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ЗАЛЕЖНІСТЬ МЕТАБОЛІЧНИХ АСОЦІАЦІЙ КАЛЬЦІЮ І ФОСФОРУ ВІД СТАНУ ГЕНОМА ФОЛАТНОГО ЦИКЛУ У ДІТЕЙ, ЯКІ ПРОЖИВАЮТЬ НА ТЕРИТОРІЇ, ЩО ПОСТРАЖДАЛА ВІД АВАРІЇ НА ЧОРНОБИЛЬСЬКІЙ АТОМНІЙ ЕЛЕКТРОСТАНЦІЇ

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THE METABOLIC RELATIONSHIP OF CALCIUM AND PHOSPHORUS TO THE STATE OF GENOME OF FOLATE METABOLISM IN CHILDREN LIVING IN THE AREAS SUFFERED FROM THE CHORNOBYL NUCLEAR POWER PLANT ACCIDENT

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Keywords: folate metabolism, genotype, homocysteine, calcium, phosphorus, hormones, radioactive contaminated territory.

Exploring the mechanisms of mineral metabolism regulation is of great importance in the organisation of curative and preventive measures of osteoporosis – a disease that leads to bone fractures [1].

Despite the wide prevalence of osteoporosis, its pathogenesis is poorly studied. A relationship has been found between the risk of osteoporosis in adults and elevated blood levels of homocysteine – a metabolite of the essential amino acid methionine [2].

It has been concluded that homocysteine is a predictor of bone fractures in adults [3]. Nearly 30 years after the accident at the Chornobyl nuclear power plant (CNPP), hyperhomocysteinemia has been reported in a large number of the children examined living under conditions of constant radiation exposure [4]. In this regard, it is important to determine a relationship of calcium and phosphorus with hormones regulating mineral metabolism taking into account the state of genome of folate metabolism affecting homocysteine formation.

The purpose of this study was to identify associations between blood levels of calcium, phosphorus and hormones regulating mineral metabolism, taking into account the state of genome of folate metabolism in children living in a district affected by the Chornobyl accident.

Material and methods. The study was conducted within the implementation of projects of the European Commission in Ukraine

ЗАЛЕЖНІСТЬ МЕТАБОЛІЧНИХ АСОЦІАЦІЙ КАЛЬЦІЮ І ФОСФОРУ ВІД СТАНУ ГЕНОМА ФОЛАТНОГО ЦИКЛУ У ДІТЕЙ, ЯКІ ПРОЖИВАЮТЬ НА ТЕРИТОРІЇ, ЩО ПОСТРАЖДАЛА ВІД АВАРІЇ НА ЧОРНОБИЛЬСЬКІЙ АТОМНІЙ ЕЛЕКТРОСТАНЦІЇ

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***Мета дослідження:** визначення кореляційних зв'язків між вмістом у крові кальцію, фосфору і гормонами, що регулюють мінеральний обмін, з урахуванням стану генома фолатного циклу у дітей, які проживають у районі, що постраждав від аварії на Чорнобильській атомній електростанції.*

***Методи дослідження:** імунохімічний, математико-статистичний.*

***Результати.** При обстеженні дітей, які мешкають у районі, що постраждав від аварії на Чорнобильській атомній електростанції, найбільшу питому вагу випадків гіпергомоцистеїнемії було виявлено у групах з генотипами T/T MTHFR:677 і G/G MTR:2756. У дітей, які проживають у районі, що постраждав від аварії на ЧАЕС, P порівняно з Ca, має більш тісні зв'язки з гормонами, які регулюють мінеральний обмін. У дітей, які проживають в умовах постійного радіаційного впливу, носійство генотипу T/T MTHFR:677, що супроводжується вираженою гіпергомоцистеїнемією, сприяє формуванню зворотного кореляційного зв'язку середньої сили між Ca і ТТГ. Водночас в усіх генетичних групах фолатного циклу відсутні кореляційні зв'язки між Ca і ПТГ, Ca і P. У групах 100% носійства алелей ризику поліморфізмів MTHFR:C677T і MTR:A2756G зв'язок між P і ПТГ був відсутнім. У групах з гомозиготним носійством зазначених алелей ризику (генотипи T/T MTHFR:677 і G/G MTR:2756) не виявлено зв'язків P з гормонами, що регулюють мінеральний обмін. Зниження активності ферментів метілентетрагідрофолатредуктази і B_{12}-залежної метіонін-синтази, у зв'язку з носійством алелей ризику генетичних поліморфізмів MTHFR:C677T і MTR:A2756G, призводить до порушення фізіологічної регуляції фосфорного обміну. Оцінку стану кальцій-фосфорного обміну у дітей із районів, що постраждали від аварії на ЧАЕС, слід проводити з урахуванням рівня гомоцистеїну у крові і генотипу фолатного циклу. Отримані результати можуть бути використаними під час розробки програми профілактики порушень мінерального обміну у дітей, які проживають у районах, що постраждали від аварії на ЧАЕС.*

