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PARTICIPATION OF HOMOCYSTEINE IN THE REGULATION OF MINERAL METABOLISM IN CHILDREN LIVING NEAR THE CHORNOBYL EXCLUSION ZONE

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- **THE AIM** of the study is to determine the participation of homocysteine (H_{cy}) in the regulation of calcium-phosphorus metabolism in children living near the Chornobyl Exclusion Zone (ChEZ).
- **MATERIALS AND METHODS.** Using the statistical processing program IBM SPSS Statistics 22 (USA), the results of laboratory, instrumental and genetic examination of 956 children aged 12–18 years who permanently reside near the ChEZ were assessed. The parameters reflecting the specific activity of ^{137}Cs radionuclides in the body, the content of H_{cy}, calcium (Ca), inorganic phosphorus (P), ionized calcium (Ca^{2+}), and parathyroid hormone (PTH) in the blood were analyzed. To determine the degree of physical development of adolescents, the Rohrer mass-height index (IR) was calculated — the quotient of dividing body weight in kilograms by body length in meters cubed.
- **RESULTS.** ^{137}Cs was registered in the body of all examined children, in the group of boys its values were from 0.78 to 95.11 Bq/kg, in the group of girls — from 1.06 to 26.96 Bq/kg. In the analyzed groups of children, an inverse correlation was established between the specific activity of ^{137}Cs radionuclides in the body and the content of Ca in the blood, as well as the IR values, reflecting the ratio of body weight to its length. Hyperhomocysteinemia was registered in most genetic subgroups of the folate cycle. The highest statistically significant proportion of hyperhomocysteinemia cases was found in subgroups with the main genotypes G/G MTR:2756 and T/TMTHFR:677. Based on a comprehensive study of the results of the correlation analysis of the parameters under study, the mechanism of participation of H_{cy}, folate cycle genes and environmental factors in the regulation of Ca–P metabolism in children is presented.
- **CONCLUSIONS.** Incorporation of ^{137}Cs into the body of people living in areas affected by the Chornobyl accident causes energy deficiency in the cells of vital organs, leading to a decrease in the intensity of anabolic processes, impaired methylation of H_{cy} and changes in Ca–P metabolism. Impaired physical development of the examined children is directly related to the content of Ca in their blood, as evidenced by the direct correlation between Ca and IR. Energy deficiency associated with the incorporation of ^{137}Cs into the body, as well as mutations of the FC genes, are the causes of hyperhomocysteinemia — an increased content of the sulfur-containing amino acid H_{cy} in the blood of children living in settlements located near the ChEZ. H_{cy}, by affecting the skeletal system, compensates for the deficiency of Ca in the blood induced by ^{137}Cs. An increase in the Ca content in the blood with hyperhomocysteinemia has a negative effect on the processes of PTH formation and, therefore, creates conditions for the disruption of P excretion from the body through the kidneys. However, in most genetic subgroups, a direct correlation between P and PTH was recorded, illustrating the ability of the child's body to stimulate the excretion of P with urine when its concentration in the blood increases. Thus, transient hyperhomocysteinemia is an element of the body's adaptation system to environmental radiation exposure. In subgroups of children with risk alleles of genetic polymorphisms MTHFR:C677T and MTR:A2756G in the genome, there was no direct correlation between P and PTH, which indicates the possibility of formation of calcium-phosphorus complexes in the blood and their deposition in soft tissues and vessel walls.

- **KEYWORDS:** *Chornobyl Exclusion Zone, homocysteine, genetic polymorphisms of the folate cycle, ^{137}Cs, mineral metabolism, children.*

