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УЧАСТЬ ГОМОЦІСТЕЇНУ У РЕГУЛЯЦІЇ ОБМІНУ ГОРМОНІВ ЩИТОПОДІБНОЇ ЗАЛОЗИ У ДІТЕЙ, ЯКІ МЕШКАЮТЬ ПОБЛИЗУ ЧОРНОБИЛЬСЬКОЇ АТОМНОЇ ЕЛЕКТРОСТАНЦІЇ

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PARTICIPATION OF HOMOCYSTEINE IN THE REGULATION OF THYROID HORMONE METABOLISM IN CHILDREN LIVING NEAR THE CHORNOBYL NUCLEAR POWER PLANT

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In recent years, the attention of the scientific community has been attracted by the sulfur-containing amino acid homocysteine (H_{cy}), which is involved in methionine metabolism.

Metabolic cycles associated with H_{cy} have been studied [1] and genetic polymorphisms affecting its metabo-

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Встановлено негативну роль гомоцистеїну (H_{cy}) у виникненні низки тяжких захворювань, що призводять до летальних наслідків або інвалідності. Однак при цьому не було визначено причинно-наслідкових механізмів. Реалізація проєктів Європейської Комісії та ради Рон-Альп (Франція) в Україні (2013-2017) дозволила виявити підвищений вміст у крові H_{cy} у 70,0% випадків, а також структурно-функціональні зміни у щитоподібній залозі (ЩЗ) та кореляційні зв'язки між H_{cy} та гормонами гіпофізарно-тиреоїдної осі у групі підлітків, які мешкають поблизу Чорнобильської атомної електростанції (ЧАЕС). Для розуміння патогенетичних механізмів патологічних процесів, пов'язаних з H_{cy} та ЩЗ, проведено дане дослідження, метою якого стала комплексна оцінка участі H_{cy} у регуляції обміну гормонів ЩЗ у дітей, які проживають поблизу Чорнобильської зони відчуження (ЧЗВ) в Іванківському районі Київської області.

***Методи дослідження**. Аналітичне дослідження проводилося з використанням статистичних показників, отриманих під час лабораторного та генетичного обстеження 178 дітей віком 12-17 років із населених пунктів, що межують з ЧЗВ. Для оцінки вивчених регуляторних процесів проведено кореляційний аналіз між показниками H_{cy}, гормонів ЩЗ, тиреотропного гормону гіпофіза (ТТГ), вітамінів B_9, B_{12}, B_6 з урахуванням різних комбінацій алелів генетичних поліморфізів фолатного циклу (ФЦ).*

***Результати**. В організмі більшості дітей, які проживають на території, що постраждала внаслідок аварії на ЧАЕС, поблизу ЧЗВ, рівень H_{cy} у крові перевищує фізіологічний рівень. Показано, що концентрація вітамінів B_9 і B_{12} у крові відображає здатність ферментів ФЦ метилювати H_{cy}. Гомозиготний варіант алеля T MTHFR:677 у геномі дітей знижує вміст активних форм вітаміну B_9 і підвищує вміст H_{cy} у крові. У гомозиготному варіанті алеля G MTR:2756 порушується утворення активної форми B_{12}, що тягне за собою активацію циклу реакцій транссульфурації і зниження рівня H_{cy} у крові. Підвищений вміст H_{cy} у крові індукує синтез ТТГ у клітинах аденогіпофіза, який бере участь у процесі дейодування T_4 і утворення T_3. Рівень T_4 у крові залежить від того, як цей метаболіт використовується периферичними органами і тканинами, і вказує на енергетичні потреби організму. Периферичні органи, включаючи печінку і нирки, відповідають за утилізацію T_4 і утворення T_3 – активної форми гормонів ЩЗ. T_3 має стимулювальну дію на ферменти ФЦ, що призводить до посилення метилювання H_{cy} та збільшення утворення власного метіоніну. Водночас він блокує утилізацію H_{cy} у циклі реакцій транссульфуризації.*

