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Genetic Markers of Thrombophilia in Children with Structural Focal Epilepsy in Hemiplegic Cerebral Palsy

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ABSTRACT

Objective: To assess the significance of genetic markers of thrombophilia in hemiparetic form of congenital cerebral palsy and structural focal epilepsy.

Methods: We initiated a study of thrombophilia markers (FV Leiden, the factor II prothrombin gene G20210A, MTHFR C677T, PAI-1) in children with structural focal epilepsy and congenital hemiparesis developed after perinatal strokes, which, according to MRI / CT, were divided into arterial strokes (ischemic and hemorrhagic - AIS, HI), venous sinus thrombosis (VST) and periventricular hemorrhage (PVH).

The study of the main markers of thrombophilia (FV Leiden, prothrombin gene G20210A factor II, MTHFR C677T, PAI-1) in children with structural focal epilepsy and congenital hemiparesis developed after perinatal strokes (PS), which, according to MRT/CT, were divided into arterial strokes (ischemic and hemorrhagic - AIS, HI), venous sinus thrombosis (VST) and periventricular hemorrhage (PVH).

Results: 42 children (60% boys, average age of 8.5 years) with perinatal strokes, congenital spastic hemiparesis and structural focal epilepsy (71% with arterial ischemic stroke, 17% with hemorrhagic stroke 2% with venous sinus thrombosis and 10% with periventricular hemorrhages) underwent examinations. The examination time period was 24 months. The number of anomalies in the genes of hemostasis was 26%, which corresponds to the demographic standards. Mutations in the genes of hemophilia were more common in arterial strokes. The frequency of mutations in the genes of thrombophilia for each of the factors studied exceeded the population indices. The frequency of FV mutations reached 7.2% in AIS cases, the mutation frequency of factor II prothrombin G20210A in AIS and PVH cases reached 7.5%, a high mutation frequency was registered in PAI-1 genes (up to 82%) and MTHFR (100%) in AIS and PVH cases. Despite the prevalence of mutations in the genes of the hemostasis system in children with AIS, the course of cerebral palsy and epilepsy are more favorable than in children with HI and PVH.

The Issue Relevance

Structural focal epilepsy in children with cerebral palsy (43-66%), often occur in spastic hemiparesis (30-35%), affecting motor, intellectual and cognitive impairments [1,2]. The perinatal risk factor for epileptic seizures is more than 85% in children with structural focal epilepsy in hemiplegic cerebral palsy [3]. The main risk factors for epilepsy and hemiplegic cerebral palsy in children include: asphyxia in labor, chronic intrauterine hypoxia, prenatal infection, preeclampsia, obesity of mother, assisted delivery [3-5]. Perinatal strokes are the main factor in the development of epileptic seizures in children with hemiplegic cerebral palsy [6,7]. Perinatal arterial

ischemic strokes associated with mutations in the genes of hemostasis are accompanied by the development of epilepsy in 40-70% of cases [8-11].

Here we are discussing the effect of mutations in the main thrombophilia genes (FV Leiden, FII protrombin, MTHFR methylenetetrahydrofolate reductase, serpine1 PAI-1 5G \ 4G) on the development of perinatal strokes and their complications are discussed [12-14]. Children with cerebral thrombosis are noted to have congenital thrombotic conditions connected with coagulation disorders in 50% of cases; the frequency of detection of congenital thrombophilic disorders can range from 10 to 62% in children with thromboembolism [16].

FV mutations are detected in 20-40% of children with venous thrombosis and thromboembolism [28]. Being in a heterozygous form, the mutation increases the risk of thrombosis by 3-7 times. In a homozygous state this risk is increased by 80-100 times. The heterozygous carrier of the mutation of hemostasis genes in children is manifested at an older age. Homozygous inheritance of hemostasis defects that affect thrombosis formation is often characterized by clinical manifestation during the neonatal period [17].

Mutations in the prothrombin gene (FII) with increased synthesis of prothrombin and the enhancement of blood coagulation increases the risk of thrombosis development by 2-5 times. The presence of two mutations (FV and FII) increases the risk of thrombosis by several times compared to the carriers of isolated mutations [16,17].

Mutations in the genes of the fibrinolytic system (polymorphism 675 5G> 4G of the gene PAI1 inhibitor of plasminogen activator type 1) also increase the likelihood of thrombus formation [16,17].