УЧАСТЬ ГОМОЦИСТЕЇНУ В РЕГУЛЯЦІЇ МІНЕРАЛЬНОГО ОБМІНУ У ДІТЕЙ, ЯКІ ПРОЖИВАЮТЬ ПОБЛИЗУ ЧОРНОБИЛЬСЬКОЇ ЗОНИ ВІДЧУЖЕННЯ

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- **МЕТА ДОСЛІДЖЕННЯ** — визначення участі гомоцистеїну (H_{cy}) в регуляції кальцій-фосфорного обміну у дітей, які проживають поблизу Чорнобильської зони відчуження (ЧЗВ).
- **МАТЕРІАЛИ ТА МЕТОДИ.** За допомогою програми статистичної обробки IBM SPSS Statistics 22 (США) було оцінено результати лабораторного, інструментального та генетичного обстеження 956 дітей віком 12–18 років, які постійно мешкають поблизу ЧЗВ. Аналізувалися показники, що відображають питому активність радіонуклідів ^{137}Cs в організмі, вміст у крові H_{cy}, кальцію (Ca), неорганічного фосфору (P), кальцію іонізованого (Ca^{2+}), паратиреоїдного гормону (ПТГ). Для визначення ступеня фізичного розвитку підлітків розраховувався масо-зростовий індекс Рорера (IR) — частку від ділення маси тіла в кілограмах на довжину тіла в метрах, зведену в куб.
- **РЕЗУЛЬТАТИ.** ^{137}Cs реєструвався в організмі всіх обстежених дітей, у групі хлопчиків його значення було в межах від 0,78 до 95,11 Бк/кг, у групі дівчаток — від 1,06 до 26,96 Бк/кг. У групах дітей, які

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аналізувались, встановлена зворотна кореляційна залежність між питомою активністю радіонуклідів ^{137}Cs в організмі та вмістом Са в крові, а також значеннями IR, що відображає відношення маси тіла щодо його довжини. Гіпергомоцистеїнемія була зареєстрована у більшості генетичних підгруп фолатного циклу. Найбільша статистично значима питома вага випадків гіпергомоцистеїнемії виявлена у підгрупах з основними генотипами G/G MTR:2756 та T/TMTHFR:677. На підставі всебічного вивчення результатів кореляційного аналізу параметрів, що вивчалися, представлений механізм участі H_{cy}, генів фолатного циклу і зовнішньосередовищного фактора в регуляції Са–Р обміну у дітей.

ВИСНОВКИ. Інкорпорація ^{137}Cs в організм осіб, які проживають у районах, що постраждали від аварії на ЧАЕС, викликає енергодефіцит у клітинах життєво важливих органів. Це призводить до зниження інтенсивності анаболічних процесів, порушення метилювання H_{cy} та зміни Са–Р обміну. Порушення фізичного розвитку обстежених дітей прямо пов'язане із вмістом в їх крові Са, про що свідчить прямий кореляційний зв'язок Са–IR. Енергодефіцит, пов'язаний з інкорпорацією ^{137}Cs в організм, а також, мутації генів фолатного циклу, є причинами гіпергомоцистеїнемії — підвищеного вмісту в крові сірковмісної амінокислоти H_{cy} у дітей, які мешкають в населених пунктах, розташованих поблизу ЧЗВ. H_{cy}, впливом на кісткову систему, поповнює дефіцит Са крові, індукований ^{137}Cs. Збільшення вмісту Са у крові при гипергомоцистеинемии негативно впливає на процеси утворення ПТГ і, отже, створює умови порушення виведення Р з організму через нирки. Однак, в більшості генетичних підгруп реєструвався прямий кореляційний зв'язок Р-ПТГ, що ілюструє здатність дитячого організму стимулювати виведення Р із сечею у разі підвищення його концентрації в крові. Таким чином, транзиторна гіпергомоцистеїнемія є елементом системи адаптації організму до зовнішнього радіаційного впливу. У підгрупах дітей з алелями ризику генетичних поліморфізмів MTHFR:C677T та MTR:A2756G у геномі, прямий кореляційний зв'язок між Р та ПТГ був відсутній, що свідчить про можливість утворення в крові кальцій-фосфорних комплексів, та відкладення їх у м'яких тканинах та стінках.

КЛЮЧОВІ СЛОВА: *Чорнобильська зона відчуження, гомоцистеїн, генетичні поліморфізми фолатного циклу, ^{137}Cs, мінеральний обмін, діти.*

Residents of settlements located near the Chornobyl exclusion zone (ChEZ) are in conditions of constant radiation exposure associated with environmental pollution with ^{137}Cs and ^{90}Sr [1].

The implementation of humanitarian projects of the European Commission and the Regional Council of Rhone-Alpes (France) in this area in 2013–2017 made it possible to identify hyperhomocysteinemia in the majority of the examined adolescents — an increased content of the sulfur-containing amino acid homocysteine (H_{cy}) in the blood [2].

Analytical and statistical studies conducted during the mentioned projects established a connection between hyperhomocysteinemia in children and genetic polymorphisms of the folate cycle (FC) [1], forest fires in the ChEZ [3], and revealed the participation of H_{cy} in the regulation of thyroid hormone metabolism [4].

