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HYPERHOMOCYSTEINEMIA AND FOLIC ACID METABOLISM IN CHILDREN LIVING NEAR THE CHERNOBYL EXCLUSION ZONE

Bandazhevskyi Yu. I., Dubova N. F.

INTRODUCTION

During the implementation in 2013–2017 in Ukraine of the projects of the European Commission "Health and Ecological Programmes around the Chernobyl Exclusion Zone: Development, training and coordination of health-related projects" and the Regional Council of Rhone-Alpes (France), in groups of examined adolescent children age from Ivankovsky and Polessky districts of the Kyiv region, in more than 70 % of cases, a state of hyperhomocysteinemia was detected – an increase in the level of homocysteine (H_{cy}) in the blood of more than 10 μmol/l[1].

Ivankovsky and Polessky districts border on the Chernobyl exclusion zone (ChEZ), the soils and forest trees of which contain long-lived radioactive elements, including ^{137}Cs, ^{90}Sr, ^{241}Am[2]. In this regard, the population living near this zone is under constant radiation exposure[3].

The registration of hyperhomocysteinemia in a large number of children forces us to look for its causes in order to organize effective preventive measures in the early stages of the formation of severe pathological processes.

During the metabolic transformations of H_{cy} into methionine, one of the most important roles is played by folic acid, or vitamin B_9.

The formation of its active form, 5-methyltetrahydrofolate (5-MTHF), is associated with the enzyme of the folate cycle, methylenetetrahydrofolate reductase (MTHFR)[4].

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The functioning of MTHFR is regulated by genetic polymorphisms, of which MTHFR:C677T is the most influential[5].

Thus, in the course of studying the causes of hyperhomocysteinemia, it is logical to determine the relationship between the content of vitamin B_9, H_{cy} in the body of children and allelic variants of MTHFR:C677T.

The purpose of the study was to assess the relationship between the blood levels of vitamin B_9, H_{cy} and the MTHFR:C677T genetic polymorphism in children from areas bordering the ChEZ.

1. Material and research methods

The study was carried out as part of the implementation of the projects of the European Commission "Health and Ecological Programs around the Chernobyl Exclusion Zone: Development, training and coordination of health-related projects" in Ukraine and the Regional Council of the Rhone-Alpes region (France). Laboratory and instrumental examinations were carried out on 260 children aged 13–17 living in the settlements of Ivankovsky and Polessky districts, the soils of which are contaminated with radioactive elements[6, 7].

Blood sampling from the cubital vein was performed in children attending school in the morning on an empty stomach.

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

The determination of H_{cy} 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.

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Allelic variants of the MTHFR:C677T genetic polymorphism were determined using the Real-time PCR method. Analyzer and test system DT-96 detecting cycler; "DNA-Technology" (Russia).

Determination of vitamin B_9 – (folacin) was carried out using an immunochemical method with electrochemiluminescent detection (ECLIA). Analyzer and test system: Cobas e411; Roche Diagnostics (Switzerland). The laboratory has set a reference interval for vitamin B_9 in the range of 4.6–18.7 ng/mL.

During the study, groups were formed, taking into account the content of vitamin B_9 in the blood, as well as subgroups, depending on the MTHFR:C677T genotypes.

Statistical processing of the obtained results was carried out using the IBM SPSS Statistics 22 program (USA). 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 hypothesis about the type of distributions was tested (Kolmogorov-Smirnov criterion). All the studied parameters did not correspond to the law of normal distribution.

The relationship between the values of vitamin B_9 and H_{cy} was determined using the 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. The statistical significance of the indicators was assessed by determining the significance level p using a statistical program.

2. Results and its discussion

In the group of examined children, the subgroup with the homozygous variant of the T allele of the MTHFR:C677T polymorphism had the smallest proportion. Subgroups with a heterozygous variant of the risk allele T and a homozygous variant of the neutral allele C were presented in approximately equal proportions (Table 1).

