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ГЕНЕТИЧНИЙ КОНТРОЛЬ ОБМІНУ ГОМОЦИСТЕЇНУ У ДІТЕЙ, ЯКІ ПРОЖИВАЮТЬ ПОБЛИЗУ ЧОРНОБИЛЬСЬКОЇ ЗОНИ ВІДЧУЖЕННЯ

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GENETIC CONTROL OF HOMOCYSTEINE METABOLISM IN CHILDREN LIVING NEAR THE CHORNOBYL EXCLUSION ZONE

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Studies conducted in 2015 in the course of socio-medical projects of the European Union, on the territory of Ivankivskyi and Poliskyi districts of the Kyiv region, adjacent to the Chornobyl exclusion zone (ChEZ), revealed a violation of the metabolism of the essential amino acid methionine in most of the examined children aged 12-17 years old. At the same time, an increase in the content of the amino acid homocysteine (H_{cy}) was registered in the blood of these children [1].

It is known from authoritative scientific sources that hyperhomocysteinemia is associated with impaired functioning of vital organs and systems, including the cardiovascular and nervous systems, and cancer [2-4].

It should be noted that in the territory of the Kyiv region, including the Ivankivskyi district, a high proportion of cases of thyroid cancer is recorded in the post-Chornobyl period [5].

In the course of ongoing studies in the group of examined children, structural changes in the thyroid gland were detected in 5.6% of cases, and in 35.5% of cases, disturbances in the production of thyroid hormones were detected [6]. At the same time, correlations of H_{cy} with pituitary thyroid stimulating hormone and tryiodothyronine were noted, which were most pronounced after forest fires in ChEZ [7].

The participation of H_{cy} in the pathogenesis of oncological diseases of the thyroid gland and other organs predetermines the determination

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Мета дослідження: *визначити участь генів фолатного циклу у виникненні гіпергомоцистеїнемії у дітей Іванківського району Київської області за 35 років після аварії на Чорнобильській атомній електростанції.*

Методи дослідження*: імунохімічний, математико-статистичний.*

Результати. *Визначено рівні гомоцистеїну у 217 дітей віком 12-17 років з Іванківського району Київської області, а також генетичні поліморфізми фолатного циклу. Перевищення гомоцистеїну у крові понад 10 мкмоль/л (стан гіпергомоцистеїнемії) виявлено у 65,44% обстежених (142 з 217), серед хлопчиків – 69,79% (67 з 96), серед дівчаток – 61,98% (75 з 121). Найбільшу питому вагу випадків гіпергомоцистеїнемії зареєстровано у підгрупі дітей з базовим поліморфізмом MTHFR:677TT – 94,44%. У більшості випадків гіпергомоцистеїнемія у дітей була пов'язана з зовнішньосередовищним фактором, що включає радіоактивні елементи та продукти їхнього розпаду. Система профілактики гіпергомоцистеїнемії та її наслідків у дітей, які проживають у районах, що постраждали від аварії на Чорнобильській атомній електростанції, має передбачати регулярний контроль над вмістом радіонуклідів в організмі дітей та продуктах харчування місцевого виробництва, вмістом гомоцистеїну у крові та оцінку стану генів фолатного циклу.*

Ключові слова: гомоцистеїн, підлітки, радіонукліди, Чорнобильська зона відчуження.

GENETIC CONTROL OF HOMOCYSTEINE METABOLISM AMONG CHILDREN, WHO LIVE NEAR THE CHORNOBYL EXCLUSION ZONE

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The aim of study: *to determine the involvement of folate cycle genes in the occurrence of hyperhomocysteinemia in children from Ivankivskyi district of Kyiv region of Ukraine 35 years after the accident at the Chornobyl nuclear power plant.*
Research methods. *Immunochemical, mathematical and statistical.*
Results*. Homocysteine levels were determined in 217 children aged 12-17 from Ivankivskyi district of Kyiv region, as well as genetic polymorphisms of the folate cycle. An excess of homocysteine in the blood over 10 µmol/l (a state of hyperhomocysteinemia) was detected in 65.44% of those examined (142 out of 217), among boys – 69.79% (67 out of 96), among girls – 61.98% (75 out of 121). The largest proportion of hyperhomocysteinemia cases was registered in the subgroup of children with the basic polymorphism MTHFR: 677TT – 94.44 % of cases. In most cases, hyperhomocysteinemia in children was associated with an environmental factor, including radioactive elements and their decay products. The system for the prevention of hyperhomocysteinemia and its consequences in children living in areas affected by the accident at the Chornobyl nuclear power plant should include regular monitoring of the content of radionuclides in the body of children and locally produced food, the content of homocysteine in the blood, and assessment of the state of folate cycle genes.*