In adults, hyperhomocysteinemia is associated with a number of serious diseases [1], including osteoporosis, leading to bone fractures [4].

In this regard, it is important to determine the role of H_{cy} in mineral metabolism processes in children whose physical development takes place under conditions of constant radiation exposure associated with the accident at the Chornobyl Nuclear Power Plant (ChNPP).

The purpose of the study is to determine the participation of H_{cy} in the regulation of calcium-phosphorus metabolism in children living near the ChEZ.

MATERIAL AND METHODS

The study was carried out in 2013–2017 within the framework of the European Commission projects «Health and Ecological Programmes around the Chornobyl Exclusion Zone: Development, training and coordination of health-related projects» and the Regional Council of Rhone-Alpes (France).

A total of 956 children aged 12–18 years living in settlements near the ChEZ, in the territory contaminated with radionuclides ^{137}Cs and ^{90}Sr [5], were examined.

Laboratory, instrumental and genetic examination of children, as well as determination of the content of ^{137}Cs in their bodies, were carried out in compliance with the rules of bioethics and signing of parental consent protocols.

Blood sampling, in order to determine biochemical parameters and genetic polymorphisms of FC, was performed from the cubital vein in the morning, on an empty stomach.

The blood of the examined children was tested for calcium (Ca), inorganic phosphorus (P) [6], ionized calcium (Ca^{2+}), parathyroid hormone (PTH), and H_{cy} [7].

Reference values for Ca were 2.1–2.55 mmol/l, Ca^{2+} — 1.16–1.32 mmol/l, P — 0.90–1.65 mmol/l, PTH — 15.0–65.0 pg/ml.

Exceeding the concentration of H_{cy} 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 C677T and A1298C of the MTHFR gene (synthesis of the enzyme methylenetetrahydrofolate reductase), A2756G of the MTR gene (synthesis of the enzyme B_{12}-dependent methionine synthase), A66G of the MTRR gene (synthesis of the enzyme methionine synthase reductase). In this case, the method used was: PCR in Real-time mode.

To assess the physical development (PD) of children, the Rohrer mass-height index (IR) was used — the quotient of body weight in kilograms divided by body length in meters, raised to a cube.

In accordance with the IR values, the following are distinguished: «1» — disharmonious (low) PD, IR<10.7 kg/m^3; «2» — harmonious PD, IR in the range ≤13.7 and ≥10.7 kg/m^3; «3» — disharmonious (high) PD, IR>13.7 kg/m^3 [8].

The specific activity of ^{137}Cs in the body of children was determined over 10 minutes, on a 3-detector spectrometer of human radiation «SICH-AKP-3» (OOO NPP «ATOMKOMPLEKSPRIBOR», Ukraine). Automatic processing of spectra with calculation of specific activity of radioactive elements was carried out using the software of the device «AKWin".

Statistical processing of the obtained results was carried out using the IBM SPSS Statistics 22 program (USA). For the analyzed indicators median (Me), interquartile range (IQR), minimum and maximum values of parameters, percentiles were calculated. The hypothesis about the type of distributions was tested (Kolmogorov–Smirnov criterion).

The statistical significance of the indicators was assessed by determining the significance level p using a statistical program.

The relationship between the analyzed indicators was determined using the Spearman rank correlation coefficient (r_{xy}). 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

^{137}Cs was registered in the body of all examined children, in the group of boys its values were from 0.78 to 95.11 Bq/kg, in the group of girls — from 1.06 to 26.96 Bq/kg.

IR had values in the group of boys from 9.0 to 30.2 kg/m^3, in the group of girls from 8.5 to 23.0 kg/m^3.

The proportion of cases with the level of Ca in the blood >2.55 mmol/l in all analyzed groups was significantly higher than the proportion of cases with the level of Ca in the blood in the range of 2.1–2.55 mmol/l (*Table 1*).

Only one girl had the level of Ca in the blood below 2.10 mmol/l (*Table 1*).

In the analyzed age groups, the most common cases were with the level of P in the blood in the range of 0.90–1.65 mmol/l. However, it should be noted that a significant number of children had blood P levels below 0.90 mmol/l (*Table 2*).

Only 20 children out of 956 had blood P levels above 1.65 mmol/l (*Table 2*).

Correlation analysis revealed an inverse relationship between ^{137}Cs and Ca in the group of boys aged 12 and 13 years, and in the group of girls aged 13 years (*Table 3*).