Table 1

The proportion of cases with MTHFR:C677T polymorphism genotypes in the study group of children

Subgroups	Genotypes MTHFR:C677T	Abs. number	The proportion of cases, %
1	T/T	26	10.00
2	C/T	111	42.69
3	T/T+C/T	137	52.69
4	C/C	123	47.31
3+4	T/T+C/T+C/C	260	100.0

The proportion of cases of hyperhomocysteinemia in the general group and its subgroups exceeded 70 % of the milestone. The highest proportion of cases of hyperhomocysteinemia was recorded in subgroup No. 1 with the basic genotype T/T MTHFR:677 (Tables 2, 3). A significant difference was registered between subgroup No. 1 (T/T genotype) and subgroup No. 4 (C/C genotype). There were no statistical differences between subgroups 3 and 4 (Tables 2, 3).

Table 2

The proportion of cases of hyperhomocysteinemia depending on the level of reference values in subgroups of children with MTHFR:C677T genotypes

Subgroups	Genotypes MTHFR: C677T	Children with H_{cy} > 10.0 μmol/l		
		abs. number	the proportion of cases[1], %	the proportion of cases[2], %
1	T/T	23	88.46	11.68
2	C/T	87	78.38	44.16
3	T/T+C/T	110	80.29	55.84
4	C/C	87	70.73	44.16
[3+4]	T/T+C/T+ C/C	197	75.77	100.0

Note. [1] – the proportion of cases of hyperhomocysteinemia in the genetic subgroup. [2] – the proportion of cases of hyperhomocysteinemia in each genetic subgroup in relation to the total number of cases of hyperhomocysteinemia.

Among the total number of cases of hyperhomocysteinemia, the number of cases of hyperhomocysteinemia in subgroup No. 1 was the smallest compared to all subgroups. At the same time, the proportion of cases with genotypes containing the T allele was statistically large compared to the proportion of cases with the C/C genotype (Tables 2, 3).

In the general group of children (n=260), cases with vitamin B_9 levels within the reference interval of 4.6–18.7 ng/ml, established by the laboratory, prevailed.

The level of vitamin B_9 below the reference range (<4.6 ng/ml) was registered in the blood of 54 children, or, in 20.77 % of cases (Tables 4, 5).

Subgroups No. 2, 3, 4, to a greater extent, were represented by cases of vitamin B_9 content in the blood within the physiological range (Tables 4, 5).

In subgroup No. 1 (T/T genotype), the relative number of cases with vitamin B_9<4.6 ng/ml did not differ significantly from the relative number of cases with vitamin B_9>4.6 ng/ml, while in subgroups No. 2, 3 and 4, statistical differences were recorded (Tables 4, 5).

Table 3

Statistical comparisons of the proportion of cases of hyperhomocysteinemia in subgroups of children with different MTHFR:C677T genotypes

Subgroups of comparison	Genotypes MTHFR:C677T	Comparison variant	Student' s t-test	Significance level, p
1 – 2	T/T	The proportion of cases[1]	1.36	0.175385
	C/T			
1 – 3	T/T	The proportion of cases[1]	1.15	0.254124
	T/T+C/T			
1 – 4	T/T	The proportion of cases[1]	2.37	0.019747
	C/C			
3 – 4	T/T+C/T	The proportion of cases[1]	1.79	0.074234
	C/C			
1 – 2	T/T	The proportion of cases[2]	7.70	0.000001
	C/T			
1 – 3	T/T	The proportion of cases[2]	10.47	0.000001
	T/T+C/T			
1 – 4	T/T	The proportion of cases[2]	7.70	0.00001
	C/C			
3 – 4	T/T+C/T	The proportion of cases[2]	2.33	0.020670
	C/C			

Note. [1] – the proportion of cases of hyperhomocysteinemia in the genetic subgroup. [2] – the proportion of cases of hyperhomocysteinemia in each genetic subgroup in relation to the total number of cases of hyperhomocysteinemia.

However, of all subgroups, subgroup No. 1 had the largest proportion of cases of vitamin B_9 deficiency in the body, and the smallest proportion among cases with vitamin B_9 levels within physiological parameters (Tables 4, 5).

The proportion of cases with vitamin B_9 levels <4.6 ng/ml in subgroup No. 1 was significantly more than in subgroups No. 2, 3 and 4, in subgroup No. 3 it was statistically more than in subgroup No. 4 (Tables 4, 5).

In the group of children with vitamin B_9 levels<4.6 ng/ml, the proportion of cases with T/T+C/T MTHFR:677 genotypes was significantly more than with the C/C MTHFR:677 genotype. At the same time, in the group of

children with vitamin B_9>4.6 ng/ml, these differences were absent (Tables 6, 7).