Ключові слова: фолатний цикл, генотип, гомоцистеїн, кальцій, фосфор, гормони, радіоактивно забруднена територія.

«Health and Ecological Programmes around the Chornobyl Exclusion Zone: Development, Training and Coordination of Health-Related Projects» and the Rhфne-Alpes Regional Council (France). 158 children (78 boys and 80 girls) from Polessky district of Kiev region underwent laboratory examination. According to data of dosimetry certification of settlements, the territory of the district has remained contaminated with radioactive substances after the CNPP accident until the present day (having the ^{137}Cs soil contamination density of 0.17 up to 1.9 Cu/km^2) [5].

The examined children's average age was (14.8±0.1) years old (95% CI 14.7-15.0 years old).

All the children who attended school had blood drawn from the ulnar vein after fasting in the morning.

The blood samples were analysed at a laboratory certified under quality standards with the agreement of the parents. Thus, we assessed blood levels of homocysteine (H_c), ionized calcium (Ca), phosphorus (P), parathyroid hormone (PTH), calcitonin (CT), pituitary thyroid-stimulating hormone (TSH), free triiodothyronine (T_3), free thyroxine (T_4), cortisol (C) and the state of the genetic system of folate metabolism (FM).

Plasma homocysteine concentrations were measured using a chemiluminescent immunoassay (CLIA) method. Analyser and test kit: Architect 1000 (ABBOT Diagnostics, USA). Plasma homocysteine levels in the children of over 10 μmol/L were defined as hyperhomocysteinemia.

Ca levels were measured using an ion-selective method. Analyser and test kit: AVL 9180; Roche Diagnostics (Switzerland). The reference values were 1.16-1.32 mmol/L.

P concentrations were determined using the spectrophotometric method. Analyser and test kit: Cobas 6000, Roche Diagnostics (Switzerland). The reference values for boys were 0.95-1.65 mmol/L, for girls – 0.90-1.55 mmol/L.

PTH concentrations were determined using an electrochemiluminescent immunoassay (ECLIA) method. Analyser and test kit: Cobas 6000; Roche Diagnostics (Switzerland). The reference values were 15.0-65.0 pg/mL.

T_3 concentrations were measured using an electrochemiluminescent immunoassay (ECLIA) method. Analyser and test kit: Cobas 6000; Roche Diagnostics (Switzerland). The reference values were 2.3-5.0 pg/mL.

T_4 levels were determined using an electrochemiluminescent immunoassay (ECLIA) method. Analyser and test kit: Cobas 6000; Roche Diagnostics (Switzerland). The reference values were 1.1-1.8 ng/dL.

TSH concentrations were determined using an electrochemiluminescent immunoassay (ECLIA) method. Analyser and test kit: Cobas 6000; Roche Diagnostics (Switzerland). The reference values were 0.27-4.2 uIU/mL.

CT levels were measured using a chemiluminescent immunoassay (CLIA) method. Analyser and test kit: Immulite (Siemens AG), Germany. The reference values were up to 11.5 pg/mL.

C levels were measured using an electrochemiluminescent immunoassay (ECLIA) method. Analyser and test kit: Cobas 6000; Roche Diagnostics (Switzerland). The reference values were 6.2-19.4 μg/dL.

The following allelic variants were identified during genetic analysis of FM: C677T and A1298C of the MTHFR gene (synthesis of the methylenetetrahydrofolate reductase enzyme), A2756G of the MTR gene (synthesis of the B_{12}-dependent methionine synthase enzyme) and A66G of the MTRR gene (synthesis of the methionine synthase reductase enzyme). A real-time PCR method was used. Analyser and test kit: DT-96 detecting thermocycler, DNA-Technology (Russia).

