CHAPTER «MEDICAL SCIENCES»

FOLATE CYCLE GENES AND THYROID HORMONES METABOLISM IN CHILDREN LIVING NEAR THE CHERNOBYL EXCLUSION ZONE

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Abstract. It is known that the thyroid gland (TG) is capable of intensively incorporating ^{137}Cs. People living near the Chernobyl Exclusion Zone (ChEZ) are at the highest risk of negative impact on the body of this and other long-lived radionuclides. As a result of the European Commission project "Health and environment programs around the Chernobyl Exclusion Zone: development, training and coordination of health-related projects" carried out in Ukraine in 2014-2017 together with the project of the Rhone-Alpes Regional Council (France), structural changes in the thyroid gland (5.6% of cases), disorders of thyroid hormone production (35.5% of cases) were detected in children living near the ChEZ. Elevated levels of the sulfur-containing amino acid homocysteine (H_{cy}) were found in the blood of most of the examined adolescents. The study of the relationship between metabolic cycles involving thyroid hormones and H_{cy} under the influence of the external radiation factor is relevant from scientific and practical points of view. At the same time, the determination of the role of folate cycle (FC) genes in the regulation of metabolic processes associated with thyroid hormones will be of great importance. *The purpose* of the study was to determine the involvement of FC genes in the regulation of thyroid hormonogenesis in children living near the ChEZ. *Methodology.*

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The research methodology predetermined the statistical evaluation of the results of laboratory and genetic examination of 690 adolescent children from settlements located near the ChEZ. Immunochemical, genetic and statistical research methods were used. *Results.* It was shown that the proportion of hyperhomocysteinemia cases in the group of examined children (H_{cy} level in the blood > 10.0 μmol/l) exceeded 50%. The established correlations between H_{cy} indicators, vitamins B_9, B_{12}, pituitary thyroid stimulating hormone (TSH), thyroxine (T_4) and triiodothyronine (T_3) made it possible to determine the participation of FC genes in the regulation of thyroid hormonogenesis in children living near the ChEZ. In the subgroup including cases with the GMTR:2756 allele in the genome, a decrease in the activity of B_{12}-methionine synthase was recorded, leading to a violation of the H_{cy} methylation process and activation of TSH synthesis, stimulating the process of T_4 deiodination and the formation of T_3 in peripheral tissues. H_{cy} is also utilized in the transsulfuration reaction cycle to form cysteine, which is a stimulating factor for T_4 deiodination and T_3 formation. A distinctive feature of the presence of the GMTR:2756 allele in the genome is the effect of T_3 on MTHFR, resulting in increased synthesis of 5-MTHF, the active form of vitamin B_9, as evidenced by the direct T_3-B_9 relationship. Children who are carriers of the TMTHFR:677 allele are predisposed to a decrease in the formation of 5-MTHF, resulting in a decrease in the intensity of the H_{cy} methylation process and a decrease in the formation of internal methionine. The consequence of this is the activation of TSH synthesis, stimulating the process of T_4 deiodination and T_3 formation. In the case of a heterozygous variant of the TMTHFR:677 allele, T_3 has a stimulating effect on MTHFR, resulting in an increase in the formation of 5-MTHF. In the case of the homozygous variant of the TMTHFR:677 risk allele, the effect of T_3 on MTHFR is absent, which leads to the most pronounced increase in the H_{cy} level in the blood. The combination of heterozygous variants of the risk alleles of the MTR:A2756G and MTHFR:C677T polymorphisms, recorded in 15.65% of cases, turned out to be the most effective in terms of the effect of H_{cy} on the hypothalamic-pituitary-thyroid axis and T_3 formation. In the combination of genotypes with the homozygous variant of the neutral alleles AMTR:2756 – CMTHFR:677, recorded among the examined children in 29.56% of cases, no correlations were found between hormones, H_{cy} and active forms of vitamins B_9 and B_{12}. *Conclusions.*

The increase in the H_{cy} level in the blood of most of the examined adolescents living near the ChEZ occurred under conditions of exposure to long-lived radionuclides on their bodies. Under certain genetic polymorphisms of FC, this contributed to the formation of T_3, the active form of thyroid hormones, and improved metabolism in the child's body. In this regard, transient hyperhomocysteinemia induced by environmental radiation exposure can be considered as an adaptation factor.