Table 4

The content of vitamin B_9 in the blood of children with genotypes MTHFR:C677T

Subgroups	Genotypes MTHFR:C677T	The level of vitamin B_9 in the blood			
		<4.6 ng/ml		>4.6 ng/ml	
		abs. number	%	abs. number	%
1	T/T	14	53.85	12	46.15
2	C/T	21	18.92	90	81.08
3	T/T+C/T	35	25.55	102	74.45
4	C/C	19	15.45	104	84.55
[3+4]	T/T+C/T+C/C	54	20.77	206	79.23

In the group of children with vitamin B_9 levels <4.6 ng/ml, the proportion of cases with the T/T, T/T+C/T MTHFR:677 genotypes was statistically more, and the proportion of cases with the C/C genotype MTHFR:677 – less compared to the group of children with vitamin B_9>4.6 ng/ml (Tables 6, 7).

In the group of children with vitamin B_9 levels <4.6 ng/ml, the proportion of cases of hyperhomocysteinemia was statistically more than in the group of children with vitamin B_9 levels >4.6 ng/ml. A similar situation was observed with respect to subgroups No. 2 and 3 of these groups. In subgroup No. 1, all cases of hyperhomocysteinemia were associated with vitamin B_9 deficiency in the body. There were no statistical differences between subgroups 3 and 4 (Tables 8, 9).

Among children with hyperhomocysteinemia, the level of vitamin B_9 <4.6 ng/ml was recorded in the general group in 54 cases – 27.41 %, in subgroup No. 1 – in 14 cases – 60.87 %, in subgroup No. 2 – in 21 cases – 24.14 %, in subgroup No. 3 – in 35 cases – 31.82 %, in subgroup No. 4 – in 19 cases – 21.84 %.

Significant statistical differences were determined between subgroups No. 1 and No. 2, No. 1 and No. 3, No. 1 and 4 (Table 10).

Correlation analysis revealed an inverse relationship of medium strength between the values of H_{cy} and vitamin B_9 in the general group and in all analyzed genetic subgroups (Table 11). It is most pronounced in subgroup No. 1 (T/T genotype), the least – in subgroup No. 4 (C/C genotype).

Table 5

Statistical comparisons of the proportion of cases with different levels of vitamin B_9 in the blood, in subgroups of children with MTHFR:C677T genotypes

Subgroups of comparison	The level of vitamin B_9 in the blood	Genotypes MTHFR:C677T	Student's t-test	Signifi-cance level, p
3 – 4	B_9 < 4.6 ng/ml	T/T+C/T	2.04	0.046667
	B_9 < 4.6 ng/ml	C/C		
[3+4] – [3+4]	B_9 < 4.6 ng/ml	T/T+C/T+C/C	16.40	0.000001
	B_9 > 4.6 ng/ml	T/T+C/T+C/C		
1 – 1	B_9 < 4.6 ng/ml	T/T	0.56	0.583096
	B_9 > 4.6 ng/ml	T/T		
2 – 2	B_9 < 4.6 ng/ml	C/T	11.82	0.000001
	B_9 > 4.6 ng/ml	C/T		
3 – 3	B_9 < 4.6 ng/ml	T/T+C/T	9.27	0.000001
	B_9 > 4.6 ng/ml	T/T+C/T		
4 – 4	B_9 < 4.6 ng/ml	C/C	14.99	0.000001
	B_9 > 4.6 ng/ml	C/C		
1 – 2	B_9 < 4.6 ng/ml	T/T	3.34	0.002150
	B_9 < 4.6 ng/ml	C/T		
1 – 3	B_9 < 4.6 ng/ml	T/T	2.70	0.009578
	B_9 < 4.6 ng/ml	T/T+C/T		
1 – 4	B_9 < 4.6 ng/ml	T/T	3.72	0.000808
	B_9 < 4.6 ng/ml	C/C		
1 – 2	B_9 > 4.6 ng/ml	T/T	3.34	0.001189
	B_9 > 4.6 ng/ml	C/T		
1 – 3	B_9 > 4.6 ng/ml	T/T	2.70	0.007937
	B_9 > 4.6 ng/ml	T/T+C/T		
1 – 4	B_9 > 4.6 ng/ml	T/T	3.72	0.000307
	B_9 > 4.6 ng/ml	C/C		