During the study, we formed groups of children with a certain genotype of the FM polymorphisms under study (table 1).

The statistical processing of the results obtained was performed using the IBM SPSS Statistics 22 software (USA). The arithmetic mean (M), ± standard error of mean (m), confidence interval for the mean value (95% CI), median (Me), interquartile range (IR), minimum and maximum parameter values and per-

Table 1

Groups of children with a certain FM polymorphism genotype

Group number	Genotype	Group number	Genotype
1	MTR:2756 A/A	7	MTHFR:677 C/C
2	MTR:2756 A/G	8	MTHFR:677 C/T
3	MTR:2756 G/G	9	MTHFR:677 T/T
4	MTHFR:1298 A/A	10	MTRR:66 A/A
5	MTHFR:1298 A/C	11	MTRR:66 A/G
6	MTHFR:1298 C/C	12	MTRR:66 G/G

Table 2

Proportion of hyperhomocysteinemia in groups of examined children

Group number	Genotype	Number of children in a group	Number of cases with H_c>10 μmol/L	
			Absolute number	%
1	MTR:2756 A/A	104	58	55.8
2	MTR:2756 A/G	45	18	40.0
3	MTR:2756 G/G	9	8	88.9
4	MTHFR:1298 A/A	82	42	51.2
5	MTHFR:1298 A/C	60	33	55.0
6	MTHFR:1298 C/C	16	9	56.3
7	MTHFR:677 C/C	79	34	43.0
8	MTHFR:677 C/T	60	35	58.3
9	MTHFR:677 T/T	19	15	79.0
10	MTRR:66 A/A	32	12	37.5
11	MTRR:66 A/G	72	37	51.4
12	MTRR:66 G/G	54	35	64.8
General group		158	84	53.2

centiles were calculated for the variables analysed. The distribution hypothesis was tested (a Kolmogorov-Smirnov test). All the parameters under study did not conform to the normal distribution law, thus, a non-parametric Mann-Whitney U test was used to compare values. The statistical significance of variables was assessed by determining a significance level for p with the help of the statistical software programme.

The Student's t-test was used to compare relative values. The critical level of significance for the null hypothesis (p) was set at 0.05. Associations between levels of H_c and Ca, Hc and P, as well as Ca and P and PTH, CT, TSH, T_3, T_4, and C were identified with the help of Spearman's rank correlation coefficient (r_{xy}). The strength of the association was assessed according to a typical scale: weak – 0 to 0.299; moderate – 0.3 to 0.699; strong – 0.7 to 1.0.

Results and discussion. The proportion of hyperhomocysteinemia in separate genetic groups reflected the state of FM. This value had statistical differences with the same value in most groups, except for the groups № 3, 5, 8, 12, and in the group № 3 in most groups, except the group № 9 (tables 2, 3).

During the study, the following associations of ionized Ca were found:

a) a weak inverse association with T_4 in the group 5, carriership of the MTHFR:1298 A/C genotype;

b) a moderate inverse association with T_4 in the group 10, carriership of the MTRR:66 A/A genotype;

c) a weak direct association with CT in the group 8, carriership of the MTHFR:677 C/T genotype;

d) a moderate inverse association with TSH in the group 9, carriership of the MTHFR:677 T/T genotype (table 4).

During the study, the following associations of P were observed:

Direct associations with PTH (moderate), with TSH and T_3 (weak); an inverse association with T_4 (weak); in the group 1 (carriership of the MTR:2756 A/A genotype);

A direct association with T_3 (moderate), an inverse association with C (moderate) in the group 2 (carriership of the MTR:2756 A/G genotype);

Direct associations with T_3 (moderate), with PTH (weak) in the group 4 (carriership of the MTHFR:1298 A/A genotype);

A direct association with PTH (weak) in the group 5 (carriership of the MTHFR:1298 A/C genotype);

A direct association with PTH (moderate) in the group 6 (carriership of the MTHFR:1298 C/C genotype);

Direct associations with PTH and T_3 (moderate), with TSH (weak) in the group 7 (carriership of the MTHFR:677 C/C genotype);

Direct associations with TSH and T_3 (weak), and an inverse association with T_4 (moderate) in the group 8 (carriership of the MTHFR:677 C/T genotype);

Direct associations with PTH and T_3 (moderate) in the group 10 (carriership of the MTRR:66 A/A genotype);

Direct associations with PTH and T_3 (weak) in the group 11 (carriership of the MTRR:66 A/G genotype);

Direct associations with PTH and TSH (weak), inverse associations with C (moderate), with T_4 (weak) in the group 12 (carriership of the MTRR:66 G/G genotype) (table 5).

