SUCCESSFUL REHABILITATION OF PATIENT DISABLED BY THE AUTISTIC SPECTRUM DISORDER AND THE MODIFIED EPIGENETIC STATUS (POLYMORPHISMS DRD2 2137 T/T, MTRR 66 A/G, MTHFR 677 C/T, MTHFR 1298 A/C) – CASE REPORT

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To date, autism spectrum disorders (ASD) are considered as an epidemic - only in the last 5 years the frequency of pathology has increased from 1: 166 to 1:68 children [7, 18, 23].

There is no single etiopathogenetic mechanism of ASD development, but there are theories of its origin (genetic and non-genetic) [2, 6, 16]. A major role in the pathogenesis of ASD now belongs to the violation of epigenetic status in the form of gene polymorphisms [15]. Gene polymorphism is a genetic event in which the structure of genes changes and this affects the function of proteins. An example of such polymorphism is the polymorphic variants of the genes of methylation cycle enzymes, which is gaining increasing interest due to its involvement in the epigenetic process of DNA methylation.

The gene DRD2, encoding the D2-receptor of dopamine, is located in the locus 11q22.3-q23.1 and many researchers associate polymorphism of this gene with bipolar disorders [1,3,4,8-12,17,19,20,22,24,25]. Dopamine receptors refer to the mesolimbic system, which are mainly expressed in the striatum, containing a number of polymorphic markers. One of them, TAQ1 A (rs1800497), located in the 3’-noncoding region of the gene, has functional consequences in the form of different expression of the receptor. The minor allele (T, or A1) is characterized by a lower expression compared with the allele (C, or A2) and leads to a decrease in receptor density in the striatum [5,13,14].

For bipolar disorders, hyperfunction of these receptors is characteristic, including an increase in density, which is associated with the development of the clinical picture [17]. However, studies on transgenic animals with increased expression of DRD2 in the striatum have shown that their behavior is characterized by reduced motivation and reduction of social interactions, hence, DRD2 receptors can be an important factor in the development of behavioral disorders [1,12,21].

Goal - to demonstrate an example of the effectiveness of correction of metabolic disorders in the autistic spectrum disorder.

Material and methods. In the process of the child’s examination, clinical-genealogical, syndromological, biochemical, molecular-genetic and instrumental methods of investigation were used.

Results and their discussion. The child N. (girl), 6 years old, was consulted in KhMSMCG-CR(O)Z in connection with complaintsabout the delay of psycho-speech development (does not speak, does not always respond to her name), hyperexcitability, excessive sweating during sleep (lower part of the head, neck and upper body), periodic subfebrile condition, thermoneurosis, increased salivation; no contact.

Observed by a neurologist and a psychiatrist. Diagnosed with: Delayed psycho-speech development, sensory alalia, autistic spectrum, ADHD. The anamnesis: the girl from I pregnancy, I physiological birth in gestation period of 39-40 weeks. She was born with a weight of 3100 grams, a height of 52 cm, with a triple wrapping of the umbilical cord around the neck and trunk. After birth, a sluggish sucking reflex were noted, the mother fattened the baby with a mixture on goat’s milk. With the introduction of complementary foods, the stool (often undigested with an admixture of mucus, a tendency to diarrhea) was disrupted, and in this connection the order of introduction of complementary foods - meat, cereals, vegetables, and then fruit was changed. The stool was normalized by 3 years after restriction in the diet of gluten-containing products, introduction of probiotics and enzyme preparations. In addition, with the onset of compliance with the gluten-free diet, the burping ceased, the periodically appearing “chemical” odor from the mouth disappeared. At 4 years the child had repeated stool disorders, parents suggest that such violations could arise due to water changes. It was advised by a children’s gastroenterologist, the diagnosis of lambliasis (ELISA method) was diagnosed, treatment was not received.

Motor development corresponded to age: at 5 months began to crawl and sit, at 6 months - to stand with support, at 10 months - to walk by the hand, at 11 months - independent walking.

At the age of 2, for no apparent reason, the parents noted that the girl is becoming less and less contactive, she does not say that her behavior has been violated. Personal hygiene skills were formed by 3.5 years.

Examined:

- nuclear magnetic tomography of the brain (2 years), conclusion: There were no abnormal volumetric changes, MR signs of bilateral sinusitis;

- EEG - moderate widespread changes in the bioelectrical activity of the brain, indicating a decrease in the functional state of the cortex, with an emphasis on changes in the irrational character in the temporal part of the right hemisphere; Epileptiform and apparent focal activity are not recorded; There are no signs of electrogenesis inconsistency with the age norm.

- coagulogram - no change;

- aggregation of platelets - moderate hypoaggregation;

- antibodies to gliadin - increased IgG titer;

- antibodies to deamidized antibodies to gliadin - the IgG titer is increased;

- search for heavy metals (hair) - decreased calcium, potassium, manganese, selenium, zinc;

- study of polymorphic variants of genes of the methylation cycle - revealed heterozygous compound polymorphisms MTRR 66 A / G, MTHFR 677 C / T, MTHFR 1298 A / C;

- full-sequence sequencing of the genome - revealed polymorphism DRD2 2137 T / T;

- blood amino acids (high-performance liquid chromatography) - moderate increase in the levels of valine, leucine, isoleucine; Reduction of methionine, glutamic acid, phenylalanine.

- virologic examination (ELISA) - a moderate increase in the IgG titer to CMV was detected;

- ECG - no echocardiographic signs of pathology;

- organic urine acids - moderately reduced 5-hydroxyproline, hippuric acid.