Table 6

Distribution of MTHFR:C677T genotypes in groups of children with different levels of vitamin B_9 in the blood

Subgroups	Genotypes MTHFR:C677T	Groups			
		B_9<4.6 ng/ml		B_9>4.6 ng/ml	
		abs. number	%	abs. number	%
1	T/T	14	25.93	12	5.83
2	C/T	21	38.89	90	43.69
3	T/T+C/T	35	64.81	102	49.51
4	C/C	19	35.19	104	50.49
[3+4]	T/T+C/T+C/C	54	100.0	206	100.0

Table 7

Statistics comparing the distribution of MTHFR:C677T genotypes in groups of children with different levels of vitamin B_9 in the blood

Subgroups of comparison	Groups	Genotypes	Student's t-test	Significance level, p
3 – 4	B_9 < 4.6 ng/ml	T/T+C/T	3.22	0.000221
	B_9 < 4.6 ng/ml	C/C		
3 – 4	B_9 > 4.6 ng/ml	T/T+C/T	0.20	0.842362
	B_9 > 4.6 ng/ml	C/C		
1 – 1	B_9 < 4.6 ng/ml	T/T	3.25	0.003504
	B_9 > 4.6 ng/ml	T/T		
2 – 2	B_9 < 4.6 ng/ml	C/T	0.64	0.522021
	B_9 > 4.6 ng/ml	C/T		
3 – 3	B_9 < 4.6 ng/ml	T/T+C/T	2.08	0.039885
	B_9 > 4.6 ng/ml	T/T+C/T		
4 – 4	B_9 < 4.6 ng/ml	C/C	2.08	0.040109
	B_9 > 4.6 ng/ml	C/C		

Table 8

The proportion of cases of hyperhomocysteinemia in subgroups of children with MTHFR:C677T genotypes from groups with different levels of vitamin B_9 in the blood

Sub-groups	Genotypes MTHFR:C677T	Number of cases H_{cv} > 10 μmol/l			
		group B_9 < 4.6 ng/ml		group B_9 >4.6 ng/ml	
		abs. number	%	abs. number	%
1	T/T	14	100.0	9	75.00
2	C/T	20	95.24	67	74.44
3	T/T+C/T	34	97.14	76	74.51
4	C/C	16	84.21	71	68.27
3+4	T/T+C/T+C/C	50	92.59	147	71.36

Table 9

The results of comparing the proportion of cases of hyperhomocysteinemia in subgroups of children with MTHFR:C677T genotypes, with different levels of vitamin B_9 in the blood

Subgroups of comparison	Groups	Genotypes MTHFR: C677T	Student's t-test	Significance level, p
1	**2**	**3**	**4**	**5**
1 – 1	B_9 < 4.6 ng/ml	T/T	2.00	0.059266
	B_9 > 4.6 ng/ml	T/T		
2 – 2	B_9 < 4.6 ng/ml	C/T	3.18	0.002063
	B_9 > 4.6 ng/ml	C/T		

End of Table 9

1	2	3	4	5
3 – 3	B_9 < 4.6 ng/ml	T/T+C/T	4.39	0.000028
	B_9 > 4.6 ng/ml	T/T+C/T		
4 – 4	B_9 < 4.6 ng/ml	C/C	1.67	0.098178
	B_9 > 4.6 ng/ml	C/C		
[3+4] – [3+4]	B_9 < 4.6 ng/ml	T/T+C/T +C/C	4.47	0.000014
	B_9 > 4.6 ng/ml	T/T+C/T+C/C		
3 – 4	B_9 < 4.6 ng/ml	T/T+C/T	1.46	0.149865
	B_9 < 4.6 ng/ml	C/C		
3 – 4	B_9 > 4.6 ng/ml	T/T+C/T	0.99	0.322171
	B_9 > 4.6 ng/ml	C/C		

Table 10

Results of comparing the proportion of cases of vitamin B_9 deficiency among children with hyperhomocysteinemia in genetic subgroups