***Висновки**. У дітей, що розвиваються в умовах постійного радіаційного опромінення, ферментна система ФЦ відіграє важливу роль у формуванні регуляторних зв'язків між гіпофізом і ЩЗ. Доведено, що T_3 підтримує необхідну концентрацію H_{cy} у організмі, збільшуючи утворення активної форми вітаміну B_9. Вплив T_3 на ФЦ виражається у гетерозиготних варіантах алелів ризику поліморфізмів MTR:2756, MTHFR:677. Радіаційний фактор у вигляді інкорпорованих в організм радіонуклідів негативно впливає на процес метилювання H_{cy}, викликаючи стан гіпергомоцистеїнемії у дітей підліткового віку, які мешкають поблизу ЧЗВ, незалежно від стану генів ФЦ.*

Ключові слова: гомоцистеїн, гормони щитоподібної залози, фолатний цикл, підлітки, радіоактивно забруднені території.

lism have been identified [2]. The negative role of H_{cy} in the development of a number of serious diseases leading to death or disability has been revealed [3-7].

In particular, a link has been established between hyperhomocysteinemia and hypothyroidism [8].

However, the cause-and-effect mechanisms have not been determined.

Studies conducted in 2013-2017 in Ukraine within the framework of projects of the European Commission and the Rhone-Alpes Regional Council (France) revealed increased H_{cy} levels in the blood in more than 70.0% of cases among adolescents living near the Chornobyl Nuclear Power Plant (ChNPP) [9].

At the same time, in 35.5% of cases, thyroid hormone production disorders were detected, and in 5.6% of cases, structural changes in the thyroid gland (TG) [10].

The obtained data suggest considering the relationship between H_{cy} and thyroid hormone metabolism in the child's body under the influence of the radiation factor.

Analytical studies have shown a number of correlations between H_{cy} and hormones of the pituitary-thyroid axis in children living near the Chornobyl Exclusion Zone (ChEZ) [11].

However, this is not enough to understand the pathogenetic mechanisms of pathological processes associated with H_{cy} and the thyroid gland.

A comprehensive assessment of the participation of H_{cy} in the regulation of thyroid hormone metabolism in children under conditions of constant radiation exposure is necessary, taking into account genetic polymorphisms of the folate cycle (FC).

The aim of this study was a comprehensive assessment of the participation of H_{cy} in the regulation of thyroid hormone metabolism in children living near the ChEZ in the Ivankivskyi district of the Kyiv region.

Material and methods. The study material was statistical indicators of thyroid hormones, pituitary thyroid stimulating hormone (TSH) and H_{cy}, as well as vitamins B_9, B_{12}, B_6 in subgroups of children from the Ivankivskyi district of the Kyiv region, with various combinations of alleles of genetic polymorphisms of FC.

The study was implemented within the framework of projects of the European Commission and the Regional Council of Rhone-Alpes (France).

Table 1

The proportion of cases of hyperhomocysteinemia in genetic subgroups of children

Main genotypes	N^1	N^2	%
A/A MTR:2756	106	78	73.58
A/G MTR:2756	61	47	77.05
G/G MTR:2756	11	5	45.45
C/C MTHFR :677	80	56	70.00
C/T MTHFR:677	83	62	74.70
T/T MTHFR:677	15	12	80.00
A/G MTR:2756-C/T MTHFR:677	27	23	85.19
A/A MTR:2756-C/C MTHFR:677	45	33	73.33
G/G MTR:2756-C/C MTHFR:677	6	3	50.00
A/A MTR:2756-T/T MTHFR:677	10	8	80.00
A/A MTR:2756-C/T MTHFR:677	51	37	72.55
A/G MTR:2756-C/C MTHFR:677	29	20	68.97
General group	178	130	73.03

Note: N is the subgroup number;
N^1 is the number of children in the subgroup;
N^2 is the number of cases of hyperhomocysteinemia.

At the same time, 178 children (86 boys and 92 girls) aged 12-17 years old, on 18.12.2015, in the morning, on an empty stomach, blood was taken from the cubital vein.

Blood samples were tested in a laboratory certified in accordance with the quality standards of the European Union.

When determining the content of H_{cy}, vitamins B_9 and B_{12} in the blood, an immunochemical method with chemiluminescent detection (ECLIA) was used.

Vitamin B_6 in the blood of children was determined by high-performance liquid chromatography.

Determination of TSH, triiodothyronine (T_3) and thyroxine (T_4) was carried out using an immunochemical method with electrochemiluminescent detection (ECLIA). Analyzer and test system: Cobas 6000, Roche Diagnostics (Switzerland).