The polymorphic variants were obtained by polymerase chain reaction on a specialized equipment «RealTime MX3005». PCR analysis included 3 laboratory steps: 1) clinical samples processing (by DNA Isolation); 2) conduction of PCR reaction (amplification); 3) detection of amplification products (in this method - obtaining results in real time).

Principle of the method is the following. The human genomic DNA isolated from blood leukocytes using DNA express-blood reagent undergoes an analysis. With a sample of isolated DNA, two amplification reactions are carried out in parallel — with two pairs of allele-specific primers. The mixture contains the intercalating dye SYBR Green, the fluorescence of which increases many times when embedded in the resulting double-stranded product. The results of the analysis allow us to give three types of conclusions: normal homozygote; heterozygote; pathological

homozygote.

Features of the phenotype: at 6 years the child was 127 cm, 24 kg, pale skin, brown hair, blue eyes, large brushes, large feet, large calves, diastema between the upper central incisors, flat-valgus deformation of the feet, muscular dystonia.

At the examination: hyperhomocysteinemia was detected (which in combination with hypomethionemia and the presence of polymorphic variants of the enzymes of the methylation cycle; enzymes indicate a change in the epigenetic status), secondary lactase deficiency (C/T polymorphism).

Based on complaints, anamnestic data, phenotype features, clinical genealogy analysis, as well as the results of additional research methods, a final diagnosiswas made:

Autistic spectrum disorder. Epigenetic disease (polymorphisms DRD2 2137 T/T, MTRR 66 A/G, MTHFR 677 C/T, MTHFR 1298 A/C). Hyperhomocysteinemia. Nonspecific aminoacidopathy. Secondary lactase insufficiency. Intolerance to gluten.

Taking into account the results obtained, cofactor therapy (P-5-P, betaine (TMG)) has been recommended, it was recommended to limit foods high in tyrosine (dopamine precursor), adherence to gluten-free and lactose-free diet, followed by control of homocysteine, blood amino acids and organic acids in Urine.

At the control examination (after 1 month) the level of organic acids of urine was normalized, but non-specific aminoacidopathy was maintained (aspartic acid, serine, glutamic acid, glycine, β-aminobutyric acid, phenylalanine, tryptophan, ornithine was lowered, alanine, proline, leucine, Isoleucine, citrulline, arginine, histidine, asparagine, lysine). The level of homocysteine decreased two times. When studying the level of vitamins of group B, an increase in cyanocobalamin, a decrease in riboflavin; The level of pyridoxine - at the lower limit of the norm.

Taking into account the received results, three courses of therapy were recommended, including a folate cofactor diet, filling the vitamin deficiency, restoring the balance of blood amino acids. Against the backdrop of treatment, the child had words, she became calmer, salivation and subfebrillitis left. At the end

of the treatment, the control of previously changed parameters, observation of the neurologist, psychiatrist, rehabilitation measures was recommended.

Conclusion. Violation of the epigenetic status in the form of disturbance of the methylation cycle and the function of the mesolimbic system in a child with autism spectrum disorders plays an important role in the pathogenesis of the clinical picture development, on the one hand, and on the other hand, it allows to develop an individual tactic of managing the patient with obtaining a positive effect.

From point of view of psychiatry, topical is a psychosocial maladjustment of patient with the disability of the autistic spectrum disorder, violation of an individual integration in the environment, the impossibility of adaptation during a long time. This requires profound follow-up by specialists in pathopsychology. Thus, further prospects correspond to deeper mutual integration

of clinical genetics and phychology.

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SUMMARY

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Autism spectrum disorders (ASD) are considered an epidemic only in the last 5 years the incidence of pathology has increased from 1: 166 to 1:68 children. The main role in the pathogenesis of ASD currently belongs to the violation of the epigenetic status in the form of gene polymorphisms. An example is the polymorphic variants of the genes of the folate-methionine cycle enzymes, which regulate the epigenetic status through a methylation process. The article presents a case of autism spectrum disorder against the background of impaired epigenetic status (metabolic dopamine neurotransmitters and the methylation cycle). Individually selected metabolic correction based on biochemical parameters allowed improving behavior, stimulating speech development, stopping long subfebrile and hypersalivation.

Keywords: autistic spectrum disorder, epigenetic disorders, dopamine, methylation.

РЕЗЮМЕ

ОПИСАНИЕ СЛУЧАЯ УСПЕШНОЙ РЕАБИЛИТАЦИИ ПАЦИЕНТА С РАССТРОЙСТВОМ АУТИСТИЧЕСКОГО СПЕКТРА И МОДИФИЦИРОВАННОГО ЭПИГЕНЕТИЧЕСКОГО СТАТУСА

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Расстройства аутистического спектра (РАС) считаются эпидемией - только за последние 5 лет частота патологии увеличилась с 1:166 до 1:68 детей. Основная роль в патогенезе РАС в настоящее время принадлежит нарушению эпигенетического статуса в виде генных полиморфизмов. Примером являются полиморфные варианты генов ферментов фолатно-метионинового цикла, которые регулируют эпигенетический статус посредством процесса метилирования.

В статье представлен случай расстройства аутистического спектра на фоне нарушенного эпигенетического статуса (нарушение метаболизма дофаминовых нейротрансмиттеров и цикла метилирования). Индивидуально подобранная метаболическая коррекция, основанная на биохимических показателях, позволила улучшить поведение, стимулировать развитие речи, купировать длительный субфебрилитет и гиперсаливацию.