1. Introduction

The TG plays a huge role in human life.

The accident at the Chernobyl Nuclear Power Plant (ChNPP) in 1986 resulted in the release of a huge amount of radioactive substances into the surrounding space, including those affecting the thyroid gland [1, p. 39]. In the first days of the Chernobyl disaster, the greatest danger to the population was ^{131}I, whose half-life is 8 days [2, p. 13].

This radionuclide was incorporated by the thyroid cells of adults and children in the case of iodine deficiency.

However, the thyroid gland is also capable of intensively incorporating ^{137}Cs [3, p. 489], the half-life of which is about 30 years.

Throughout all the post-accident Chernobyl years, this radionuclide penetrated through the food chain and with air masses into the bodies of millions of people around the world.

The greatest risk of negative impact on the body of this and other long-lived radioactive elements exists for people living near the ChEZ.

During the implementation in 2014-2017 in Ukraine of the European Commission project “Health and Ecology Programs around the Chernobyl Exclusion Zone: Development, Training and Coordination of Health-Related Projects” jointly with the project of the Regional Council of Rhone-Alpes (France), in a group of children living near the ChEZ, in 35.5% of cases, thyroid hormone production disorders were detected, and in 5.6% of cases, structural changes in TG [4, p. 264].

In the blood of most of these children, an elevated level of the sulfur-containing amino acid H_{cy} was detected [5, p. 31].

This amino acid is the main intermediate in the metabolic cycles of methionine.

Regulation of H_{cy} and internal methionine metabolism is largely associated with enzymes of the FC and the cycle of transsulfuration reactions [5, p. 32].

Genetic polymorphisms affecting the activity of these enzymes have been identified [5, p. 37].

In adults, elevated levels of H_{cy} in the blood, or hyperhomocysteinemia, were recorded in the event of severe cardiovascular and nervous system diseases, cancer, and pregnancy pathology [6, p. 270].

Among the child population, hyperhomocysteinemia was much less common, and therefore there is a need to determine the cause of this condition in a large number of children living in the territory affected by the Chernobyl accident, in conditions of constant contact with radioactive elements.

The study of the relationship between metabolic cycles involving thyroid hormones and H_{cy} under conditions of exposure to environmental radiation is relevant from a scientific and practical point of view.

In this case, determining the role of FC genes in the regulation of metabolic processes associated with thyroid hormones will be of great importance.

The purpose of the study was to determine the involvement of FC genes in the regulation of thyroid hormonogenesis in children living near the ChEZ.

2. Material and methods

The material for the analytical study was the results of genetic and laboratory testing of 690 children living near the ChEZ, in the Kyiv region of Ukraine, contaminated with radioactive elements due to the Chernobyl accident [5, 120,121; 7, p. 49, 50, 51].

An assessment was made of the correlations between the indicators reflecting the exchange of H_{cy} and thyroid hormones, taking into account the genes that control the functioning of the FC, in groups of children from families permanently residing near the ChEZ.

In the morning, on an empty stomach, blood was taken from the cubital vein of children from the Ivankovsky and Polesie districts. The blood samples were tested in agreement with the children's parents in a laboratory certified according to the quality standards of the European Union.

The H_{cy} level in the blood was determined in all children, and the genetic system of the FC was also examined.

The H_{cy} level in the blood was determined using the immunochemical method with chemiluminescent detection (ECLIA). Analyzer and test system: Architect 1000 (ABBOT Diagnostics (USA).

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

The genetic study of the FC included the determination of allelic variants of the MTHFR:C677T polymorphism, affecting the activity of methylenetetrahydrofolate reductase (MTHFR) and the MTR: A2756G polymorphism associated with B_{12} methionine synthase (MS).

The method used was: PCR in Real-time mode. Analyzer and test system Detecting amplifier "DT-96"; "DNA-Technology" (Russia).

In 178 children from the Ivankovsky district, the content of thyroid-stimulating hormone of the TSH, free T_4, free T_3, vitamins B_9, B_{12} and B_6 were determined in the blood taken.

TSH, T_4 and T_3 were determined using an immunochemical method with electrochemiluminescent detection (ECLIA). Analyzer and test system: Cobas 6000, Roche Diagnostics (Switzerland).

