THE ROLE OF FOLATE METABOLISM GENES POLYMORPHISMS IN INTELLECTUAL DISORDER IN CHILDREN WITH CEREBRAL PALSY

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Abstract. *We studied polymorphisms of C677T in the MTHFR gene, A1298C in the MTHFR gene, A276G in the MTR gene, II22Met in the MTRR gene and their influence on the psychological development of cerebral palsy. Based on this, we examined 97 children aged 1 to 14 years who suffered from various forms of cerebral palsy and were at risk of developing cerebral palsy. The gender ratio is 3:2, 59 boys and 38 girls. V.K. Registered in Republican Children's Psychoneurological Hospital named after Kurbanova. for 2020-2022. The control group consisted of 90 healthy children. The diagnosis is made on the basis of anamnesis, neurological condition, results of instrumental and genetic studies.*

Keywords: *cerebral palsy, risk factors, clinical presentation, diagnosis, children, folate cycle gene polymorphism, GMFCS, MTHFR, MTRR, MTR, developmental delays, mental retardation, specific development of school skills.*

Relevance. Cerebral palsy (CP) is a group of stable disorders of the development of motor skills and maintaining posture, which lead to limited functional activity and motor disorders caused by a non-progressive course as a consequence of an abnormal development of the brain in the fetus or newborn child [1,3,4,7] Impaired motor function is often combined with impairment of sensory systems (most often vision and hearing), cognitive dysfunction, speech and child development disorders, symptomatic epilepsy, autonomic disorders, and secondary orthopedic problems [5,6,8]. According to European authors, the incidence of cerebral palsy ranges from 1-2 per 1000 newborns. The male to female ratio is 1.9:1. In the Russian Federation, the prevalence of cerebral palsy reaches 2.2–6.0 cases per 1000 newborns. According to the State Statistics Committee of the Republic of Uzbekistan, this figure is 3.7-4.0 per 1000 live births. In recent years, the incidence of the disease has been increasing, which is associated with wide opportunities for caring for very premature infants and children with extremely low body weight [11,12].

Over the past 5 years, many researchers, as well as the authors at the ICNA 2022 Congress, point out that there is now more and more evidence in favor of the significant role of genetics in the occurrence of cerebral palsy. It is assumed that modern sequencing methods will make it possible to establish an accurate diagnosis [9,10,12]. Genomic analysis will identify true conditions masquerading as cerebral palsy in full-term infants without signs of pathological changes on an MRI study.

The variety of genetically determined diseases that mimic the clinical picture of cerebral palsy dictates the need for the participation of clinical geneticists, as well as conducting genetic studies in patients with suspected cerebral palsy as early as possible.

Purpose of the study : to study the role of polymorphisms of the folate cycle genes C677T in the MTHFR gene, A1298C in the MTHFR gene, A276G in the MTR gene, II22Met in the MTRR gene on intellectual development in children with cerebral palsy .

Material and methods :

We studied the mutations polymorphisms of the folate cycle genes C677T in the MTHFR gene, A1298C in the MTHFR gene, A276G in the MTR gene, II22Met in the MTRR gene and their effect on the psychological development of cerebral palsy. Based on this, we examined 97 children aged from 1 year to 14 years, with various forms of cerebral palsy and children at risk of developing cerebral palsy. Gender ratio 3:2, 59 boys and 38 girls, who are registered at the Republican Children's Psychoneurological Hospital named after W.K. Kurbanova. For the period 2020-2022. The control group consisted of 90 healthy children. The diagnosis of cerebral palsy was established on the basis of medical history, neurological status, and the results of instrumental and genetic studies . The assessment of psychological status was carried out jointly with a psychiatrist and psychologist.

One of the important problems in the management of children with cerebral palsy is timely and adequate psychological correction of mental retardation. At the same time, early diagnosis plays a key role in this aspect, and therefore, at this stage of the work, the influence of the studied polymorphisms of folate cycle genes on the psychological status of children with cerebral palsy was studied . To solve this problem, the main group of sick children was stratified according to the level of intellectual impairment into 3 groups:

1) children with delayed developmental stages and specific developmental disorders of school skills (DED/SDRS), n=49

2) children with preserved intelligence - preserved intelligence (IS), n=13

3) children with mental retardation (MR), n= 35.