Thus, during the study we found associations between Ca

Table 3

Results of statistically significant differences when comparing blood H_c levels in the children examined

Comparison groups	Statistical significance	Comparison groups	Statistical significance
1	t=2.88 p=0.005	1	t=4.81 p=0.000010
9		3	
2	t=4.02 p=0.0004	2	t=5.57 p=0.000011
9		3	
3	t=1.23 p=0.23	4	t=3.26 p=0,0021
9		3	
4	t=2.26 p=0.028	5	t=2.93 p=0.006
9		3	
5	t=1.59 p=0.06	6	t=4.05 p=0.001
9		3	
6	t=2.50 p=0.02	7	t=6.18 p=0.00001
9		3	
7	t=4.23 p=0.0001	8	t=2.64 p=0.0012
9		3	
8	t=1.68 p=0.099	9	t=1.23 p=0.23
9		3	
10	t=3.87 p=0.0007	10	t=5.2 p=0.00007
9		3	
11	t=3.17 p=0.0026	11	t=4.9 p=0.00002
9		3	
12	t=1.63 p=0.109	12	t=3.15 p=0.003
9		3	

and hormones involved in mineral metabolism in certain genetic groups of children from the raions affected by the CNPP accident. An inverse association between Ca and TSH in the group 9 with the MTHFR:677 T/T genotype was the most pronounced (table 4). The greatest number of cases of hyperhomocysteinemia (tables 2, 3) and the highest blood levels of homocysteine were found in this group [6].

The heterozygous version of carriership of the T allele of this polymorphism – group 8 – MTHFR:677 C/T genotype – was accompanied by a smaller proportion of cases of hyperhomocysteinemia and lower blood levels of H_c, moreover, there was no association between Ca and TSH, as well as in the case of absence of carriership of the T allele – group 7 – MTHFR:677 C/C genotype.

Thus, the formation of an inverse association between Ca and TSH occurred in the groups of carriership of the MTHFR:677 T/T genotype in the presence of the largest proportion of cases of hyperhomocysteinemia and the highest blood H_c levels.

The studies conducted showed a moderate inverse association between Ca and T_4 in the group 10 – MTRR:66 A/A genotype, and a weak inverse association between Ca and T_4 in the group 5 – MTHFR: 1298 A/C genotype, as well as a weak association between Ca and CT in the group 8 – MTHFR:677 C/T genotype (table 4).

No associations were found between Ca and PTH, Ca and P in all the genetic groups of FM of the cohort of children examined.

P had more associations than Ca (table 5). First of all, these are moderate direct associations between P and PTH in the groups of carriers of homozygous variants of neutral polymorphisms: group 1 – MTR:2756 A/A, group 7 – MTHFR:677 C/C, group 10 – MTRR:66 A/A, as well as associations between P and T_3 in the following groups: 1 – MTR:2756 A/A, 4 – MTHFR:1298 A/A, 7 – MTHFR:677 C/C, 10 – MTRR:66 A/A.

A moderate direct association was observed between P and TSH in the group 12 – MTRR:66 G/G. A moderate association was reported with cortisol in the same group and in the group 2 – MTR:2756 A/G. A moderate inverse association was detected between P and T_4 in the group 8 – MTHFR:677 C/T, and weak inverse associations were found between P and T_4 in the groups 1 – MTR:2756 A/A and 12 – MTRR:66 G/G.

Thus, it should be noted that there is a presence of associations between P and PTH, P and T_3 in the groups formed on the basis of 100% carriership of homozygous variants of neutral alleles of FM polymorphisms. No associations were observed between P and hormones regulating mineral metabolism in the group 9 – MTHFR:677 T/T and in the group 3 – MTR:2756 G/G.