Vitamin B_9 was determined using an immunochemical method with electrochemiluminescent detection (ECLIA). Analyzer and test system: Cobas e411; Roche Diagnostics (Switzerland).

Vitamin B_{12} – holotranscobalamin (active vitamin B_{12}) was determined using an immunochemical method with chemiluminescent detection (CLIA). Analyzer and test system: Architect 1000 (Abbott Diagnostics), USA.

Vitamin B_6 (HPLC) was determined using the high-performance liquid chromatography method. Analyzer and test system: HPLC-System 1100, Agilent with fluorescence detection; Recipe complete Kit (Germany).

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

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

To compare relative indicators, Student's t-test was used. The critical level of reliability of the null statistical hypothesis (p) was taken as 0.05.

The relationship between the H_{cy}, TSH, T_4, T_3, B_9, B_{12}, B_6 indicators and the T_3/T_4 index was determined using the Spearman's 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.

3. Research results and their discussion

In the examined group of children, the proportion of cases with a homozygous variant of the AMTR:2756 neutral allele (subgroup No. 4) is significantly greater than the proportion of cases in which the GMTR: 2756 risk allele (subgroup No. 1) was present.

At the same time, the proportion of cases with the homozygous variant of the CMTHFR: 677 neutral allele (subgroup No. 8) is less than the proportion of cases with the TMTHFR: 677 risk allele (subgroup No. 5).

The variant of the combination of neutral alleles of the indicated polymorphisms is more common than the variant of the combination of their risk alleles (Table 1).

In genotypes including the GMTR:2756 allele (Figure 1), a decrease in MS activity leads to a disruption of the H_{cy} methylation process.

Under the influence of a high H_{cy} level in the blood, activation of TSH synthesis occurs, stimulating the process of T_3 formation in peripheral tissues.

In addition, H_{cy} is utilized in the cycle of transsulfuration reactions with the formation of cysteine, which is a stimulating factor for deiodinase [8, p. 33].

T_3, formed as a result of T_4 deiodination, interacts with MTHFR, resulting in increased synthesis of 5-MTHF, as evidenced by the direct T_3-B_9 relationship.

In the subgroup including only the heterozygous variant of the GMTR:2756 allele (Figure 2), the role of TSH in the process of T_4 deiodination (an inverse TSH-T_4 association) is even more pronounced.

Table 1

The proportion of hyperhomocysteinemia cases in genetic subgroups of children

N	Main genotype	Number of children in a subgroup		Number of cases of hyperhomocysteinemia	
		n^1	$\%^1$	n^2	$\%^2$
1	A/G, G/GMTR: 2756	263	38.12	160	60.84
2	A/GMTR: 2756	226	32.76	137	60.62
3	G/GMTR: 2756	37	5.36	23	62.16
4	A/AMTR: 2756	427	61.88	271	63.47
5	C/T, T/TMTHFR: 677	370	53.62	244	65.95
6	C/TMTHFR: 677	311	45.07	199	63.99
7	T/TMTHFR: 677	59	8.55	45	76.27
8	C/CMTHFR: 677	320	46.38	187	58.44
9	A/AMTR:2756-C/CMTHFR:677	204	29.56	120	58.82
10	A/GMTR:2756-C/TMTHFR:677	108	15.65	69	63.89

Note. N is the subgroup number; n^1 is the number of children in the subgroup; $\%^1$ is the proportion in the total group of children; n^2 is the number of cases of hyperhomocysteinemia; $\%^2$ is the proportion in the subgroup.

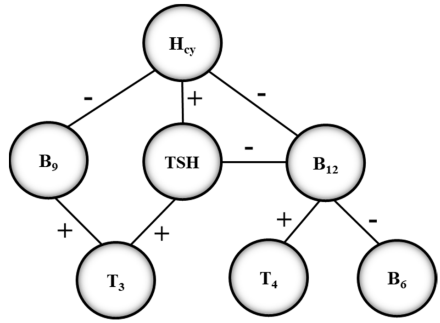

Figure 1. Correlation links in the subgroup with genotypes including the GMTR:2756 allele

In the case of the homozygous variant of the GMTR:2756 allele (Figure 3), a stimulating effect of high concentrations of H_{cy} in the blood on enzymes of the transsulfuration reaction cycle was noted –

a direct H_{cy}-B_6 association, as well as stimulation of T_3 formation of 5-MTHF – a direct T_3-B_9 association (Table 2).