Keywords: homocysteine, adolescent children, radionuclides, Chornobyl exclusion zone.

of the causes leading to hyperhomocysteinemia. This applies to both an internal factor associated with genes that regulate the process of homocysteine methylation, and an external factor that influences the activity of the corresponding enzymes of the folate cycle from the outside.

The purpose of the study was to determine the involvement of folate cycle genes in the occurrence of hyperhomocysteinemia in children of the Ivankivskyi district of the Kyiv region of Ukraine 35 years after the accident at the Chornobyl nuclear power plant.

Material and research methods. The study was carried out with the financial support of the public organization «Children of Chornobyl» (France).

In January 2022, 217 children aged 12-17 from the Ivankivskyi districts of the Kyiv region were subjected to a laboratory examination, the territory of which was contaminated with radioactive elements after the accident at the Chornobyl nuclear power plant in 1986, in particular, ^{137}Cs and ^{90}Sr [8]. Blood samples were taken from children attending school on an empty stomach.

The blood samples were tested in a quality-certified laboratory and agreed with the parents.

The determination of Hcy in the blood was carried out using the immunochemical method with chemiluminescent detection (ECLIA). Analyzer and test system: Architect 1000 (ABBOT Diagnostics, USA).

The level of H_{cy} in the blood of children over 10 µmol/l was defined as a state of hyperhomocysteinemia.

In a genetic study of the folate cycle (FC), allelic variants C677T and A1298C of the MTHFR gene (methylenetetrahydrofolate reductase),

Table 1

Percentage of hyperhomocysteinemia cases in groups of children from Ivankivskyi district

Groups	Polymorphisms, genotypes	Number of children in groups	Number ofhyperhomocysteinemia cases		
			Absolute number	Percentage among children in a group, %	Statistical differences with a group № 9
1	MTR:2756AA	133	92	69.17	t=3.76; p=0.000278
2	MTR:2756AG	74	45	60.81	t=4.30; p=0.000066
3	MTR:2756GG	10	5	50.00	t=2.66; p=0.015465
4	MTHFR:1298AA	105	74	70.48	t=3.42; p=0.000938
5	MTHFR:1298AC	92	57	61.96	t=4.00; p=0.000153
6	MTHFR:1298CC	20	11	55.00	t=3.19; p=0.003804
7	MTHFR:677CC	99	63	63.64	t=4.25; p=0.000059
8	MTHFR:677CT	100	62	62.00	t=4.47; p=0.000027
9	MTHFR:677TT	18	17	94.44	-
10	MTRR:66AA	43	25	58.14	t=3.92; p=0.000347
11	MTRR:66AG	106	72	67.92	t=3.76; p=0.000308
12	MTRR:66GG	68	45	66.18	t=3.59; p=0.000683

*Note: * — statistically significant differences between values of all groups and that of a group № 9 (MTHFR:677TT genotype)*

A2756G of the MTR gene (B_{12}-dependent methionine synthase), A66G of the MTRR gene (methionine synthase reductase) were determined. The method used was: PCR in Real-time mode. Analyzer and test system DT-96 detecting cycler; «DNA-Technology» (Russia).

Genetic subgroups were formed, taking into account the genotypes of FC, 100% representation of one specific genotype, or a combination of genotypes.

Statistical processing of the obtained results was carried out using the IBM SPSS Statistics 22 program (USA). For the analyzed indicators, the arithmetic mean (M), standard error of the mean (m), confidence interval of the mean value (95% CI), median (Me), interquartile range (IQR), minimum and maximum values of the parameters, percentiles were calculated. The hypothesis about the type of distributions was tested (Kolmogorov-Smirnov criterion). The studied parameters did not correspond to the normal distribution law, and therefore, the non-parametric U-testU Mann-Whitney was used to compare the values.