The level of H_{cy} in the blood of children over 10.0 μmol/l was defined as a state of hyperhomocysteinemia.

The reference interval of extreme values, designated by the laboratory, was: for B_9 (folacin) – 4.6-18.7 ng/ml, for B_{12} (holotranscobalamin, or active vitamin B_{12}) – 191.0-663.0 pg/ml, for B_6 – 8.7-27.2 μg/l, for TSH – 0.28-4.3 μMO/ml; for T_3 – 2.3-5.0 pg/ml; for T_4 – 1.1-1.8 ng/dl.

During the genetic study of FC, allelic variants of the MTHFR:C677T polymorphism affecting the activity of methylenetetrahydrofolate reductase (MTHFR), and the MTR:A2756 G polymorphism associated with B_{12}-dependent methionine synthase (MTR) were determined. The method used was Real-time PCR. Analyzer and test system Detecting amplifier «DT-96»; «DNA-Technology» (Russia).

Statistical processing of the obtained results was carried out using the IBM SPSS Statistics 22 program (USA).

The relationship between the H_{cy}, B_9, B_{12}, B_6, TSH, T_4, T_3 indicators and the T_3/T_4 index was determined using the Spearman rank correlation coefficient (r_{xy}). Direct «+» and inverse «-» correlations were recorded.

The strength of the correlation was assessed using the traditional scale: weak – from 0 to 0.299; average – from 0.3 to 0.699; strong – from 0.7 to 1.0.

Results and discussion. In the analyzed group of children, in most cases, the level of thyroid and adenohypophysis hormones corresponded to the established physiological parameters [12].

At the same time, in most children, the level of H_{cy} in the blood significantly exceeded the age physiological barrier (Table 1).

Many children had risk alleles of genetic polymorphisms affecting H_{cy} metabolism [13].

At the same time, the phenotypic realization of genetic polymorphisms of FC in the body of children occurred under conditions of constant radiation exposure [14].

In this situation, to assess the studied regulatory processes, it is informative to determine the correlation links between the analyzed indicators.

In the general group of children, there were complex combinations of correlations (Table 2), which do not allow a full assessment of the participation of H_{cy} in the regulation of thyroid hormone metabolism.

In this regard, it is advisable to determine the correlation links between the analyzed parameters in subgroups of children with different combinations of FC genotypes (Table 2).

Polymorphisms MTHFR: C677T and MTR:A2756 G have the greatest impact on the activity of the main FC enzymes involved in the process of H_{cy} methylation and the formation of internal methionine.

With homozygous variants of the risk alleles T MTHFR: 677 and G MTR:2756, the number of correlations between the analyzed parameters is minimal (Table 2).

In particular, in the subgroup where the T/T MTHFR:677 genotype was the main one (present in 100% of cases), the links – B_9-H_{cy} and + TSH-T_3 were determined.

They indicate that deficiency of the active form of B_9 leads to an increase in the level of H_{cy} in the blood and activation of hormonal activity in the pituitary-thyroid axis.

Ultimately, under the influence of TSH, an increase in the formation of T_3 occurs (Table 3).

In the subgroup where the main genotype was G/G MTR:2756, the following relationships were recorded: - B_{12}-H_{cy}, + H_{cy}-B_6.

These relationships reflect the participation of B_{12} in the

Table 2

Correlation links between H_{cy}, hormones of the pituitary-thyroid axis and B vitamins in genetic subgroups of children of the Ivankivskyi district