At the same time, in the groups of boys and girls, an inverse correlation was recorded between ^{137}Cs and IR (Table 3).

A direct correlation was found between the indicators reflecting the content of Ca and P in the blood in the groups of boys aged 13 years and girls aged 12 and 13 years (*Table 3*).

In most genetic subgroups of children from the Polesie region, the proportion of hyperhomocysteinemia cases was > 50% (*Table 4*).

The highest, statistically significant, proportion of hyperhomocysteinemia cases was recorded in subgroups with the main genotypes G/G MTR:2756 and T/TMTHFR:677, which significantly disrupt the functioning of methionine synthase and methylenetetrahydrofolate reductase (*Table 4*) [7].

In the general group and a number of genetic subgroups, a combination of direct correlations

Table 1. **Statistical indicators reflecting the content of Ca in the blood of the examined children**

Age groups	N	Blood Ca level					
		> 2.55 mmol/l		2.1–2.55 mmol/l		<2.10 mmol/l	
		abs.	%	abs.	%	abs.	%
Boys aged 12–18 years	444	295	66.4	149	33.6	0	0
Girls aged 12–18 years	512	327	63.9	184	35.9	1	0.2
Boys 12 years old	88	63	71.6	25	28.4	0	0
Girls 12 years old	98	67	68.4	31	31.6	0	0
Boys 13 years old	101	64	63.4	37	36.6	0	0
Girls 13 years old	102	62	60.8	39	38.2	1	1.0

Note. N is the number of children in a group.

Table 2. **Statistical indicators reflecting the content of P in the blood of examined children**

Age groups	N	Blood P level					
		>1.65 mmol/l		0.90–1.65 mmol/l		<0.90 mmol/l	
		abs.	%	abs.	%	abs.	%
Boys aged 12–18 years	444	14	3.2	278	62.6	152	34.2
Girls aged 12–18 years	512	6	1.2	228	44.5	278	54.3
Boys 12 years old	88	6	6.8	63	71.6	19	21.6
Girls 12 years old	98	4	4.1	67	68.4	27	27.5
Boys 13 years old	101	5	5.0	74	73.3	22	21.7
Girls 13 years old	102	1	1.0	56	54.9	45	44.1

Note. N is the number of children in a group.

Table 3. **Results of correlation analysis in groups of boys and girls living near the ChEZ**

Age groups	Correlation coefficient	Correlations			
		^{137}Cs–Ca	^{137}Cs–IR	Ca–IR	Ca–P
Boys 12 years old	Spearman's	–0.277**	–0.564**	0.161	0.124
	Sign. (2-tailed), p	0.009	0.0001	0.133	0.248
	N	88	88	88	88
Girls 12 years old	Spearman's	–0.068	–0.591**	0.274**	0.231*
	Sign. (2-tailed), p	0.503	0.0001	0.006	0.022
	N	98	98	98	98
Boys 13 years old	Spearman's	–0.216*	–0.485**	0.079	0.296**
	Sign. (2-tailed), p	0.030	0.0001	0.431	0.003
	N	101	101	101	101
Girls 13 years old	Spearman's	–0.218*	–0.578**	0.049	0.313**
	Sign. (2-tailed), p	0.028	0.0001	0.628	0.001
	N	102	102	102	102

Note. * — correlation is significant at the 0.05 level (two-sided); ** — correlation is significant at the 0.01 level (two-sided); IR — Rohrer index; Ca — calcium; P — phosphorus.

Table 4. **The proportion of cases of hyperhomocysteinemia in genetic subgroups of children in the Polesie region [7]**

N_1	Genotype main	N_2	Number of cases H_{cy} >10.0 µmol/l	
			abs.	%
1	A/A MTR:2756	104	58	55.8
2	A/G MTR:2756	45	18	40.0
3	G/G MTR:2756	9	8	88.9
4	A/A MTHFR:1298	82	42	51.2
5	A/CMTHFR:1298	60	33	55.0
6	C/C MTHFR:1298	16	9	56.3
7	C/C MTHFR:677	79	34	43.0
8	C/T MTHFR:677	60	35	58.3
9	T/T MTHFR:677	19	15	79.0
10	A/AMTRR:66	32	12	37.5
11	A/G MTRR:66	72	37	51.4
12	G/G MTRR:66	54	35	64.8
General group		158	84	53.2

Note. N_1 is the subgroup number; N_2 is the number of cases in the subgroup.

of H_{cy}–Ca^{2+} and P-PTH was recorded (*Table 5*) [1]. In the subgroup with the main genotype T/TMTHFR:677, the most pronounced direct correlation between H_{cy} and Ca^{2+} was recorded compared to other subgroups, with no correlation between H_{cy} and PTH, P and PTH (*Table 5*) [1].