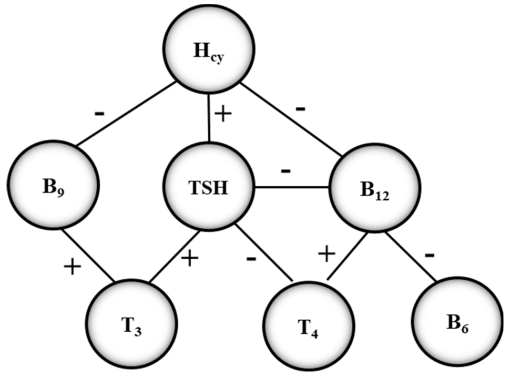

Figure 2. Correlation links in the subgroup with the A/GMTR:2756 genotype

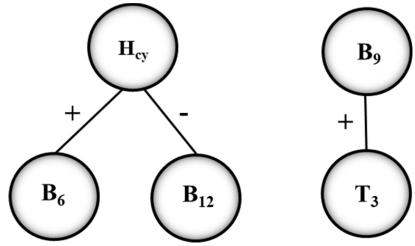

Figure 3. Correlation relationships in the subgroup with the G/G MTR:2756 genotype

However, 5-MTHF cannot affect the H_{cy} methylation process, since MS functioning is impaired.

The result is an excess of 5-MTHF and T_3 in the blood, which is typical for hyperthyroidism. At the same time, the thyroid gland does not produce prohormone T_4 in increased quantities.

In the subgroup with the main A/AMTR: 2756 genotype (Figure 4), the combination of inverse B_9-H_{cy} and B_{12}-H_{cy} associations reflects the

importance of vitamins B_9 and B_{12} for H_{cy} methylation and the formation of internal Met.

The direct connection B_9-B_{12} is an illustration of the process of transferring a methyl group from B_9 to B_{12}.

Vitamins B_9 and B_{12} maintain the concentration of T_4 at a physiological level, as evidenced by the direct connections between these metabolites. TSH has a stimulating effect on the process of T_4 deiodination and the formation of T_3 (a direct TSH-T_3 association).

Table 2

Correlations in the subgroup of children with the G/G MTR:2756 genotype

Correlation coefficient, significance p	Parameters		
	B_{12}-H_{cy}	H_{cy}-B_6	T_3/T_4-B_9
Spearman's	- 0.918**	0.724*	0.609*
Sign. (2-tailed)	0.0001	0.012	0.047
N	11	11	11

Note. * – correlation is significant at the 0.05 level (2-tailed); ** – correlation is significant at the 0.01 level (2-tailed).

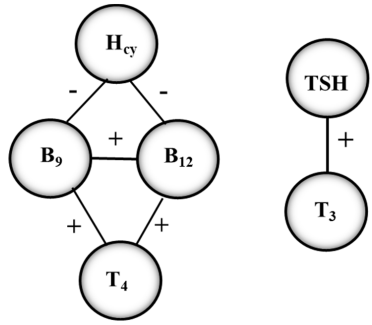

Figure 4. Correlation links in the subgroup with the A/AMTR:2756 genotype

In genotypes that include only the TMTHFR:677 allele (Figure 5), a deficiency of active forms of vitamin B_{12} occurs, the cause of which is reduced MTHFR activity, leading to a decrease in the formation of 5-MTHF.

As a result, the level of H_{cy} and TSH in the blood increases, which is a stimulating factor for the process of T_4 deiodination and T_3 formation in peripheral tissues.

However, in this case, H_{cy} is not utilized, or is poorly utilized, in the cycle of transsulfuration reactions.

Vitamins B_9 and B_{12} have direct connections with T_4, indicating their participation in the metabolism of thyroid hormones.

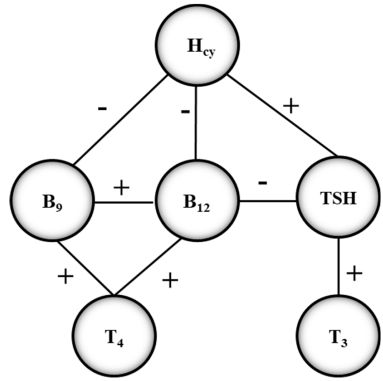

Figure 5. Correlation links in the subgroup with genotypes, including cases with the TMTHFR:677 allele

In the case of the heterozygous variant of the TMTHFR:677 allele, a direct T_3-B_9 association was revealed (Figure 6), indicating the stimulating effect of T_3 on MTHFR, resulting in an increase in the formation of the active form of vitamin B_9 – 5-MTHF.