Main genotype	Correlation links
A/AMTR:2756	+ B_9-T_4, + B_{12}-T_4, - B_{12}-H_{cy}, - B_9-H_{cy}, + B_9-B_{12} , + TSH-T_3, + TSH-T_3/T_4
A/GMTR:2756	+ T_3-B_9, + B_{12}-T_4, - B_{12}-TSH, - B_9-H_{cy}, - B_{12}-H_{cy}, - B_{12}-B_6, + H_{cy}-TSH, + TSH-T_3, + TSH-T_3/T_4, - TSH-T_4
G/GMTR:2756	- B_{12}-H_{cy}, + H_{cy}-B_6
C/C MTHFR:677	- B_{12}-H_{cy}, - B_9-H_{cy}, + H_{cy}-T_3, + TSH-T_3, + TSH-T_3/T_4, - TSH-T_4
C/T MTHFR:677	+ T_3-B_9, + B_9-T_4, + B_{12}-T_4, - B_{12}-TSH, - B_{12}-H_{cy}, - B_9-H_{cy}, + B_9-B_{12}, + H_{cy}-TSH
T/T MTHFR:677	- B_9-H_{cy}, + TSH-T_3
A/GMTR:2756-C/TMTHFR:677	+ H_{cy}-TSH, - B_{12} -B_6, + B_{12}-T_4, + T_3-B_9
A/AMTR:2756-C/CMTHFR:677	- B_{12}-H_{cy}, + B_9-B_{12}
G/GMTR:2756- C/C MTHFR:677	+ H_{cy}-B_6, - B_{12}-H_{cy}, - B_{12}-B_6
A/AMTR:2756-T/TMTHFR:677	there are no correlations
A/AMTR:2756-C/TMTHFR:677	- B_9-H_{cy}, + B_9-B_{12}, + B_9-T_4
A/GMTR:2756-C/CMTHFR:677	+ TSH-T_3, - T_3-B_6, - B_{12}-H_{cy}
General group	+ T_3-B_9, + B_9-T_4, + B_{12}-T_4, - B_{12}-H_{cy}, - B_9-H_{cy}, + B_9- B_{12}, + H_{cy}-TSH, + H_{cy}-T_3, + TSH-T_3, + TSH-T_3/T_4, - TSH-T_4

Note: «+» direct correlation; «-» inverse correlation.

process of H_{cy} methylation.

The active form of B_{12} is formed under the influence of the active form of B_9 (methyltetrahydrofolate) as a result of the transfer of a methyl group through the mediation of MTR.

With the genotype G/G MTR:2756, the activity of MTR is sharply reduced, as a result of which the deficiency of the active form of B_{12} causes a violation of H_{cy} methylation. However, the H_{cy} level in the blood does not increase (Table 1), since H_{cy} is utilized in the transsulfuration reaction cycle, as evidenced by the direct relationship + H_{cy}-B_6 (Table 3).

With heterozygous variants of the T MTHFR:677 and G MTR:2756 alleles, the number of correlations between the analyzed indicators is significantly greater.

The subgroup with the main genotype C/T MTHFR:677 included correlations + B_9-B_{12}, - B_{12}-H_{cy}, - B_9-H_{cy}, - B_{12}-TSH, + H_{cy}-TSH, characterizing the participation of B_9 and B_{12} in the process of H_{cy} methylation and TSH formation.

The correlations + B_9-T_4, + B_{12}-T_4 reflect the participation of B_9 and B_{12} in the regulation of thyroid hormone metabolism.

The correlation + T_3-B_9 reflects the influence of T_3 on the process of formation of the active form B_9 (Table 2).

The subgroup with the main genotype A/G MTR:2756 is characterized by a combination of two cycles of correlations involving H_{cy} and TSH, confirming the influence of MTR on the processes of exchange of H_{cy} and hormones of the pituitary-thyroid axis (Table 2):

a) The cycle of correlations based on the active form of B_{12}. It includes correlations - B_{12}-H_{cy}, - B_{12}-TSH, + H_{cy}-TSH, - TSH-T_4, + B_{12}-T_4, - B_{12}-B_6.

A decrease in the formation of the active form of B_{12} leads to an increase in the level of H_{cy} in the blood and activation of TSH formation in the adenohypophysis.

At the same time, the content of T_4 in the blood decreases and the activity of the transsulfuration cycle increases, as evidenced by the relationship - B_{12}-B_6.

b) A cycle of correlations confirming the influence of H_{cy} on the process of formation of TSH and T_3.

It includes correlations - H_{cy}-B_9, + H_{cy}-TSH, + TSH-T_3, + TSH-T_3/T_4, + T_3-B_9.

Just as in the case of the genotype C/T MTHFR:677, T_3 promotes the formation of the active form B_9, which reduces the level of H_{cy} in the blood.