The strongest direct correlation P–PTH was recorded in subgroups with the absence of the GMTR:2756 allele in the genome — the A/AMTR:2756 genotype, as well as the TMTHFR:677 allele — the C/C MTHFR:677 and C/CMTHFR:1298 genotypes (*Table 5*).

Table 5. **Results of correlation analysis in genetic subgroups of children in the Polesie region [1]**

Genetic subgroup	Correlation coefficient	Parameters		
		H_{cy}–Ca^{2+}	H_{cy}–PTH	P–PTH
A/A MTR:2756	Spearman's	0.319**	0.025	0.482**
	Sign. (2-tailed), p	0.001	0.800	0.0001
	N	104	104	104
A/G MTR:2756	Spearman's	0.362*	–0.048	–0.234
	Sign. (2-tailed), p	0.014	0.755	0.121
	N	45	45	45
G/G MTR:2756	Spearman's	0.201	0.767*	0.150
	Sign. (2-tailed), p	0.604	0.016	0.700
	N	9	9	9
A/AMTHFR:1298	Spearman's	0.462**	0.020	0.280*
	Sign. (2-tailed), p	0.0001	0.858	0.011
	N	82	82	82
A/CMTHFR:1298	Spearman's	0.216	0.126	0.283*
	Sign. (2-tailed), p	0.097	0.338	0.029
	N	60	60	60
C/CMTHFR:1298	Spearman's	–0.192	–0.389	0.519*
	Sign. (2-tailed), p	0.476	0.137	0.039
	N	16	16	16
C/C MTHFR:677	Spearman's	0.169	0.099	0.411**
	Sign. (2-tailed), p	0.136	0.386	0.0001
	N	79	79	79
C/T MTHFR:677	Spearman's	0.399**	0.073	0.115
	Sign. (2-tailed), p	0.002	0.580	0.380
	N	60	60	60
T/T MTHFR:677	Spearman's	0.619**	0.326	0.394
	Sign. (2-tailed), p	0.005	0.173	0.095
	N	19	19	19
A/A MTRR:66	Spearman's	0.403*	0.123	0.405**
	Sign. (2-tailed), p	0.022	0.502	0.021
	N	32	32	32
A/G MTRR:66	Spearman's	0.319**	0.074	0.260*
	Sign. (2-tailed), p	0.006	0.537	0.027
	N	72	72	72
G/G MTRR:66	Spearman's	0.276*	0.067	0.270*
	Sign. (2-tailed), p	0.044	0.633	0.049
	N	54	54	54
General group	Spearman's	0.314**	0.013	0.301**
	Sign. (2-tailed), p	0.0001	0.869	0.0001
	N	158	158	158

Note. * — correlation is significant at the 0.05 level (two-sided); ** — correlation is significant at the 0.01 level (two-sided); H_{cy} — homocysteine; PTH — parathyroid hormone; Ca^{2+} — ionized calcium; P — phosphorus.

The correlation between Ca^{2+} and PTH was absent in the overall group and genetic subgroups. The correlation between H_{cy} and PTH was absent in most genetic subgroups, with the exception of the subgroup with the main genotype G/G MTR:2756, where it was inversely directed (*Table 5*).

It should be noted that in the subgroup with the main genotype T/TMTHFR:677, the value of the indicator reflecting the content of PTH in the blood is less than in most other subgroups (*Table 6*) [9].

The conducted studies indicate the presence of ^{137}Cs in the bodies of children living near the ChEZ many years after the Chornobyl accident.

Internal radiation exposure caused by the incorporation of ^{137}Cs causes an energy deficit in the child's body associated with damage to mitochondria and a decrease in ATP formation.

A marker of this condition, in particular, is an increase in the activity of serum aspartate aminotransferase (AST) in children from areas affected by the Chornobyl accident [1].

At the same time, in the cells of internal organs and skeletal muscles, there is a decrease in the intensity of anabolic processes, which is reflected in the inverse correlation relationship ^{137}Cs-IR (*Table 3*).

A direct relationship has been traced between the physical development of children and the content of Ca in the blood (Ca–IR).