In the case of the homozygous variant of the TMTHFR:677 allele (Figure 7), there is a pronounced deficiency in the production of 5-MTHF, which leads to an increase in the concentration of H_{cy} in the blood (Table 3).

As a result, the synthesis of TSH, which has a stimulating effect on the process of T_4 deiodination and the formation of T_3, also increases in the cells of the adenohypophysis.

However, due to the homozygous variant of the TMTHFR:677 allele, T_3 cannot affect MTHFR and stimulate the formation of 5-MTHF, as evidenced by the lack of a direct correlation between T_3 and B_9.

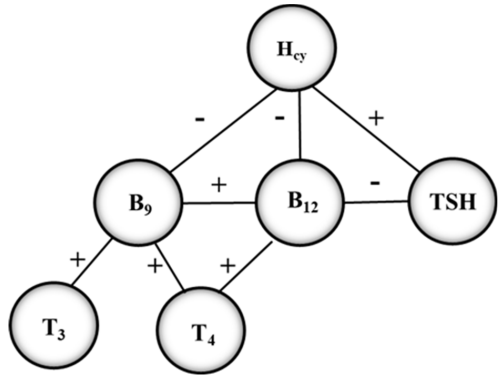

Figure 6. Correlation links in the subgroup with the C/TMTHFR:677 genotype

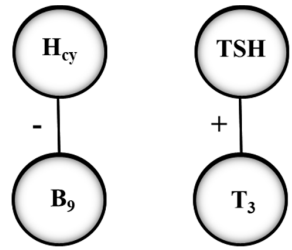

Figure 7. Correlation links in the subgroup with the T/TMTHFR:677 genotype

Table 3

Correlations in the subgroup of children with the T/TMTHFR:677 genotype

Correlation coefficient, significance p	Parameters	
	B_9-H_{cy}	TSH-T_3
Spearman's	- 0.674**	0.693**
Sign. (2-tailed)	0.006	0.004
N	15	15

Note. * – correlation is significant at the 0.05 level (2-tailed); ** – correlation is significant at the 0.01 level (2-tailed).

In the case of the homozygous variant of the CMTHFR:677 neutral allele (Figure 8), correlation links were identified reflecting the influence of vitamins B_9 and B_{12} on the process of H_{cy} methylation, as well as the stimulating effect of H_{cy} and TSH on the process of T_4 deiodination and T_3 formation.

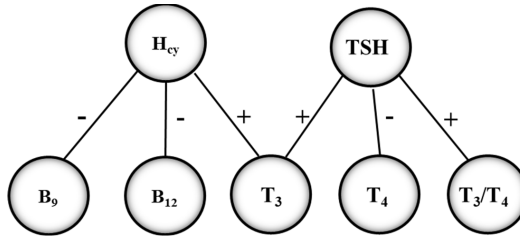

Figure 8. Correlation links in the subgroup with the C/CMTHFR:677 genotype

The combination of A/GMTR:2756 – C/TMTHFR:677 genotypes (Figure 9) in the analyzed group of children occurred in 15.65% of cases (Table 1).

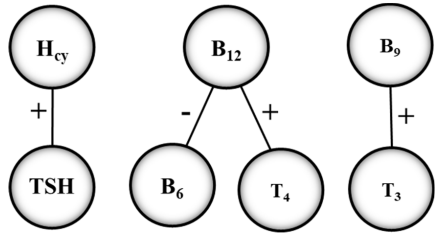

Figure 9. Correlation links in the subgroup with the combination of A/GMTR:2756 – C/TMTHFR:677 genotypes

In this case, the participation of H_{cy} in the activation of TSH, the effect of vitamin B_{12} on the transsulfuration cycle and the process of T_4 deiodination were revealed. T_3 has a stimulating effect on MTHFR and the process of 5-MTHF formation, as evidenced by the direct T_3-B_9 relationship (Table 4).