The subgroup with the main genotype C/C MTHFR:677 (homozygous variant of the neutral allele C MTHFR:677) included correlations - B_{12}-$H_{cy,}$ - B_9-H_{cy}, reflecting the influence of B_9 and B_{12} on the process of H_{cy} methylation. The correlations + H_{cy}-T_3, + TSH-T_3, + TSH-T_3/T_4, - TSH -T_4, characterize the participation of H_{cy} and TSH in the process of T_4 deiodination and the formation of T_3 (Table 2).

The subgroup with the main genotype A/A MTR:2756 (homozygous variant of the neutral allele A MTR:2756) included correlations + B_9-T_4, + B_{12}-T_4, - H_{cy}-B_{12}, - H_{cy}-B_9, + B_9-B_{12}, + TSH-T_3, + TSH-T_3/T_4, reflecting the role of vitamins B_9 and B_{12} in the processes of H_{cy} methylation and T_4 content in the blood, as well as the effect of TSH on the process of T_4 deiodination and T_3 formation.

In the analyzed subgroups with the risk allele and the neutral allele of the MTHFR: C677T polymorphism, the presence of the risk allele MTR:A2756G polymorphism and vice versa was established (Table 4).

The subgroup with a combination of genotypes A/G MTR:2756-C/T MTHFR:677, simultaneously reducing the activity of two main enzymes of the FC, included correlations characterizing: the effect of B_{12} on the content of T_4 in the blood (+ B_{12}-T_4), the effect of H_{cy} on the formation of TSH (+ H_{cy}-TSH), activation of the transsulfuration cycle (- B_{12}-B_6), and stimulation of the formation of vitamin B_9 under the influence of T_3 (+ T_3-B_9).

The subgroup with a combination of genotypes consisting of neutral alleles A/A MTR: 2756-C/C MTHFR:677 in-

Table 3

Correlation links in subgroups with the main genotypes

Main genotype	Correlation	Spearman's (r_{xy})	Sign. (2 tailed), p	n
T/T MTHFR:677	B_9-H_{cy}	- 0.674**	0.006	15
	TSH-T_3	0.693**	0.004	15
G/G MTR:2756	B_{12}-H_{cy}	- 0.918**	0.000	11
	H_{cy}-B_6	0.724*	0.012	11

Note: n – the number of cases.

Table 4

Proportion of cases with T allele MTHFR:677 and G allele MTR:2756 in genetic subgroups

Main genotype	N_1	Allele T MTHFR:677		Allele G MTR:2756	
		N_2	%	N_2	%
A/A MTR:2756	106	61	57.6	0	0
A/G MTR:2756	61	32	52.5	61	100.0
G/G MTR:2756	11	5	45.5	11	100.0
C/C MTHFR:677	80	0	0	35	43.8
C/T MTHFR:677	83	83	100.0	32	38.6
T/T MTHFR:677	15	15	100.0	5	33.3
General group	178	98	55.1	72	40.5

PARTICIPATION OF HOMOCYSTEINE IN THE REGULATION OF THYROID HORMONE METABOLISM IN CHILDREN LIVING NEAR THE CHORNOBYL NUCLEAR POWER PLANT

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The negative role of homocysteine (H_{cy}) in the occurrence of a number of severe diseases leading to death or disability has been established. However, the cause-and-effect mechanisms have not been determined. The implementation of projects of the European Commission and the Rhone-Alpes Council (France) in Ukraine (2013-2017) made it possible to identify elevated H_{cy} blood levels in 70.0% of cases, as well as structural and functional changes in the thyroid gland (TG) and correlations between H_{cy} and hormones of the pituitary-thyroid axis in a group of adolescents living near the Chornobyl Nuclear Power Plant (CNPP). To understand the pathogenetic mechanisms of pathological processes associated with H_{cy} and the thyroid gland, the present study was conducted, the aim of which was a comprehensive assessment of the participation of H_{cy} in the regulation of thyroid hormone metabolism in children living near the Chornobyl Exclusion Zone (ChEZ) in the Ivankivskyi district of the Kyiv region.