In our opinion, this may be due to a larger proportion of cases of hyperhomocysteinemia in these groups (tables 2, 3). The association between P and PTH disappears and the one between P and T_3 weakens significantly already in the presence of heterozygous carriership of risk alleles in the groups 8 (MTHFR:677 C/T genotype) and 2 (MTR:2756 A/G genotype) (table 5).

Given that H_c contributes to the development of osteoporosis [2], its increased production in the group of children – carriers of the MTHFR:677 T/T genotype may be regarded as an event that contributes to bone demineralization and the release of Ca into the blood.

At the same time, folic acid status should be taken into account. The homozygous carriership of the T allele of the MTHFR:C677T polymorphism was accompanied by the lowest blood levels of folic acid [7, 8] in the groups of children from the districts affected by the CNPP accident.

The negative effect of the T/T MTHFR:C677T genotype and low levels of folic acid, as well as riboflavin in the blood on bone mineralization in adults is known [9].

It also should be noted that the MTR:2756 G/G genotype has a negative effect on mineral metabolism, since there is a blocking of transfer of the methyl group to H_c, because of the lack of activity of the B_{12}-dependent methionine synthase enzyme.

Thus, there are no associations between P and hormones involved in mineral metabolism, in particular PTH and T_3 in the groups of children who are carriers of the MTHFR:677 T/T and MTR:2756 G/G genotypes.

The findings show that the genome of FM plays an important role for the physiological regulation of calcium/phosphorus metabolism in the body of children living under conditions of environmental distress associated with the accident at the CNPP.

Table 4

Associations between Ca and hormones values in groups of children with different genetic polymorphisms

Group №	Parameter	Correlation coefficient	Parameters		
			T_4, ng/dL	CT, pg/mL	TSH, ulU/mL
5	Ca, mmol/L	Spearman's	-0.276[1]		
		Sign. (2-tailed), p	0.033		
		N	60		
8	Ca, mmol/L	Spearman's		0.255[1]	
		Sign. (2-tailed), p		0.049	
		N		60	
9	Ca, mmol/L	Spearman's			-0.638[2]
		Sign. (2-tailed), p			0.003
		N			19
10	Ca, mmol/L	Spearman's	-0.359[1]		
		Sign. (2-tailed), p	0.044		
		N	32		

Notes: 1 – correlation is significant at the 0.05 level (2-tailed); 2 – correlation is significant at the 0.01 level (2-tailed).

In light of this, it is necessary to take into account the state of genome of folate metabolism and blood homocysteine concentrations when organising medical preventive activities against osteoporosis in children living in districts affected by the CNPP accident.

Conclusions

The largest proportion of cases of hyperhomocysteinemia was found in the groups with the MTHFR:677 T/T and MTR:2756 G/G genotypes when examining the children living in the districts affected by the CNPP accident.

In the children living in the district affected by the CNPP accident, P has stronger associations with hormones that regulate mineral metabolism compared to Ca.

In the children living under constant radiation exposure, the carriership of the MTHFR:677 T/T genotype accompanied by marked hyperhomocysteinemia contributes to the formation of the moderate inverse association between Ca and TSH. At the same time, no associations were found between Ca and PTH, Ca and P in all genetic groups of folate metabolism.

There was no association between P and PTH in the groups with 100% carriership of the risk alleles of the MTHFR:C677T and MTR:A2756G polymorphisms.

No associations were observed between P and hormones that regulate mineral metabolism in the groups with homozygous carriership of the above risk alleles (MTHFR:677 T/T and MTR:2756 G/G genotypes).

The decrease in the activity of the methylenetetrahydrofolate reductase and B_{12}-dependent methionine synthase enzymes due to the carriership of risk alleles of the MTHFR:C677T and MTR:A2756G genetic polymorphisms leads to impaired physiological regulation of phosphorus metabolism.

The assessment of calcium/phosphorus metabolism in children from districts affected by the CNPP accident should be carried out taking into account blood homocysteine levels and folate metabolism genotype.

The findings can be used in developing a programme for the prevention of mineral metabolism diseases in children living in areas affected by the CNPP accident.

