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GENETIC PARALLELS IN PERIVENTRICULAR LEUKEMATOGRAPHY IN NEWBORNS

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Abstract— *The use of modern technologies in perinatal practice has made it possible to clarify the etiology, pathogenetic mechanisms of the development of periventricular leukemalacia (PVL), we believe it is possible that genetic variants of coagulation factors may play a role in the development of certain states of the disease in children born with low weight.*

Keywords—*central nervous system in newborns, periventricular leukemomalacia, gene polymorphism.*

I. INTRODUCTION

Modern technologies in perinatal practice have made it possible to clarify the etiology, pathogenetic mechanisms of the development of periventricular leukemalacia (PVL), we believe that genetic variants of coagulation factors can play a role in The of certain states of the disease in children born with low weight. The main directions are molecular genetic research to identify the so-called candidate genes. However, research on the results of genetic background measurement is still at an early stage. In order to confirm preliminary studies of genetic connections on cerebral vascular disorders, we studied the impact of genetic variants biochemically related to hemostasis (Leiden's factor V, prothrombin **G20210A** and factor II) on large numbers in newborn children.

II. RESEARCH MATERIALS AND METHODS

Out of 200 newborns from mothers born in National Specialized Scientific Obstetrics And Gynecology Practice Centre of the Ministry of Health of the Republic of Uzbekistan, as well as in the Department of DPN № 5 of the hospital of Mirobad district, studied the influence of variants of genes involved in hemostasis, born with low weight, from 2007 to 2010 (including the criteria: gestation period from 28 to 36 weeks, weight at birth - 1500g).; excluding criteria: lethal malformations, chromosomal hereditary diseases: trisomy 13 and trisomy 18). Many homozygous children from parents of one Uzbek nationality had an identical genetic background of the order of 50% to 100%. This large genetic impact causes confusion in clinical data, i.e. genotypic/ phenotypic relationships are more common in children than in children born of different nationalities. However, these relationships may arise from other genetic factors that have not been investigated. For this purpose, DNA samples distributed according to the appropriate numbers in the children have been taken.

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A research was conducted on the genetic associations of a large number of complex diseases to identify high-risk groups. These thrombophilic disorders include a mutation of Factor V Leiden, which makes Factor V resistant to the cleavage of activated protein C, and a mutation of prothrombin **G20210A** associated with an increased concentration of prothrombin in plasma.

Clinical and laboratory methods of research included the analysis of obstetric gynecological and somatic history of mothers, the course of a real pregnancy. Chest X-ray data, neurosonography and dopplerography of brain vessels, as well as other studies, combined with common neonatal surveillance tactics.

III. RESULTS AND DISCUSSIONS

Molecular genetic polymorphism of genes of factor V Leiden, prothrombin mutation G20210A of factor FII were studied in 200 children of early age in the laboratory of functional genomics of the Research Institute of Genetics and Experimental Biology. Sick children made up 150 children, and the control group consisted of 50 conditionally healthy children with no relation to each other.

We studied clinical and molecular genetic parameters in Uzbek children with PVL and its complications depending on polymorphism of FII, FV genes and their combinations. To confirm preliminary studies of genetic connections with cerebral-vascular disorders, we studied the impact of genetic variants biochemically related to hemostasis (Factor V Leiden, prothrombin G20210A of FII factor) on a large number of children. In addition, we analysed the impact of these genotypes on other parameters.

The frequencies of normal genotype A/A distribution in the studied groups of patients and control were 2.7% (4/150) and 0 (0/50), respectively. Such differences in normal genotype distribution in the studied groups were also statistically unreliable (χ^2=0.4; P=0.5). Distribution of mutant heterozygous G/A genotype of the given genetic marker in the investigated main group of patients was 17.3% (26/150). As expected, a rare homozygous G/A mutation of this marker in both research groups was found to be 80% (120/150) χ^2=2.3; P=0.1.

According to the odds ratio (OR), the risk of development in the presence of genotype A/G increases by more than 1.9 times compared to those not carrying the mutation. However, despite this increase in the frequency distribution of heterozygous G/A genotype, no statistically significant differences were found (χ^2=1.54; P=0.2; OR=1.9; 95%CI 0.6832-5.212).