Mitochondria are not only a producer of ATP, but also a spatial buffer of Ca^{2+}, regulating its concentration in the cell [10].

There is a certain rhythm of Ca^{2+} entry into mitochondria from the endoplasmic reticulum.

The dynamic interaction between mitochondria and the endoplasmic reticulum is a key aspect of Ca^{2+} homeostasis [11]. Its disruption suppresses mitochondrial metabolism [10].

The incorporation of ^{137}Cs into the cells of vital organs [12] disrupts the transport of Ca^{2+} through membrane structures, including its release into the intercellular space and blood, due to a decrease in the activity of Ca^{2+}–ATPase, which receives most of its energy from ATP hydrolysis.

Ca^{2+} is retained in the cells and its concentration in the blood decreases.

An illustration of this is the inverse correlation between the indicators reflecting the specific activity of ^{137}Cs and the concentration of Ca in the blood (*Table 3*). Thus, with an increase in the content of ^{137}Cs in the body of children, the level of Ca in their blood should decrease.

However, in the majority of children we examined, living in conditions of constant contact with ^{137}Cs radionuclides, an increase in the level of serum Ca above the established physiological limit was detected (*Table 1*).

This apparent contradiction is explained if we take into account the state of hyperhomocysteinemia recorded in a large number of children examined (*Table 4*).

The cause of the disruption of the H_{cy} methylation process and the occurrence of hyperhomocysteinemia is the same cellular energy deficiency that arose with the incorporation of ^{137}Cs radionuclides into the body of children.

Hyperhomocysteinemia contributed to an increase in the Ca content in the blood, as evidenced

Table 6. **Statistical characteristics in genetic subgroups of children in the Polesie region [9]**

Genetic subgroup	H_{cy}, μmol/l		PTH, pg/ml		Ca^{2+}, mmol/l	
	Me	IQR	Me	IQR	Me	IQR
A/A MTR:2756	10.26	8.39–13.56	35.00	26.03–44.40	1.26	1.22–1.31
A/G MTR:2756	9.37	7.75–10.95	34.20	28.60–41.90	1.24	1.21–1.30
G/G MTR:2756	11.13	10.17–12.32	35.60	30.65–48.80	1.24	1.21–1.31
A/A MTHFR:1298	10.14	7.99–13.04	34.85	29.18–42.15	1.26	1.21–1.30
A/CMTHFR:1298	10.19	9.01–13.19	35.00	25.18–44.40	1.26	1.22–1.31
C/C MTHFR:1298	10.31	7.99–12.69	36.40	24.75–45.93	1.24	1.21–1.28
C/C MTHFR:677	9.44	7.93–11.16	34.30	28.40–41.80	1.24	1.21–1.31
C/T MTHFR:677	10.24	8.42–13.18	35.60	28.73–45.60	1.26	1.21–1.30
T/T MTHFR:677	14.47	10.15–22.78	31.20	24.60–36.10	1.26	1.24–1.29
A/AMTRR:66	9.26	8.03–13.13	36.10	29.33–50.78	1.26	1.22–1.31
A/G MTRR:66	10.08	7.98–11.99	35.90	29.50–44.95	1.26	1.22–1.30
G/G MTRR:66	10.81	9.13–14.18	30.75	24.56–37.50	1.24	1.21–1.29
General group	10.17	8.30–13.10	35.00	28.20–43.58	1.25	1.21–1.30

Note. Me — median, IQR — interquartile range; H_{cy} — homocysteine; PTH — parathyroid hormone; Ca^{2+} — ionized calcium.

by the direct relationship H_{cy}–Ca^{2+}, most pronounced in the subgroup with the main genotype T/TMTHFR:677, with the highest, of all subgroups, level of H_{cy} in the blood and the proportion of cases of hyperhomocysteinemia (*Tables 4, 6*).

An increase in the Ca content in the blood with hyperhomocysteinemia may be associated with the ability of H_{cy} to affect N-methyl-D-aspartate (NMDA) receptors located on the surface of bone tissue cells [13].

H_{cy} also affects NMDA receptors of cardiomyocytes and myocytes of the vascular wall, as a result of which the penetration of Ca^{2+} ions into the cytoplasm of these cells is enhanced [1].

The ability of H_{cy} to directly activate the formation and activity of osteoclasts is also known. In this case, the formation of active forms of oxygen increases. Mild and moderate hyperhomocysteinemia, increasing the resorption of bone structures, can contribute to osteoporosis [14].