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Table 5

Associations between the values of P and hormones in groups of children with different genetic polymorphisms

Group №	Parameter	Correlation coefficient	Parameters				
			PTH, pg/mL	TSH, uIU/mL	T_3, pg/mL	T_4, ng/dL	C, µg/dL
1	P, mmol/L	Spearman's	0.482[2]	0.201[1]	0.259[2]	-0.216[1]	
		Sign. (2-tailed), p	0.0001	0.041	0.008	0.028	
		N	104	104	104	104	
2	P, mmol/L	Spearman's			0.303[1]		-0.310[1]
		Sign. (2-tailed), p			0.043		0.038
		N			45		45
4	P, mmol/L	Spearman's	0.280[1]		0.397[2]		
		Sign. (2-tailed), p	0.011		0.0001		
		N	82		82		
5	P, mmol/L	Spearman's	0.283[1]				
		Sign. (2-tailed), p	0.029				
		N	60				
6	P, mmol/L	Spearman's	0.519[1]				
		Sign. (2-tailed), p	0.039				
		N	16				
7	P, mmol/L	Spearman's	0.411[2]	0.224[1]	0.326[2]		
		Sign. (2-tailed), p	0.0001	0.047	0.003		
		N	79	79	79		
8	P, mmol/L	Spearman's		0.284[1]	0.293[1]	-0.376[2]	
		Sign. (2-tailed), p		0.028	0.023	0.003	
		N		60	60	60	
10	P, mmol/L	Spearman's	0.405[1]		0.481[2]		
		Sign. (2-tailed), p	0.021		0.005		
		N	32		32		
11	P, mmol/L	Spearman's	0.260[1]		0.272[1]		
		Sign. (2-tailed), p	0.027		0.021		
		N	72		72		
12	P, mmol/L	Spearman's	0.270[1]	0.326[1]		-0.270[1]	-0.328[1]
		Sign. (2-tailed), p	0.049	0.016		0.049	0.016
		N	54	54		54	54

Notes: 1 – correlation is significant at the 0.05 level (2-tailed); 2 – correlation is significant at the 0.01 level (2-tailed).

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A state of hyperhomocysteinemia was revealed in the large number of examined children living under conditions of constant radiation exposure. At the same time, taking into account the connection of homocysteine with the processes of osteogenesis, it is important to show the connection of calcium and phosphorus with hormones that regulate mineral metabolism, including the state of the folate cycle genome.
Objective: *We identified the correlations between blood levels of calcium, phosphorus, and hormones regulating mineral metabolism, taking into account the state of genome of folate metabolism in children living in a district suffered from the accident at the Chornobyl nuclear power plant.*
Methods: *We used immunochemical and mathematical-and-statistical methods.*
Results: *When examining children living in the area suffered from the accident at the Chornobyl nuclear power plant, the largest proportion of cases of hyperhomocysteinemia was found in the groups with T/T MTHFR: 677 and G/G MTR: 2756 genotypes. In children living in the area suffered from the accident at the ChNPP, P, in comparison with Ca, has closer links with hormones that regulate mineral metabolism. In children living under conditions of constant radiation exposure, the bearing of T/T MTHFR: 677genotype, accompanying by the severe hyperhomocysteinemia, contributes to the formation of the inverse correlation of the medium force between Ca and TSH. At the same time, there are no correlations between Ca and PTH, Ca and P in all genetic groups of the folate cycle. There was no connection between P and PTH in the groups of 100% bearing of risk alleles of MTHFR: C677T and MTR: A2756G polymorphisms. There were no connections of P with hormones that regulate mineral metabolism in the groups with homozygous bearing of noted risk alleles (genotypes T/T MTHFR: 677 and G/G MTR: 2756). A decrease in the activity of methylenetetrahydrofolate reductase and B_{12}-dependent methionine synthase enzymes, in connection with the bearing of risk alleles of MTHFR: C677T and MTR: A2756G genetic polymorphisms, leads to impaired physiological regulation of phosphoric metabolism. Assessment of calcium-phosphorus metabolism in children from the areas suffered from the accident at the Chornobyl NPP should be carried out taking into account the level of homocysteine in blood and the genotype of folate cycle. The obtained results can be used in the development of the program on the prevention of mineral metabolism disorders in children living in the areas suffered from the accident at the ChNPP.*

Keywords: folate metabolism, genotype, homocysteine, calcium, phosphorus, hormones, radioactive contaminated territory.

у детей, проживающих на территории, загрязненной радионуклидами в результате аварии на Чернобыльской атомной электростанции. *Педиатрия. Восточная Европа.* 2017. Т. 5. № 1. С. 25-32.

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