Subgroups of comparison	Groups	Genotypes	Student's t-test	Significance level, p
1 – 2	B_9 < 4,6 нг/мл	T/T	3.29	0.002448
	B_9 < 4,6 нг/мл	C/T		
1 – 3	B_9 <4,6 нг/мл	T/T	2.62	0.012004
	B_9 < 4,6 нг/мл	T/T+C/T		
1 – 4	B_9 < 4,6 нг/мл	T/T	3.52	0.001417
	B_9 < 4,6 нг/мл	C/C		
3 – 4	B_9 < 4,6 нг/мл	T/T+C/T	1.59	0.117747
	B_9 < 4,6 нг/мл	C/C		

The results of the studies carried out indicate the dependence of the metabolic relationships between vitamin B_9 and H_{cy} on the state of the genetic apparatus that controls MTHFR.

The largest proportion of cases of vitamin B_9 deficiency in the body was recorded in the subgroup of children with the homozygous variant of the T allele – 53.85 %, while in the subgroup of children with the homozygous variant of the allele C – 15.45 %.

Given that the variant of the T allele accounted for 64.81 % of the total number of cases of B_9 deficiency, it can be concluded that the level of vitamin B_9 in the bodies of the examined children from the Chernobyl regions depended on the MTHFR:C677T genetic polymorphism.

If in the general group the proportion of vitamin B_9 deficiency was recorded in 20.77 % of cases, then the state of hyperhomocysteinemia was determined in 75.77 % of cases. At the same time, the largest proportion of cases of hyperhomocysteinemia was detected in the subgroup with a homozygous variant of the T allele – 88.46 %. However, this subgroup is the smallest in terms of numbers in the general group of children (10.0 %),

therefore, its contribution to the total number of cases of hyperhomocysteinemia is also the smallest, only 11.68 %.

Table 11

Relationship between Hcy and vitamin B_9 in subgroups of children with genotypes MTHFR:C677T

Subgroups	Genotypes MTHFR:C677T	Correlation coefficient	Parameter	
			H_{cy}	B_9
1	T/T	Spearman's	–0.545**	
		Sign. (2-tailed), p	0.004	
		N	26	
2	C/T	Spearman's	–0.378**	
		Sign. (2-tailed), p	0.000	
		N	111	
3	T/T+C/T	Spearman's	–0.465**	
		Sign. (2-tailed), p	0.000	
		N	137	
4	C/C	Spearman's	–0.330**	
		Sign. (2-tailed), p	0.000	
		N	123	
General group	T/T+C/T+C/C	Spearman's	–0.414**	
		Sign. (2-tailed), p	0.000	
		N	260	

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

The total number of cases with the T allele dominated in the group of children with H_{cy} level > 10 μmol/l due to cases of heterozygous variants of this allele. It should be noted that in the subgroup of children with a homozygous variant of the C allele, the proportion of cases of hyperhomocysteinemia was 70.73 %.

Among the total number of cases of hyperhomocysteinemia, 44.16 % of cases were associated with the C/C MTHFR:C677T genotype. We tend to consider this a manifestation of external environmental impact, in the form of radionuclides incorporated into the body.

Thus, hyperhomocysteinemia and folate deficiency in the bodies of examined children from Ivankovsky and Polessky districts are associated with the risk allele T of the MTHFR:C677T genetic polymorphism.

These states are also related.

The state of hyperhomocysteinemia was recorded in the group of children with B_9 deficiency in 92.59 % of cases of children, which is significantly more than in the group of children with vitamin B_9 levels

within the reference values. The same situation was observed in subgroups of children with the T allele.

In the subgroup of children with hyperhomocysteinemia and a homozygous variant of the T allele in the genome, the largest, of all subgroups, the proportion of cases of vitamin B_9 deficiency was 60.87 %, while in the homozygous variant of the allele C, the proportion of cases of deficiency of this vitamin was 21.84 %.

The inverse correlation between the indicators reflecting the content of H_{cy} and vitamin B_9 in the blood also indicates the participation of a genetic factor in the occurrence of vitamin B_9 deficiency and the state of hyperhomocysteinemia in the body of children living near the ChEZ.

Most children with hyperhomocysteinemia were found to be vitamin B_9 deficient, most pronounced in the T allele of the MTHFR:677 genetic polymorphism.