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

Student's t-test was used to compare relative scores. The critical confidence level of the null hypothesis (p) was taken as 0.05.

The relationship between H_{cy} and risk levels of the analyzed genetic polymorphisms was determined using Spearman's rank correlation coefficient (r_{xy}). The strength of the correlation was assessed according to the traditional scale: weak – from 0 to 0.299; medium – from 0.3 to 0.699; strong – from 0.7 to 1.0.

Results and its discussion. The proportion of cases of hyperhomocysteinemia in the general group of children from the Ivankivskyi district was 65.44% (142 out of 217), among boys – 69.79% (67 out of 96), among girls – 61.98% (75 out of 121).

The largest proportion of cases of hyperhomocysteinemia was registered in the subgroup of children with the basic MTHFR:677TT polymorphism – 94.44% of cases (table 1).

In other genetic subgroups, this indicator was significantly lower, however, in most of them, it exceeded the 50% barrier (table 1).

The level of H_{cy} in the blood of children from the subgroup

Table 2

Statistical characteristics of homocysteine levels within genetic groups in children from Ivankivskyi district, (μmol/L)

Polymorphism, genotype	H_{cy}, μmol/L	
	Me	IQR
MTR:2756AA	11.30	9.10-13.15
MTR:2756AG	11.80	9.20-13.45
MTR:2756GG	10.70	8.33-16.03
MTHFR:1298AA	11.60	9.55-14.65
MTHFR:1298AC	10.90	9.13-12.68
MTHFR:1298CC	10.25	8.40-12.90
MTHFR:677CC	10.80	9.10-12.70
MTHFR:677CT	10.90	9.10-12.98
MTHFR:677TT	18.10	14.33-38.28
MTRR:66AA	10.90	8.90-12.50
MTRR:66AG	11.00	9.20-13.63
MTRR:66GG	11.65	9.33-14.48

Note: Me – median, IR – interquartile range.

Table 3

Results of quantitative comparison (Ivankivskyi district) of populations (nonparametric analysis)

Polymorphism, genotype		H_{cy}, μmol/L		
		Number ofcases	Average rank	U Mann-Whitney test, statistical significance, p
MTR:A2756G MTHFR:C677T	AA	133	69.69	U = 358.00; p = 0.0001
	TT	18	122.61	
MTR:A2756G MTHFR:C677T	AG	74	40.24	U =203.00; p = 0.0001
	TT	18	72.22	
MTR:A2756G MTHFR:C677T	GG	10	9.30	U = 38.00; p = 0.013
	TT	18	17.39	
MTHFR:A1298C MTHFR:C677T	AA	105	56.43	U = 360.00; p = 0.0001
	TT	18	94.50	
MTHFR:A1298C MTHFR:C677T	AC	92	48.68	U = 200.50; p = 0.0001
	TT	18	90.36	
MTHFR:A1298C MTHFR:C677T	CC	20	12.43	U = 38.50; p = 0.0001
	TT	18	27.36	
MTHFR:C677T MTHFR:C677T	CC	99	52.19	U = 216.50; p = 0.0001
	TT	18	96.47	
MTHFR:C677T MTHFR:C677T	CT	100	52.71	U = 220.50; p = 0.0001
	TT	18	97.25	
MTRR:A66G MTHFR:C677T	AA	43	23.86	U = 80.00; p = 0.0001
	TT	18	48.06	
MTRR:A66G MTHFR:C677T	AG	106	56.32	U = 298.50; p = 0.0001
	TT	18	98.92	
MTRR:A66G MTHFR:C677T	GG	68	37.74	U = 220.50; p = 0.0001
	TT	18	65.25	

ГЕНЕТИЧЕСКИЙ КОНТРОЛЬ ОБМЕНА ГОМОЦИСТЕИНА У ДЕТЕЙ, ПРОЖИВАЮЩИХ ВБЛИЗИ ЧЕРНОБЫЛЬСКОЙ ЗОНЫ ОТЧУЖДЕНИЯ

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Цель исследования: *определить участие генов фолатного цикла в возникновении гипергомоцистеинемии у детей Иванковского района Киевской области Украины спустя 35 лет после аварии на Чернобыльской атомной электростанции.*