The most significant differences between the patient groups and controls were found in polymorphism analysis in the FV factor gene. Table 1 shows the results of the analysis of genotype distribution of polymorphic marker G1691A of FV gene in the main and control groups of G/A16%-20% (χ^2=0.4; P=0.5; OR=0.8;95% CI 0.335-1.728), the frequency of allele FV1691A in patients significantly exceeded that in healthy groups. The difference in the carrier frequency of healthy G/G genotype among the studied groups was also statistically unreliable (76.7 vs. 80% respectively, χ^2=0.2; P=0.6).

The heterozygous carrier of the polymorphism G1691A of the FV gene was observed A/A 7.3% χ^2=3.9; P=0.05; more than 3.9 times more frequently in patients than the control group, whereas no homozygotes by this variant were found among the healthy subjects surveyed.

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The studies showed that out of 150 patients reported 69, 81 were premature and the control group was the most statistically significant FII 20210A Genotype G/G52 - 75.4% - 45 - 90.0% χ^2=4.1; P=0.04, i.e. highly differed from each other in the distribution of allele and genotype frequencies in general by this DNA locus.

In the first examined group the frequencies of occurrence of the mutant allele "1691A" of the FV gene were A/A6-7.4% χ^2=3.9; P=0.05; in the denunciated group and in the control group a positive association was also found when carrying the FV Leiden mutation, the difference revealed reached the limits of statistical significance.

The distribution frequencies of genotypes G/G and G/A of the FV gene in the research groups were: 72.5-80.0% χ^2=0.9; P=0.3 and 20.3% - 20.0% χ^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 or among themselves. As can be seen from the obtained data, there was a trend towards a reliable increase in the frequency of the homozygous genotype FII 20210A G/G 52-75.4%-45-90.0% χ^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 to those not carrying the genotype FV G1691A 72.5%-80.0% χ^2=0.9; P=0.3 Thus, our findings prove the high significance of FII marker 20210A genotype G/G52-75.4%-45-90.0% χ^2=4.1; P=0.04 premature infants and FV-Leiden were in the genotype A/A6-7.4% χ^2=3.9; P=0.05; in the group of premature infants in the development of PVL. The presence of molecular marker FII 20210A and FV 1691A in the genotype is associated with an increased risk of developing PVL in premature infants than in prematurely born children.

According to a research conducted among 150 patients in 121 Uzbek children only, the mutation of FII genes is more common in heterozygous and homozygous variants, FII 20210A (G/A) - in 19.0%, FII 20210A (A/A) - in 3.3% (χ^2=0.575, P>0.05); control 20210A (G/A) - in 112.2%, 20210A (A/A) - in 0 (χ^2=0.356, P>0.05).

Mutation of FV G1691A genes was also authentically more frequently found in heterozygous and homozygous variants in Uzbek ethnicity, G1691A (G/A) was found in 15.7%, G169A (A/A) in 7.4% (χ^2=0.456, P>0.05) of children, G169A (G/A) in 22.0%, G169A (A/A) in 0 (χ^2=1.967, P>0.05). The homozygous variant of FII, FV genes were not found in the control group of Uzbek nationality.

Among patients with PVL (n=60) with G/A-genotype (6.7 and 15.0%, respectively) and A/A-genotype (1.7 and 15.0%) with polymorphic marker of FII gene, differences in A/A values were revealed in 1.7% with some prevalence of average parameter values at carrying A/A-genotypes of FV factor - in 15.0%.

Among patients withpolyvinylcaprolactam(PVC) (n=47) with G/A-genotype in 14.9 and 23.4% and A/A-genotypes of 0 and 4.3% of polymorphic marker of FII gene, differences in A/A values of 0% with some prevalence of average parameter values at carrying A/A-genotypes of FV factor in 4.3% were revealed. Thus, homozygous variant was found less frequently in the group with PVC than in the group with PVL.

Estimating the PVL group with G/A-genotype in 11.6 and 9.3% and A/A-genotypes 7.0 and 0% of the polymorphic marker of the FII gene, differences in A/A values of 0% were revealed with some predominance of the mean parameter values when carrying G/A-genotypes of Factor FII in 11.6%. Thus, the heterozygous variant was registered less frequently in the PVL group with PVC than in the group.