The analysis showed that two polymorphisms C677T A in the MTHFR gene and A2756G in the MTR gene turned out to be significant factors in the development of various forms of intellectual disability in the examined children with cerebral palsy.

Thus, the mutant allele T of the C677T A polymorphism in the MTHFR gene is statistically significantly more common almost 5 times more often in children with cerebral palsy with preserved intelligence (IS, n=13) than in the population sample: OR=4.9, 95%CI: 2 .09-11.52; $\chi 2$=15.14, p <0.001. Homozygous carriage of a polymorphic allele increases the risk of cerebral palsy with preserved intelligence almost 8 times: OR=7.64, 95%CI: 1.73-33.69; $\chi 2$=9.19, p =0.003, it should be noted that the sample size was small.

In the other two subgroups with more severe intellectual disability ZER/SRRSHN and UO, the frequencies of alleles and genotypes for the C677T A polymorphism in the MTHFR gene did not differ significantly from the control, however, they were significantly different from the frequencies of alleles and genotypes in the IS group, therefore, the data were further compared between the group with intact intelligence versus a group with impaired intelligence, which included children from the ZER/SRRSHN and UO groups together (n=84). As it turned out, the T allele of the C677T A polymorphism in the MTHFR gene occurs in children with moderate and severe intellectual disabilities in cerebral palsy and is almost 3.5 times less than in sick children

with intact intelligence (OR=0.29, 95%CI: 0 .12-0.67; $\chi 2$=9.12, p =0.003), and with homozygous carriage - 5 times less (OR=0.21, 95%CI: 0.05-0.84; $\chi 2$=5.64, p =0.018). As a result, carriage of a polymorphic allele is a prognostically favorable factor for cerebral palsy , indicating a greater likelihood of the disease progressing with intact intelligence. Taking into account the lack of differences between the population sample and children with moderate and severe intellectual disabilities with cerebral palsy for the C677T A polymorphism in the MTHFR gene, we can conclude that this polymorphism is a risk factor for cerebral palsy with intact intelligence.

The next polymorphism studied, early A2756G in the MTR gene, was also associated with intellectual disability. Statistically significant, the mutant G allele is a factor of severe intellectual impairment in these patients: the probability of detecting the polymorphic G allele in patients with mental retardation increases 3 times (OR=3.12, 95%CI: 1.67-5.83; $\chi 2$=13 .33, p =0.0004) and 5.5 times - homozygous genotype G/G (OR=5.44, 95%CI: 1.48-19.96; $\chi 2$=6.17, p =0.013) .

When comparing data on the distribution of alleles and genotypes for this polymorphism among sick children with milder intellectual disabilities and with intact intelligence with a population sample, the absence of significant differences was noted. Combining these children into one group (ZER/SRRSHN+IS, n=62) showed that the G allele was statistically significantly more than 2 times less common than in the UR group (OR=0.47, 95%CI: 0.25 -0.90; $\chi 2$=5.32, p =0.022), characterizing this polymorphism as a risk factor for cerebral palsy with severe intellectual impairment.

For polymorphisms A66G in the MTRR gene and A1298C in the MTHFR gene, no significant differences were detected in the distribution of alleles and genotypes relative to control values in the population group by psychological status.

Conclusions:

Polymorphism A2756G in the MTR gene is a risk factor for the development of cerebral palsy with severe intellectual disability (OR=3.12, 95%CI: 1.67-5.83; $\chi 2$=13.33, p =0.0004 – when carrying the G allele , OR=5.44, 95%CI: 1.48-19.96; $\chi 2$=6.17, p=0.013 – with homozygous genotype G/G).

Polymorphism C677T A in the MTHFR gene is a risk factor for cerebral palsy with preserved intelligence (OR=4.9, 95%CI: 2.09-11.52; $\chi 2$=15.14, p<0.001 – when carrying the T allele , OR=7 .64, 95%CI: 1.73-33.69; $\chi 2$=9.19, p=0.003 – with homozygous genotype T /T).

Folate cycle gene polymorphisms C677T in the MTHFR gene and A2756G in the MTR gene that are significant in the development of intelligence contribute to early psychological correction and improvement of management and treatment tactics for patients with cerebral palsy, depending on the level of intellectual impairment.

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