Violation of the functioning of MTHFR led to a decrease in the formation of the active form of vitamin B_9-5-MTHF, and subsequently, to an increase in the level of H_{cy} in the blood.

The results obtained in the examination of adolescent children from the areas affected by the accident at the Chernobyl nuclear power plant are consistent with the results of a survey of adults from other countries in terms of correlations between H_{cy}, vitamin B_9 and MTHFR:C677T polymorphism[8, 9].

However, the results of our studies reveal the dependence of the occurrence of folic acid deficiency and the state of hyperhomocysteinemia on the T allele of the MTHFR:C677T polymorphism.

Violation of the functioning of the enzyme systems of the folate cycle is associated not only with an internal genetic factor, but also with an external environmental impact. In particular, disruption of the functioning of B_{12} methionine synthase leads to the fact that 5-MTHF is not used in the H_{cy} methylation reaction.

In this regard, the reference values provided by the laboratory cannot always be used to assess the availability of folic acid in the body of children living under conditions of constant radiation exposure.

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Therefore, in assessing the provision of the organism of children with folic acid, it is imperative to take into account the level of H_{cy} in the blood of children, and also pay attention to the genetic component, namely, the MTHFR:C677T polymorphism, which has the greatest effect on the activity of MTHFR and the formation of the active form of vitamin B_9-5-MTHF.

CONCLUSIONS

1. In the group of children aged 13–17 living near the ChEZ, in 75.77 % of cases, the level of H_{cy} in the blood exceeded the reference level.
2. In the subgroup of children with the T/T MTHFR:677 genotype, the proportion of cases of hyperhomocysteinemia was statistically more compared to the subgroup of children with the C/C MTHFR:677 genotype.
3. A decrease in the level of vitamin B_9 in the blood was recorded in the general group of children in 20.77 % of cases, in the subgroup of children with the homozygous variant of the T allele of the MTHFR:677 polymorphism – in 53.85 % of cases, while in the subgroup with the homozygous variant C – in 15.45 % of cases.
4. In the group of children with vitamin B_9 deficiency in the body, the proportion of cases with the T allele in the genome was significantly more than the proportion of cases with the homozygous variant of the C allele.
5. The proportion of cases of hyperhomocysteinemia in the group of children with vitamin B_9 levels below 4.6 μmol/l was more than in the group of children with blood levels of vitamin B_9 within the reference interval. At the same time, the association with the T allele of the MTHFR:C677T polymorphism was determined.
6. Among children with hyperhomocysteinemia in the subgroup with a homozygous variant of the T allele in the genome, the proportion of cases of vitamin B_9 deficiency was the largest compared to other genetic subgroups.
7. Vitamin B_9 deficiency in the body is associated with the T allele of the MTHFR:677 polymorphism, and is most pronounced in the homozygous T/T variant. The consequence of this is a violation of the processes of H_{cy} methylation and an increase in its concentration in the blood.
8. In addition to the genetically determined deficiency of vitamin B_9, as an inducer of hyperhomocysteinemia in children living near the ChEZ, one should consider the environmental radiation factor.
9. When assessing the availability of folic acid in the body of children living near the ChEZ, one should take into account the level of H_{cy} in the blood and the state of the genes that affect the activity of MTHFR.

SUMMARY

The study is devoted to the study of the causes of hyperhomocysteinemia in adolescent children living in the territories of the Kyiv region of Ukraine, located near the Chernobyl exclusion zone. The relationship between the content of vitamin B_9, homocysteine and allelic variants of MTHFR:C677T in the body of children was studied. It has been established that vitamin B_9 deficiency in the body is associated with the T allele of the MTHFR:677 polymorphism, and is most pronounced in the homozygous T/T variant. As an inducer of hyperhomocysteinemia, one should also take into account the environmental radiation factor.

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Information about the authors:
Bandazhevskyi Yury Ivanovych,
Doctor of Medical Sciences, Professor,
Head of the Board
PI Coordination and Analytical Center "Ecology and Health",
65, Poliska Str., Ivankiv, Kyiv region, 07200, Ukraine

Dubova Nataliia Fedorivna,
Candidate of Medical Sciences,
Associate Professor at the Department of Public Health
Shupyk National Healthcare University of Ukraine,
9, Dorohozhytska Str., Kyiv, 04112, Ukraine