***Research methods**. An analytical study was conducted using statistical indicators obtained during laboratory and genetic examination of 178 children aged 12-17 years from settlements bordering the ChEZ. To assess the regulatory processes under study, a correlation analysis was performed between the indicators H_{cy}, thyroid hormones, pituitary thyroid stimulating hormone (TSH), vitamins B_9, B_{12}, B_6, taking into account various combinations of alleles of genetic polymorphisms of the folate cycle (FC).*

***Results**. In the body of most children living in the area affected by the Chernobyl accident, near the ChEZ, the level of H_{cy} in the blood exceeds the physiological level. It is shown that the concentration of vitamins B_9 and B_{12} in the blood reflects the ability of FC enzymes to methylate H_{cy}.*

The homozygous variant of the T allele MTHFR:677 in the genome of children reduces the content of active forms of vitamin B_9 and increases the content of H_{cy} in the blood. In the case of the homozygous variant of the G allele MTR:2756, the process of formation of the active form of B_{12} is disrupted, which entails activation of the transsulfuration reaction cycle and a decrease in the H_{cy} level in the blood.

Increased H_{cy} content in the blood induces the synthesis of TSH, which is involved in the process of T_4 deiodination and the formation of T_3. The level of T_4 in the blood depends on how this metabolite is used by peripheral organs and tissues and indicates what the energy needs of the body are. Peripheral organs, including the liver and kidneys, are responsible for the utilization of T_4 and the formation of T_3 - the active form of thyroid hormones. T_3 has a stimulating effect on FC enzymes, which leads to increased methylation of H_{cy} and an increase in the formation of internal methionine. At the same time, it blocks the utilization of H_{cy} in the transsulfuration reaction cycle.

***Conclusions**. In children developing under conditions of constant radiation exposure, the FC enzyme system plays an important role in the formation of regulatory connections between the pituitary gland and the thyroid gland. It has been proven that T_3 maintains the required concentration of H_{cy} in the body, increasing the formation of the active form of vitamin B_9. The effect of T_3 on FC is expressed in heterozygous variants of the risk alleles of the MTR:2756, MTHFR:677 polymorphisms. The radiation factor, in the form of radionuclides incorporated into the body, has a negative effect on the H_{cy} methylation process, causing a state of hyperhomocysteinemia in adolescents living near the ChEZ, regardless of the state of the FC genes.*

Keywords: homocysteine, thyroid hormones, folate cycle, adolescents, radioactively contaminated area.

cluded correlations + B_9-B_{12}, - H_{cy}-B_{12}, reflecting the entire process of H_{cy} methylation.

The subgroup with the combination of genotypes G/G MTR:2756-C/C MTHFR:677 included correlations - H_{cy}-B_{12},+ H_{cy}-B_6, - B_{12}-B_6, reflecting the activation of the transsulfuration cycle with a lack of formation of the active form of B_{12} and an increase in the level of H_{cy} in the blood.

In the subgroup with the combination of genotypes A/G MTR:2756-C/C MTHFR:677, correlations were found reflecting the participation of B_{12} in the process of H_{cy} methylation (- B_{12}-H_{cy}), the stimulating effect of TSH on the process of T_3 formation (+ TSH-T_3), and the blocking effect of the T_3 cycle of transsulfuration reactions (- T_3-B_6).

The subgroup with the genotype combination A/A MTR:2756-C/T MTHFR:677 included correlations - B_9-H_{cy}, + B_9-B_{12}, + B_9-T_4, reflecting the dependence of H_{cy} methylation and T_4 content in the blood on the active form of B_9.

In the subgroup with the genotype combination A/A MTR:2756-T/T MTHFR:677, no correlations were found.

Thus, heterozygous forms of the T MTHFR:677 and G MTR:2756 alleles are characterized by correlations indicating a stimulating effect of H_{cy} on the process of TSH formation.

In the subgroup with the A/G MTR:2756 genotype, direct correlations of TSH-T_3 indicate the effect of TSH on the process of T_4 deoidination and T_3 formation.

The studies conducted revealed the importance of the G MTR:2756 allele for the activation of the transsulfuration reaction cycle (correlations – B_{12}-B_6 and + H_{cy} -B_6), in which H_{cy} is utilized.

With the heterozygous variant of this allele, the H_{cy} level does not differ significantly from most other genetic groups, since MTR activity is reduced by no more than 20-30% (Table 1).