Table 4

Correlations in the subgroup of children with a combination of A/GMTR:2756 - C/TMTHFR:677 genotypes

Correlation coefficient, significance p	Parameters			
	B_{12}-B_6	B_{12}-T_4	H_{cy}-TSH	T_3-B_9
Spearman's	0.429*	0.442*	0.444*	0.488**
Sign. (2-tailed)	0.026	0.021	0.020	0.010
N	27	27	27	27

Note. * – correlation is significant at the 0.05 level (2-tailed); ** – correlation is significant at the 0.01 level (2-tailed).

The combination of genotypes including only neutral alleles – A/AMTR:2756 – C/CMTHFR:677 (Figure 10) in the analyzed group of children was identified in 29.56% of cases (Table 1).

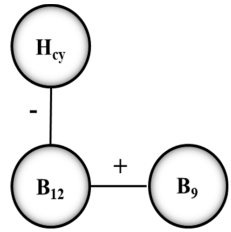

Figure 10. Correlation links in the subgroup with the combination A/AMTR:2756-C/CMTHFR:677 of genotypes

The B_9-B_{12} and B_{12}-H_{cy} correlations reflect the influence of MTHFR and MS on the H_{cy} methylation process (Table 5).

Correlations involving TSH and thyroid hormones were absent in this subgroup.

In the absence of serious mutations in the main enzyme systems of the FC, an increase in the H_{cy} level in the blood may be associated with environmental radiation exposure to mitochondrial structures responsible for cellular energetics.

It should be noted that the examined children living near the ChEZ experienced constant radiation exposure.

Radionuclides that were distributed after the Chernobyl accident in the environment entered their bodies through food chains.

The specific activity of ^{137}Cs in the children's bodies was recorded in the range of 1.1-199.0 Bq/kg.

Incorporation of ^{137}Cs contributed to the occurrence of pathological changes in vital organs and systems of the child's body, including the cardiovascular system.

In particular, excess of serum aspartate aminotransferase (AST) values of the reference range was recorded in 37.5% of cases, which indicates damage to the mitochondria of cardiomyocytes.

Table 5

Correlations in the subgroup of children with a combination of genotypes A/AMTR:2756 - C/CMTHFR:677

Correlation coefficient, significance p	Parameters	
	B_9-B_{12}	B_{12}-H_{cy}
Spearman's	0.331*	0.536**
Sign. (2-tailed)	0.027	0.0001
N	45	45

Note. * – correlation is significant at the 0.05 level (2-tailed); ** – correlation is significant at the 0.01 level (2-tailed).

At the same time, a direct correlation was established between the values of the specific activity of ^{137}Cs in the body and the values reflecting the activity of serum AST, as well as the values of the de Ritis coefficient (Table 6) [5, p. 28, 29].

The conducted study shows that even more than 30 years after the Chernobyl accident, the external radiation factor affects the metabolism in the body of children of the second Chernobyl generation.

The incorporation of ^{137}Cs into the body leads to a disruption of cellular energy, and, as a consequence, regulatory processes in metabolic cycles.

At the same time, the activity of the main enzymes of the FC is suppressed and the formation of active forms of vitamins B_9 and B_{12} is reduced.

The level of H_{cy} in the blood increases. At the same time, the genetic factor is not of primary importance.

This is also evidenced by the fact that the occurrence of hyperhomocysteinemia in the subgroup of children with the absence of risk alleles of the MTR: A2756G and MTHFR:C677T polymorphisms in the genome was recorded in 58.82% of cases (Table 1).

Table 6

Correlation relationships between the values of specific activity of ^{137}Cs (Bq/kg) and the activity of transaminases in the blood serum of the examined children

Parameter	Correlation coefficient, r_{xy}	Parameters		
		AST	ALT	AST/ALT
Specific activity of ^{137}Cs, Bq/kg	Spearman's	0.295**	- 0.027	0.285**
	Знач. (2-х сторонняя), p	0.0001	0.328	0.0001
	n	1320	1320	1320

Note. n – number of cases; * – correlation is significant at the 0.05 level (2-tailed); ** – correlation is significant at the 0.01 level (2-tailed). AST – aspartate aminotransferase; ALT – alanine aminotransferase; AST/ALT – de Ritis ratio.