Mutations of the MTHFR gene involved in the metabolism of homocysteine with the development of hyperhomocysteinemia and the toxic effect of homocysteine on the vascular endothelium lead to an increase in the procoagulatory potential of endothelial cells, acting as a factor for thrombophilia [15,16]. With the simultaneous presence of the Leiden factor mutation and hyperhomocysteinemia, the risk of thrombosis increases by 10–20 times [17].

Severe brain tissue damage involving gray matter and the development of structural forms of epilepsy in hemiplegic cerebral palsy, arising from infectious pathology, sepsis, DIC syndrome, congenital heart diseases, surgical interventions, craniocerebral trauma, nephrotic syndrome, antiphospholipid syndrome and hyperhomocysteinemia, can be considered as a result of clinical manifestation of genetically determined or acquired forms of hemostatic disorders. [3,4].

The presence of thrombophilia in children with hemiparetic cerebral palsy may be associated with an increased risk of structural epilepsy. Despite the huge number of scientific papers on thrombophilia, the data often contradict each other [8-10].

The purpose of this study was to study the prevalence of mutations of hemostasis genes in various types of perinatal strokes (PS) in children with cerebral hemiparesis and structural focal epilepsy.

Materials and Methods

Examinations were carried out in the catamnesis of 42 children with hemiplegic cerebral palsy resulted by perinatal stroke and structural focal epilepsy, undergoing inpatient treatment in the department of psycho-neurology and receiving outpatient counseling at the polyclinics of Sechenov University Children's Clinical Hospital in 2017-2018.

The study included children who had cerebrovascular accident during the neonatal period, confirmed by the clinical and radiological picture of perinatal stroke according to the International Classification Kirton and deVeber [18] developed in the period up to 28 days of life, with the identification of the effects of cerebral circulation in one or more vascular basins, cortical atrophy, parencephalitic cysts. According to the PS classification, all patients were divided into 4 groups: arterial ischemic strokes (AIS), hemorrhagic strokes (HS), venous sinus thrombosis (VST), and periventricular hemorrhage (PH). Each of these 4 groups was divided into 2 subgroups: full-term (> 36 weeks) and preterm (<36 weeks).

The criteria for inclusion in the study group were also: the presence of congenital spastic hemiparesis, identified on the basis of the International Classification with the assessment of clinical symptoms in accordance with the child's age [19,20] and structural focal epilepsy, determined in the presence of 2 or more unprovoked focal or bilateral epileptic seizures with focal onset, correlating with structural brain pathology, confirmed by MRI / CT and regional epileptiform activity according to data of EEG and video EEG monitoring with a follow-up of at least 24 months.

Exclusion criteria were other forms of cerebral palsy, cerebral malformations, chromosomal pathology, strokes that occurred in children older than 28 days of life, after surgical treatment of heart disease, bacterial meningitis, isolated epidural or subdural hemorrhages and genetic forms of epilepsy.

We studied maternal risk factors for perinatal strokes: maternal age, somatic, obstetric and gynecological history, features of pregnancy (anemia, threatened abortion, gestosis, placental insufficiency, chronic hypoxia, viral diseases), childbirth (cesarean section, vaginal), after birth period and condition of newborns (estimated on the Apgar scale, time of onset of stroke, neonatal seizures). The age and sex of patients, the time of detection and the severity of hemiparesis, the time of debut and the severity of epileptic seizures, the pharmacological sensitivity of seizures (resistance) to anti-epileptic therapy, and concomitant cognitive impairments (IQ <70) were studied.

All the children underwent a complete analysis of hemostasis gene polymorphism by the PCR method, including 4 genes: Leiden FV, prothrombin factor II G20210A, MTHFR C677T, PAI-1.

Results

42 children (25 boys and 17 girls) with confirmed perinatal stroke, congenital hemiparesis and focal epilepsy underwent an examination; 39 full-term (> 37 weeks) and 11 premature (labor at the time of 32-36 weeks).

When analyzing the history, the clinical picture of the disease, the results of MRI and CT of the brain, 30 children were diagnosed with arterial ischemic stroke (AIS-71%), 7 children - with hemorrhagic stroke (HI-17%), 1 child - with venous sinus thrombosis (VST - 2%), 4 children had periventricular hemorrhage (PVH - 10%).