With an increase in the content of Ca^{2+} in the blood, due to a violation of the methylation process of H_{cy} and the occurrence of hyperhomocysteinemia, the production of PTH decreases, and is even blocked, which should lead to an increase in the concentration of serum P. This is confirmed by the direct correlation of Ca–P.

H_{cy}, increasing the level of Ca in the blood, contributes to a delay in the elimination of P from the body.

However, in most groups, a direct correlation between P and PTH is recorded, indicating a stimulating effect of P on the process of PTH formation (*Table 5*).

Other authors also noted the ability of P to directly influence the processes of PTH formation in hypercalcemia [15]. This compensatory mechanism allows the body to excrete excess P through the kidneys. At the same time, other mechanisms for regulating the level of P in the blood cannot be ruled out.

The FC genes play an important role in regulating calcium-phosphorus metabolism.

In subgroups with the main genotypes, including the risk alleles of the MTHFR:C677T and MTR:A2756G polymorphisms, there was no direct correlation of P–PTH.

Thus, when the H_{cy} methylation process is blocked, the levels of Ca and P in the blood increase, which can lead to the formation of calcium–phosphate complexes with their deposition in soft tissues and the walls of blood vessels.

In other genetic subgroups, a combination of direct correlations of H_{cy}–Ca^{2+} and P–PTH was recorded (*Table 5*), indicating the ability of the child's body to excrete P with urine, despite the increased content of Ca in the blood.

The inverse correlation of H_{cy}–PTH in the genetic subgroup with the main genotype G/GMTR:2756 associated with B_{12}–methionine synthase reflects a direct negative effect of H_{cy} on the process of PTH formation.

In addition to PTH and serum Ca, the level of P in the blood is regulated by calcitriol (the active form of vitamin D) and fibroblast growth factor 23 (FGF23) [16, 17].

Despite possible fluctuations in the level of Ca in the blood, the level of Ca^{2+} in the blood should be in the physiological range and is strictly controlled in the body by regulators of mineral metabolism.

With the incorporation of ^{137}Cs, H_{cy}, affecting the skeletal system, helps to restore the required level of Ca^{2+} in the blood.

In this regard, transient hyperhomocysteinemia should be considered as an element of the body's adaptation system to environmental conditions.

With prolonged hyperhomocysteinemia, the content of Ca and P in the blood increases significantly, which can lead to the formation of mineral deposits in soft tissues and vessel walls.

This is an extreme version of hyperhomocysteinemia, which occurs as a result of genetic disorders of FC (homozygous variants of risk alleles of polymorphisms affecting the activity of the main enzymes of FC) and the negative impact of environmental factors, including radiation.

CONCLUSIONS

The incorporation of ^{137}Cs into the body of children living in areas affected by the Chornobyl accident causes energy deficiency in the cells of vital organs, leading to a decrease in the intensity of anabolic processes, disruption of H_{cy} methylation and changes in calcium-phosphorus metabolism.

In children living near the ChEZ, an inverse correlation was found between the specific activity of ^{137}Cs radionuclides in the body and the Ca content in the blood, as well as the IR values, reflecting the ratio of body weight to its length.

Impaired physical development of the examined children is directly related to the Ca content in their blood, as evidenced by the direct correlation between Ca and IR.

Energy deficiency associated with the incorporation of ^{137}Cs into the body, as well as mutations in the FC genes, are the causes of hyperhomocysteinemia — an increased content of the sulfur-contain-

ing amino acid H_{cy} in the blood in children living in populated areas located near the ChEZ.

H_{cy}, by affecting the skeletal system, compensates for the Ca deficiency in the blood induced by ^{137}Cs.

An increase in the Ca content in the blood with hyperhomocysteinemia negatively affects the processes of PTH formation and, therefore, creates conditions for impaired excretion of P from the body through the kidneys. However, in most genetic subgroups, a direct correlation between P and PTH was recorded, illustrating the ability of the child's body to stimulate the excretion of P with urine when its concentration in the blood increases.

Thus, transient hyperhomocysteinemia is an element of the body's adaptation system to environmental radiation exposure.

In subgroups of children with risk alleles of genetic polymorphisms MTHFR:C677T and MTR: A2756G in the genome, a direct correlation between P and PTH was absent, which indicates the possibility of the formation of calcium-phosphorus complexes in the blood and their deposition in soft tissues and vascular walls.

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