The proportion of hyperhomocysteinemia cases in the considered genetic subgroups of children exceeded 50% level, and, at the same time, had no significant differences.

Only in the subgroup with the main T/TMTHFR: 677 genotype the value of this indicator was higher (Table 1).

With an increase in the level of H_{cy} in the blood, the hypothalamic-pituitary system is activated, as a result of which the synthesis of TSH increases.

In addition, in the body of children whose genome contains the GMTR:2756 allele, H_{cy} utilization occurs in the cycle of transsulfuration reactions.

As a result of the above processes in peripheral tissues (liver, kidneys), T_4 deiodination and T_3 formation occur.

T_3 affects mitochondria [9, p. 4], while it is able to stimulate the activity of FC enzymes, primarily MTHFR, which is involved in the formation of 5-MTHFR [8, p. 34; 10, p. 16;].

The consequence of this is an increase in the process of H_{cy} methylation.

This is confirmed by the fact that with hyperthyroidism, the content of folic acid in the blood increases and the level of H_{cy} decreases [11, p. 122].

Thus, the formation of T_3 as a result of changes in the process of H_{cy} methylation plays a protective role for the body in unfavorable environmental conditions.

Improvement of energy processes under the influence of T_3 has a positive effect not only on H_{cy} metabolism, but also on other metabolic cycles.

The increase in the H_{cy} level in the blood of a large number of children living in areas affected by the Chernobyl accident can be considered as a factor in the correction of metabolism under the influence of the radiation factor.

Thus, transient hyperhomocysteinemia, which occurs in children as a result of radiation exposure, helps to improve their metabolism. At the same time, it can also be a marker of this effect.

4. Conclusions

In the group of children permanently residing near the ChEZ, the proportion of hyperhomocysteinemia cases (H_{cy} level in the blood > 10.0 μmol/l) exceeded 50%.

Correlation links between H_{cy} indicators, vitamins B_9, B_{12}, TSH, T_4 and T_3 allow us to determine the participation of FC genes in the regulation of thyroid hormonogenesis in children living near the ChEZ.

In the subgroup, including cases with the GMTR:2756 allele in the genome, a decrease in MS activity is recorded, leading to a disruption in the H_{cy} methylation process and activation of TSH synthesis, stimulating the process of T_4 deiodination and T_3 formation in peripheral tissues.

H_{cy} is also utilized in the cycle of transsulfuration reactions with the formation of cysteine, which is a stimulating factor for T_4 deiodination and T_3 formation.

A distinctive feature of the presence of the GMTR:2756 allele in the genome is the effect of T_3 on MTHFR, resulting in increased synthesis of 5-MTHF, as evidenced by the direct T_3-B_9 relationship.

Children – carriers of the TMTHFR:677 allele are predisposed to a decrease in the formation of the active form of vitamin B_9 – 5 MTHF,

resulting in a decrease in the intensity of the H_{cy} methylation process and a decrease in the formation of internal methionine.

The consequence of this is the activation of the synthesis of TSH, stimulating the process of T_4 deiodination and the formation of T_3.

In the case of a heterozygous variant of the TMTHFR:677 allele, T_3 has a stimulating effect on MTHFR, resulting in an increase in the formation of 5-MTHF.

With a homozygous variant of the TMTHFR:677 risk allele, the effect of T_3 on MTHFR is absent, which leads to the most pronounced increase in the level of H_{cy} in the blood.

The combination of heterozygous variants of risk alleles of MTR: A2756G and MTHFR:C677T polymorphisms, recorded in 15.65% of cases, turned out to be the most effective in terms of the effect of H_{cy} on the hypothalamic-pituitary-thyroid axis and the formation of T_3.

With a combination of genotypes with a homozygous variant of neutral alleles - AMTR:2756 - CMTHFR:677, recorded among children living near the ChEZ, in 29.56% of cases, no correlation was found between hormones, H_{cy} and active forms of vitamins B_9 and B_{12}.

The increase in the H_{cy} level in the blood of most of the examined adolescents living near the ChEZ occurred under conditions of exposure to long-lived radionuclides on their bodies.

Under certain genetic polymorphisms of FC, this contributed to the formation of T_3 – the active form of thyroid hormones and improved metabolism in the child's body.

In this regard, transient hyperhomocysteinemia induced by environmental radiation exposure can be considered as an adaptation factor.

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