Методы исследования: *иммунохимический, математико-статистический.*

Результаты*. Определены уровни гомоцистеина у 217 детей в возрасте 12-17 лет из Иванковского района Киевской области, а также генетические полиморфизмы фолатного цикла. Превышение гомоцистеина в крови свыше 10 мкмоль/л (состояние гипергомоцистеинемии) выявлено у 65,44% обследованных (142 из 217), среди мальчиков – 69,79% (67 из 96), среди девочек – 61,98% (75 из 121). Наибольший удельный вес случаев гипергомоцистеинемии зарегистрирован в подгруппе детей с базовым полиморфизмом MTHFR:677TT - 94,44% случаев. В основном гипергомоцистеинемия у детей была связана с внешнесредовым фактором, включающим радиоактивные элементы и продукты их распада. Система профилактики гипергомоцистеинемии и ее последствий у детей, проживающих в районах, пострадавших от аварии на Чернобыльской атомной электростанции, должна включать регулярный контроль над содержанием радионуклидов в организме детей и продуктах питания местного производства, содержанием гомоцистеина в крови и оценку состояния генов фолатного цикла.*

Ключевые слова: гомоцистеин, гены фолатного цикла, подростки, радионуклиды, Чернобыльская зона отчуждения.

with the basic genotype MTHFR:677TT was also the highest among all genetic subgroups (tables 2 and 3).

Thus, children with a significant blockage of methylenetetrahydrofolate reductase activity due to the homozygous variant of carriage of the T allele of the MTHFR:677 genetic polymorphism had the highest levels of H_{cy} in the blood.

Children with this genotype accounted for 8.3% of cases in the study group. Carriers of the heterozygous variant of the T allele or the absence of this allele were found much more often in equal parts – about 46.0% of cases (table 4).

The participation of the risk allele T in the occurrence of hyperhomocysteinemia is confirmed by a direct correlation between H_{cy} and the severity of the genetic risk of the MTHFR:C677T polymorphism (table 5). This relationship is more pronounced in the group of children with H_{cy} levels exceeding 10 µmol/l (table 6).

The inverse relationship between H_{cy} and the severity of the genetic risk of the MTHFR:1298 polymorphism is due to the fact that the number of cases involving the T allele of the MTHFR:677 polymorphism progressively decreases along the line of the A/A, A/G, G/G MTHFR:1298 genotypes (table 7).

The conducted studies showed that the genetic factor, in the form of the T allele of the MTHFR:677 polymorphism, negatively affects the activity of methylenetetrahydrofolate reductase, and significantly disrupts the H_{cy} metabolism in the child's body.

At the same time, an increase in the H_{cy} level was also noted in 63.64% of cases in the subgroup of children who were not carriers of the T allele (table 1).

In this regard, one should take into account the constant impact on the child's body of long-lived radioactive elements ^{137}Cs and its decay product Ba, ^{90}Sr, present in the environment of the Ivankivskyi district, located near the ChEZ [8].

Table 4

Percentage of polymorphic alleles of folate metabolism genes in the examined children from Ivankivskyi district

Gene, polymorphism	Genotypevariants					
	«Neutral» allele Homozygous variant		«Riskallele» Heterozygous variant		«Riskallele» Homozygous variant	
	Abs. number	%	Abs. number	%	Abs. number	%
MTR:A2756G	133	61.29	74	34.10	10	4.61
MTHFR:A1298C	105	48.39	92	42.40	20	9.21
MTHFR:C677T	99	45.62	100	46.08	18	8.30
MTRR:A66G	43	19.82	106	48.85	68	31.33

This environmental factor has a pronounced negative impact on the developing organism, and also stimulates the manifestation of genetic defects in the folate cycle. The result of this impact is hyperhomocysteinemia and structural and functional disorders of vital organs and systems [8, 9].

Given the danger of hyperhomocysteinemia for a developing organism, it is necessary to organize regular monitoring of the content of H_{cy} in the blood of children living near the ChEZ, taking into account the state of the genetic system of FC.

