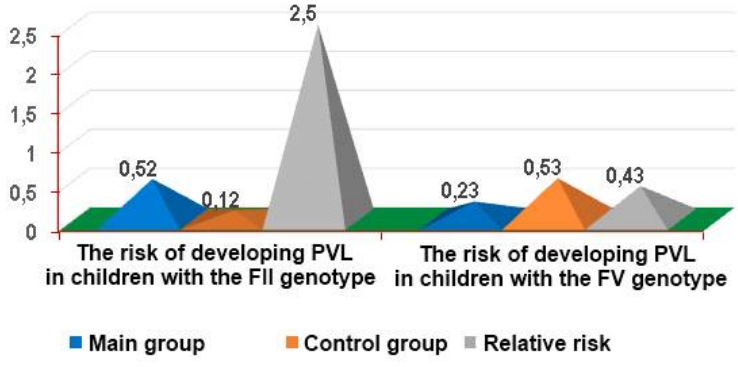

Fig. 2. Causal relationships between existence complications of PVL or diseases complicating PVL and PVH, in main and control groups

There were 121 children in the main group (total of 150 children) of Uzbek nationality, in the control group (total of 50 children) - 41. The main group included 27 infants with PVL and 25 without PVL, in the control group - 5 with PVL and 19 without it. There were 76 patients in total.

In patients of the main group, the chance of developing PVL is 4.1 times higher than in the control group, which proves the presence of heterozygous and homozygous occurrence of FII gene polymorphisms in sick children of Uzbek nationality with various types of PVL. The relative risk of developing the disease is 2.5 times higher.

In premature babies, the risk of illness and death increases exponentially. Our findings show that genetic variants of clotting factors may play an important role in the development of certain conditions in preterm infants. The thrombophilic risk factors studied by us, such as Leiden factor V and the prothrombin G20210A mutation, can influence the development of intracranial hemorrhage in premature infants.

In sick children of Uzbek nationality with PVL, combinations of genotypes FII 20210A + FVG1691A were more often detected. With a combination of genotypes FII 20210A + FV G1691A, the chance of developing PVL in the FV factor in healthy children increases 11.6 times.

Output:

1.Neurological symptoms in the early neonatal period with clear objectification in 75.5% of cases are caused by damage to cerebral structures, which dictates the need for a complex of neuroimaging studies in the first 5-7 days.

2.The nature and frequency of PVL complicated by periventricular hemorrhage depend on gestational and postnatal age. The most frequent hemorrhagic disorders in premature infants are peri-intraventricular hemorrhages, in term infants - hemorrhages in the choroid plexus. Studies have shown that among ischemic disorders in premature infants, periventricular leukomalacia is diagnosed in 68.3% of cases, and subcortical leukomalacia in full-term infants in 33.3%.

3.It was revealed that the development of intracranial hemorrhages in premature infants in all studied genotypes is influenced by thrombophilic risk factors (factor V Leiden and prothrombin G20210A mutation), the relative risk of PVL with mutations in FII gene polymorphism increases 2.5 times, the chance of PVL development in the healthy group the FV factor is 11.6 times higher.

4.Analysis of "gene-gene interactions" in persons of Uzbek nationality with PVL revealed the genotypic type of combination of genotypes "FII 20210A + FV G1691A" associated with the risk of developing this pathology.

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