However, with the homozygous variant of the G MTR:2756 allele, MTR activity decreases by 80% and the proportion of hyperhomocysteinemia cases decreases to 45% (Table 1)

Thus, the presence of the G MTR:2756 allele in the genome of children plays an important role in activating the cycle of transsulfuration reactions and utilization of excess H_{cy}.

Full formation of the active form of B_{12} is carried out with the help of 5-methyltetrahydrofolate (correlation + B_9-B_{12}), with the homozygous variant of the neutral allele A MTR:2756, which ensures the functioning of MTR.

Formation of the active form of B_9 depends on the functional activity of MTHFR.

The correlation + T_3-B_9 indicates a stimulating effect of T_3 on MTHFR, resulting in the formation of 5-methyltetrahydrofolate – the active form of vitamin B_9.

The correlation + T_3-B_9 is present in subgroups with heterozygous variants of the T alleles MTHFR:677 and G alleles MTR:2756, and is absent in subgroups with homozygous variants of these alleles and homozygous variants of the neutral alleles C MTHFR: 677 and A MTR:2756.

The participation of T_3 in the formation of the active form of B_9 is confirmed by the fact that in a state of hyperthyroidism, the level of H_{cy} in the blood decreases and the content of B vitamins involved in the methylation of H_{cy} increases [15].

Thus, the functioning of MTHFR determines the entire process of methylation of H_{cy} and the hormonal activity of the pituitary-thyroid axis.

It is with this enzyme that T_3 interacts.

But only when the neutral allele C MTHFR:677 is present in the genome.

An increase in the formation of T_3 under conditions of elevated H_{cy} levels in the blood should be considered as an adaptation factor aimed at improving metabolic processes in the body under conditions of genetic instability.

In addition to the genetic factor, an exogenous factor should be noted among the causes of hyperhomocysteinemia.

In areas bordering the ChEZ, radioactive elements have contaminated the soil [16] and are constantly entering the bodies of local residents through biological chains.

When incorporated into vital organs [17], radionuclides ^{137}Cs and ^{90}Sr affect cellular energy, contributing to the disruption of amino acid metabolism, in particular methionine and H_{cy}.

As a result, an increase in the H_{cy} level was recorded even with homozygous variants of neutral alleles of genetic polymorphisms that control the main enzymes of the FC (Table 1).

Conclusions

In the body of most children living in the area affected by the Chornobyl accident, near the ChEZ, the level of H_{cy} in the blood exceeds the physiological level.

H_{cy} metabolism is associated with the FC enzyme systems, transsulfuration and deiodination cycles, TSH and thyroid hormones.

In children developing under conditions of constant radiation exposure, the FC enzyme system plays an important role in the formation of regulatory connections between the pituitary gland and the thyroid gland.

The concentration of vitamins B_9 and B_{12} in the blood reflects the ability of FC enzymes to methylate H_{cy}.

The homozygous variant of the T allele MTHFR:677 in the genome of children reduces the content of active forms of vitamin B_9 and increases the content of H_{cy} in the blood.

With the homozygous variant of the G allele MTR:2756, the process of formation of the active form of B_{12} is disrupted, which entails activation of the transsulfuration reaction cycle and a decrease in the level of H_{cy} in the blood.

An increased content of H_{cy} in the blood induces the synthesis of TSH in the cells of the adenohypophysis, which is involved in the process of T_4 deiodination and the formation of T_3.

The level of T_4 in the blood depends on how this metabolite is used by peripheral organs and tissues, and indicates what the energy needs of the body are.

Peripheral organs, including the liver and kidneys, are responsible for the utilization of T_4 and the formation of T_3, the active form of thyroid hormones.

T_3 has a stimulating effect on FC enzymes, which leads to increased methylation of H_{cy} and increased formation of internal methionine.

At the same time, T_3 blocks the utilization of H_{cy} in the cycle of transsulfuration reactions.

Thus, T_3 maintains the required concentration of H_{cy} in the body.

The effect of T_3 on FC is expressed in heterozygous variants of the risk alleles of the MTR:2756, MTHFR:677 polymorphisms.

The radiation factor, in the form of radionuclides incorporated into the body, has a negative effect on the process of H_{cy} methylation, causing a

state of hyperhomocysteinemia in adolescent children living near the ChEZ, regardless of the state of the FC genes.

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