Due to the etiological factors that have come to PVL in Uzbek children, hypoxia is the most common: in the polymorphism of the FII gene (G/A) - in 15.4% (A/A) - in 5.8% (χ^2=1.627 and P>0.05). Mutation of FV genes

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G1691A was also studied in heterozygous and homozygous variants in Uzbek, G1691A (G/A) - in 19.2%, G1691A (A/A) - in 5.8% (χ^2=3.165 and P>0.05); etiological factor of asphyxia (n=53): occurs in polymorphism of the FII gene (G/A) - in 17.0%, (A/A) - in 1.9% (χ2 5,410 and P > 0.05). Also FV gene mutation G1691A was studied in heterozygous and homozygous variants in Uzbek nationality, G1691A (G/A) - in 15.1%, G1691A (A/A) - in 7.5% (χ^2 0.846 and P>0.05); etiological factor as injury (n=104): occurs in polymorphism of the FII gene (G/A) in 16.3%, (A/A) in 2.9% (χ^2 9.616 and P > 0.01). Mutation of FV genes G1691A was also studied in heterozygous and homozygous variants in Uzbek nationality, G1691A (G/A) - in 15.4%, G1691A (A/A) - in 4.8% (χ^2 5.297 and P<0.05); etiological factor of infection (n=62): occurs in polymorphism of the FII gene (G/A) - in 14.5%, (A/A) - in 4.8% (χ^2 2,307 and P>0.05). Also FV gene mutation G1691A was studied in heterozygous and homozygous variants in Uzbek, G1691A (G/A) - in 16.1%, G1691A (A/A) - in 6.5% (χ^2 2.013 and P>0.05).

Given the heterogeneous nature of the clinical manifestations of periventricular leukemomania and its complications, we analyzed the distribution of the studied polymorphisms, as well as "gene interactions" between them. Most often such combinations were determined in a combination of genotype polymorphisms (FII + FV), in groups with PVL G/A - in 24.5%; with PVL G/A - in 15.8%; with PVL in combination with PVL G/A - in 14.7%.

But homozygous mutant is also found in patients with PVL, PVC, with reduced carrier A/A in 14.3 and 5.3% and only in FV genotype.

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

Motor disorders (n=55) were the most frequent in periventricular leukematography: occurs in polymorphism of FII gene (G/A) - in 12.7%, (A/A) - in 1.8% (χ^2 3.370 and P>0.05), also FV gene mutation G1691A was studied in heterozygous and homozygous variant in Uzbek nationality, G1691A (G/A) - in 10.9%, G1691A (A/A) - in 9.1% (χ^2 0.000 and P>0).05); in oppression syndrome (n=38): occurs in FII gene polymorphism (G/A) - in 18.4%, (A/A) - in 2.6% (χ^2 3,493 and P>0.05), also mutation of FV genes G1691A was studied in heterozygous and homozygous variants in Uzbek nationality, G1691A (G/A) - in 15.8%, G1691A (A/A) - in 2.6% (χ^2 2.518 and P>0.105); in hypertensive syndrome (n=37): occurs in polymorphism of the FII gene (G/A) - to 13.5%, (A/A) - to 2.7% (χ^2 1,632 and P>0.05), The mutation of FV genes G1691A was also studied in heterozygous and homozygous variants in Uzbek nationality, G1691A (G/A) - in 16.2%, G1691A (A/A) - in 5.4% (χ^2 1.261 and P>0.05); in seizure syndrome (n=18): occurs in polymorphism of FII gene (G/A) - in 22.2%, (A/A) - in 5.6% (χ2 0.929 and P>0.05); also FV gene mutation of G1691A was investigated in heterozygous and homozygous variant in Uzbek G1691A (G/A) - in 11.1%, G1691A (A/A) - in 0% (χ^2 0.529 and P>0.05).

IV. CONCLUSIONS

In order to identify the causal relationship between the existence of complications of PVL or diseases that complicate PVL and PVC, the chance and risk of young children suffering from PVL in the main and control groups (control cases) were calculated.

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

Patients in the main group had 4.1 times higher chance of developing PVL than in the control group, which proves the presence of heterozygous and homozygous occurrence of FII gene polymorphisms in Uzbek children with different types of PVL. The relative risk of disease development is 2.5 times higher.

Premature children have a dramatically increased risk of disease and death. Our research shows that genetic variants of coagulation factors can play an important role in the development of certain conditions in prematurely born children. The thrombophilic risk factors we have studied, such as Factor V Leiden and the prothrombin mutation G20210A, can influence the development of intracranial hemorrhage in prematurely born children.

Combinations of FII 20210A+ FV G1691A genotypes were found more frequently in Uzbek patients with PVL. The combination of FII 20210A + FV G1691A genotypes increases the chance of developing PVL in FV factor in healthy children by 11.6 times.

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