In all groups, most mothers were at an average reproductive age. A significant incidence of chronic pathology of mothers was revealed: 46% in arterial ischemic stroke, 42% in HI and reaching 100% in PVH cases. Aggravated obstetrical anamnesis prevailed in AIS and PVH cases. The frequency rate of anemia during pregnancy in all groups was high, especially in AIS and PVH cases. Threat of miscarriage was significant in all groups: AIS- 73%, HI -71% PVH-100%. The occurrence of gestosis was 50% in mothers of children with AIS and 28% in case of PVH. Feto-placental insufficiency and chronic fetal hypoxia prevailed in the HI group (42% and 71%, respectively). The frequency of ARVI during pregnancy with AIS and PVH was 76% and 75% respectively, which was significantly higher as compared with 28% in case of HI. The early age of the manifestation of the disease was 73% in case of AIS, 75% in case of PVH and only 28% in case of HI. Among all the patients we revealed the following: 14 (43%) children with AIS (n = 30), 3 (42%) children with HI and 2 (50%) children with PVH were born with cesarean section. The Apgar score did not exceed 6-7 points in 75% of children with PVH, 42% with HI and 25% of children with AIS. All the children had a high percentage of pathological conditions of the antenatal period associated with infectious, inflammatory, immunological and hereditary diseases of the mother, leading to the disruption of adaptation of the newborn.

Children with congenital hemiparesis and structural focal epilepsy had prevailing occurrence of AIS in 30 (71%) cases, HI in 7 (17%) cases, VST in 1 (2%) case and PVH in 4 (10%) cases. In the group of children with AIS (n = 30), 86% of the children were full-term. Among those with HI (n = 7), the full-term children also prevailed (71%), but there were 75 % of premature children with PVH (n = 4). Among full-term children with AIS in 14 (46.6%) cases and HI in 3 (42.9%) cases, there were more boys than girls but the ratio of boys and girls was equal in the other subgroups. Right-sided hemiparesis predominated in children with arterial ischemic and hemorrhagic strokes: 16 (53%) in full-term and 3 (10%) in premature infants with AIS; 3 (42.8%) in full-term and 2 (28.6%) in premature infants with HI; Hemiparesis was diagnosed in 3 (10%) premature and in 10 (33.3%) full-term infants before the age of 6 months of life, as well as in 1 (3.4%) premature and 16 (53.3%) full-term infants after 6 months of life. Left-sided hemiparesis was dominant in children with PVH and was diagnosed mainly before 6 months of life.

Neonatal seizures prevailed in full-term infants with arterial ischemic and hemorrhagic strokes: 11 (36.7%) in infants with AIS, 2 (28.6%) with HI, and less often in preterm infants: 2 (6.7%) and 1 (14.2%), respectively. 50% of premature and only 25% of full-term infants with PVH had neonatal seizures. The onset of epilepsy in children with arterial ischemic stroke prevailed at a younger age, from 1 to 3 years and from 4 to 10 years, whereas in the group with HI it prevailed at a younger age (from 1 to 3 years), and in the first year of life in infants with PVH. Resistant epilepsy in children with PVH was diagnosed in 50%, and was found to a lesser extent in infants with AIS.

IQ was less than 70% in 30% of children in the group with AIS and in 17.5% of children in the group with HI, reaching 75% in the group of children with PVH.

Case Report

A boy after an arterial ischemic stroke and infantile spasms. 9 months. From a 40-year-old mother, suffering from obesity, from the second pregnancy (there is a 10-year-old boy from the first pregnancy, healthy), with gestosis during the first half, a threat of miscarriage in the 2nd trimester, the second natural childbirth in the cranial presentation. Shouted at once, height 52 cm, weight 4.100 g, 8/9 points according to Apgar score. On the 2nd day of life a sharp deterioration of the condition due to the syndrome of oppression with the development of generalized seizures that stopped themselves. Was on treatment in the Department of Newborn Pathology for the first 2 weeks, was diagnosed with an ischemic stroke in the basin of the left MCA. Right-sided hemiparesis was detected from birth.