Particular attention should be paid to the functional deficiency of vitamins B_9 and B_{12} in the body of these children [1].

Regular monitoring of the content of radionuclides in their bodies and locally produced food products should be mandatory.

An elevated level of H_{cy} in the blood of children indicates the need for early prevention of cardiovascular and oncological diseases, which are the cause of disability and mortality in the adult population.

Table 5

Correlations between H_{cy} and the genetic risk index (Risk) of analyzed polymorphisms in a group of children

Parameter	Correlation coefficient, (r_{xy})	Parameters			
		[1]Risk MTHFR: C677T	[2]Risk MTHFR: A1298C	[3]Risk MTR: A2756G	[4]Risk MTRR: A66G
H_{cy}	Spearman's	0.206**	- 0.165*	- 0.034	0.093
	Sign. (2-tailed)	0.002	0.015	0.618	0.172
	N	217	217	217	217

*Note: * – correlation is significant at the 0.05 level (2-tailed). ** – correlation is significant at the 0.01 level (2-tailed). [1]Risk MTHFR:677 – CC, CT, TT; [2]Risk MTHFR:1298 – AA, AC, CC; [3]Risk MTR:2756 – AA, AG, GG; [4]Risk MTRR:66 – AA, AG, GG.*

Table 6

Correlations between H_{cy} and the genetic risk index (Risk) of the analyzed polymorphisms in the group of children with hyperhomocysteinemia

Parameter	Correlation coefficient, (r_{xy})	Parameters			
		[1]Risk MTHFR: C677T	[2]Risk MTHFR: A1298C	[3]Risk MTR: A2756G	[4]Risk MTRR: A66G
H_{cy}	Spearman's	0.308**	- 0.161	0.098	0.146
	Sign. (2-tailed)	0.000	0.056	0.244	0.083
	N	142	142	142	142

*Note: * – correlation is significant at the 0.05 level (2-tailed). ** – correlation is significant at the 0.01 level (2-tailed). [1]Risk MTHFR:677 – CC, CT, TT; [2]Risk MTHFR:1298 – AA, AC, CC; [3]Risk MTR:2756 – AA, AG, GG; [4]Risk MTRR:66 – AA, AG, GG.*

Table 7

Percentage of the T allele of the MTHFR:C677T genetic polymorphism in subgroups of children in the Ivankivskyi district

Subgroups	Polymorphisms, genotypes	Number of children in subgroups	Number of cases with allele T MTHFR:C677T polymorphism	
			Abs. number	%
1	MTR:2756AA	133	66	49.62
2	MTR:2756AG	74	46	62.16
3	MTR:2756GG	10	6	60.00
4	MTHFR:1298AA	105	72	68.57
5	MTHFR:1298AC	92	46	50.00
6	MTHFR:1298CC	20	0	0
7	MTHFR:677CC	99	0	0
8	MTHFR:677CT	100	100	100.0
9	MTHFR:677TT	18	18	100.0
10	MTRR:66AA	43	26	60.47
11	MTRR:66AG	105	56	53.33
12	MTRR:66GG	68	36	52.94

Conclusions

1. Violation of H_{cy} metabolism in the form of a state of hyperhomocysteinemia was registered in 65.44% of cases in a group of children from the Ivankivskyi district of the Kyiv region, 35 years after the accident at the Chornobyl nuclear power plant.

2. A direct relationship has been traced between the carriage of the risk allele T of the MTHFR:677 polymorphism and the level of H_{cy} in the blood. Hyperhomocysteinemia is most pronounced in the subgroup of children with a homozygous variant of this allele.

3. In most cases, hyperhomocysteinemia in children of the Ivankivskyi district was associated with an environmental factor, including radioactive elements and their decay products.

4. Preventive measures for hyperhomocysteinemia and its consequences in children living in areas affected by the accident at the Chornobyl nuclear power plant should include regular monitoring of the content of radionuclides in the body of children and locally produced food, the content of H_{cy} in the blood and assessment of the state of FC genes.

5. Registration of hyperhomocysteinemia in children living in areas affected by the accident at the Chornobyl nuclear power plant predeter-

mines the early prevention of cardiovascular and oncological diseases, which are the causes of disability and mortality in the adult population.

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