In the axial view of the T1-weighted MRI image, a cystic transformation of the left hemisphere, a major ischemic lesion of the left hemisphere of the brain in the basin of the middle and posterior cerebral arteries, are revealed. The onset of epilepsy at the age of 6 months of life - serial, asymmetric tonic infantile spasms mainly after awakening with a frequency of up to 4 episodes per day, up to 5-6 attacks per series. On the EEG conducted in accordance with the standard protocol in a state of wakefulness and sleep, stable interhemispheric asymmetry is registered due to a decrease in the amplitude of potentials and the severity of physiological patterns on the left. Regional epileptiform activity in the left frontal region of the brain with periodic lateral lateralization in the left hemisphere and an augmentation in index during sleep are recorded. Against a background of antiepileptic therapy, attacks were stopped.

In a genetic study, factors predisposing to the development of thrombosis (FV GA, PAI-1 5G / 4G, MTHFR C / T) were identified.

The analysis revealed 11 (26%) patients with mutations in the hemostasis genes, 9 patients with AIS and 2 patients with PVH. A heterozygous mutation was found in the prothrombin gene in 3 children, including 2 children with AIS and 1 child with PVH. In the group of children with AIS, mutations in the FV GA gene were found in 3 children. All the patients had mutations in the MTHFR gene (1 child with AIS in homozygous form, 9 children in heterozygous form and 1 child with PVH). Most children had mutations in the PAI gene (5 children with AIS in heterozygous form and 3 children with AIS in homozygous form. In the group of children with PVH there was 1 child with a heterozygous and 1 child with homozygous form of the mutation).

In most cases, the mutations were of a combined nature. Among children with AIS, combinations of MTHFR CT and PAI-1 mutations (in 5 children) prevailed; combinations of mutations MTHFR CT and FV GA (in 2 children) and MTHFR and prothrombin gene (in 2 children) were less common. Among the children with PVH, 1 child was identified with a combination of MTHFR CT and prothrombin gene mutations and 1 child was with a combination of MTHFR CT and PAI-1 mutations.

In children with AIS heterozygous forms of mutations prevailed in the genes coding the synthesis of MTHFR (27%) and PAI-1 (23.8%) and their combinations. No homozygous forms of prothrombin and FV mutations were identified, but heterozygous forms of prothrombin and FV gene mutations were revealed in 7.2% of children. Mutations in the prothrombin gene occur twice as often in children with AIS as in those with PVH, and FV mutations were found only in AIS cases.

Discussion

Among the children with hemiparesis and epilepsy, developed as a result of PS, patients with AIS predominate (71%), HI (17%) and PVH (10%) were less common, which is comparable with other authors (71%, 23% and 6 % respectively) [6,9,11]. Among the children with ischemic and hemorrhagic perinatal strokes, full-term predominated (AIS - 86%, HI - 71%), premature prevailed in the group with PVH (75%). Perinatal risk factors for the development of cerebral circulation in the fetus and newborn (poor completion of previous pregnancies, threat of interruption, chronic intrauterine hypoxia, infectious diseases of the mother, prematurity), expressed in all groups (from 25 to 75%), which is comparable with the data of other authors (48-68%) [3,10] and prevailing in AIS, can be trigger for the realization of genetic defects in the genes of hemostasis. Epileptic seizures resistant to treatment prevailed in the group of children with PVH (50%), less common with AIS (13.5%), HI (3.3%), according to foreign authors, the number of resistant attacks with AIS can reach from 11 to 33% [21-23].

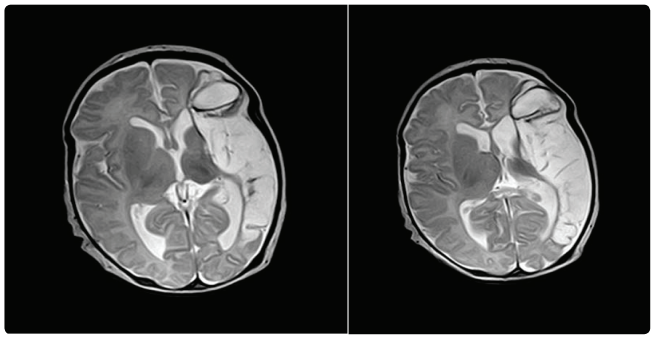

Figure 1: Axial view of the T1-weighted MRI image shows a large left-sided proximal medial cerebral artery stroke with enlarged left ventricle with damage in the thalamus, basal ganglia, insula, and frontotemporal lobes at the age of 5 months.

Hereditary thrombophilia cases were revealed in children with arterial and venous strokes with a frequency of 13% to 78% [24-27]. The total number of mutations in our study was 26%, which does not exceed population indices. The largest number of patients with mutations in the hemostasis genes was detected in AIS (82%) In most cases, the mutations were combined. The frequency of FV mutations in healthy children is 2–4% [24]. In our study, this figure reaches 7.2%. The frequency of mutation of prothrombin G20210A factor II in children with cerebral thrombosis is 4-11% [24]. In our study, the figure does not exceed 7.5%. The mutation rate of the PAI-1 and MTHFR genes in the population reaches 30-50% [23,29] and there is no consensus concerning the effect of heterozygous mutation carriage in the PAI-1 gene (4G / 5G) on the development of thromboses. Our study revealed a high frequency of mutations of the PAI-1 genes (up to 82%) and MTHFR (100%) in children with perinatal strokes.

Conclusion

Structural epilepsy in hemiplegic cerebral palsy in children arises mainly as a result of arterial ischemic stroke, in the formation of which the perinatal risk factors are leading, often acting as triggers for the clinical implementation of the genetic predisposition to thrombophilia.

Thrombophilic gene polymorphism, generally not exceeding population values, predominates in AIS (82%), in many cases it is combined with the most frequent mutation in the MTHFR (up to 100%) and PAI-1 genes (up to 82%) and is independent risk factor for the implementation of PS and associated hemiparesis as well as epileptic seizures.

Taking into account the compensatory possibilities of the organism, it is possible to reduce the risk of congenital central hemiparesis and accompanying structural focal epilepsy by using a personified approach to the tactics of managing pregnancy and providing timely help to a newborn child.

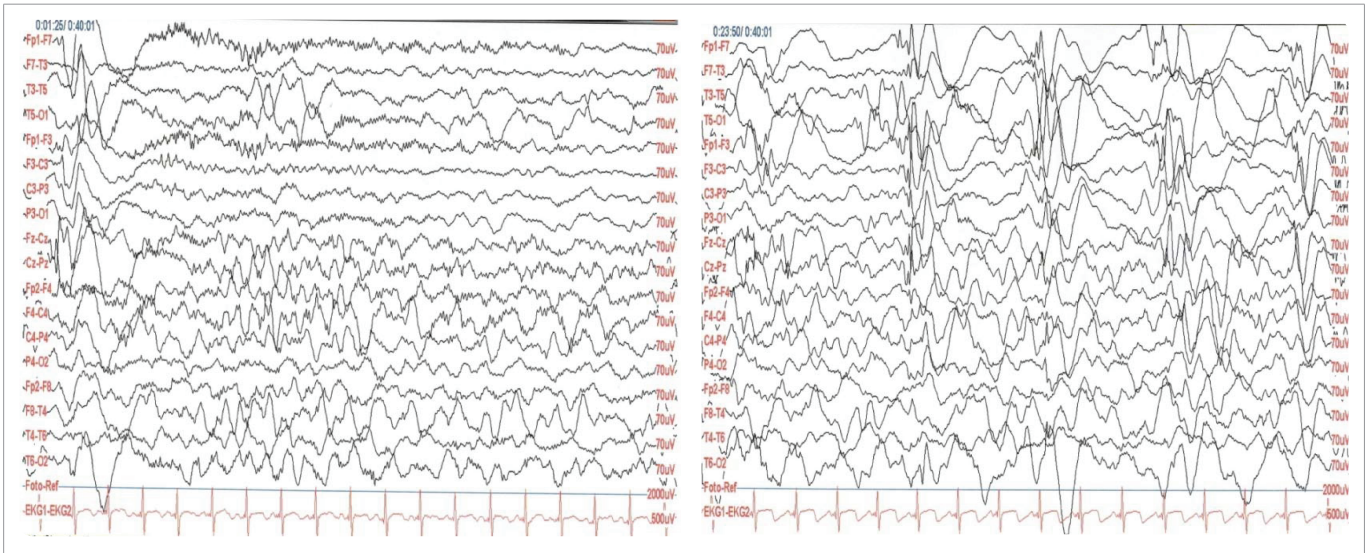

Figure 2: EEG revealed hypsarrhythmia in the left hemisphere.

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