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Association between Folate Metabolism and Hypothalamic-Pituitary-Thyroid Axis in Children, who Live in the Regions Affected by the Chernobyl Nuclear Power Plant Accident

Связь фолатного цикла и гипоталамо-гипофизарно-тиреоидной оси у детей, проживающих в районах, пострадавших в результате аварии на Чернобыльской атомной электростанции

Abstract

Introduction. The problem of thyroid pathologies is acute in the regions affected by the Chernobyl nuclear power plant accident.
At the same time, a large number of cases of abnormal methionine metabolism were observed among children, who live in the regions contaminated with radionuclides. In this regard, it is reasonable to determine the associations between folate metabolism and the hypothalamic-pituitary-thyroid axis and physical growth in children, who live in the regions affected by the Chernobyl nuclear power plant accident.
Purpose. To determine the associations between thyroid and pituitary hormones, the state of folate metabolism and physical growth in children, who live in the regions contaminated with radioactive substances as a result of the Chernobyl nuclear power plant accident.
Methods. Immunochemical, anthropometric, mathematical and statistical.
Results and discussion. The studies showed that the fact of being a carrier of the T allele of the MTHFR:C677T genetic polymorphism in children, who live in the regions affected by the Chernobyl nuclear power plant accident is accompanied by a number of significant peculiarities of their body's metabolism.
Blood homocysteine levels are statistically higher and physical growth index is lower in children, who are the carriers of the T allele of the MTHFR:C677T genetic polymorphism than in those, who do not have this allele.
The correlations were identified between homocysteine and hormones of the hypothalamic-pituitary-thyroid axis, in particular, thyroid-stimulating hormone of the pituitary gland, thyroxine and triiodothyronine in the context of different variants of carriership of folate metabolism genetic polymorphisms.

The role of a missense mutation (replacement of cytosine with thymine) at the position 677 in the MTHFR gene in the occurrence of associations between the sulphur-containing amino acid homocysteine, thyroid-stimulating hormone of the pituitary gland and triiodothyronine was determined.
Carriership of the T allele of the MTHFR:C677T genetic polymorphism predetermines the occurrence of direct association between the serum levels of homocysteine and thyroid-stimulating hormone of the pituitary gland.
In the absence of mutation at the position 677 in the MTHFR gene, serum homocysteine values correlate directly with the serum triiodothyronine values.
The findings can be used in the development of measures for prevention of pathological conditions associated with abnormal functioning of vital systems in the population living in the areas contaminated with radioactive substances as a result of the Chernobyl nuclear power plant accident.
Keywords: correlation, homocysteine, thyroid-stimulating hormone of the pituitary gland, triiodothyronine, thyroxine, folate metabolism, genetic polymorphism, physical development, radiation-contaminated areas.

Резюме

Введение. Проблема патологии щитовидной железы остро стоит в районах, пострадавших от аварии на Чернобыльской атомной электростанции.
В то же время среди популяции детей, проживающих в районах, загрязненных радионуклидами, выявлено большое число случаев нарушения обмена метионина. В связи с этим целесообразно определить связь между фолатным циклом и гипотоламо-гипофизарно-тиреоидной осью, а также физическим развитием у детей, проживающих в районах, пострадавших от аварии на Чернобыльской атомной электростанции.
Цель. Определение связи между гормонами щитовидной железы и гипофиза, состоянием фолатного цикла и физическим развитием у детей, проживающих в районе, загрязненном радиоактивными элементами в результате аварии на Чернобыльской атомной электростанции.
Методы. Иммунохимический, антропометрический, математико-статистический.
Результаты и обсуждение. Проведенные исследования показали то, что носительство аллели Т генетического полиморфизма MTHFR:C677T детьми, проживающими в районах, пострадавших от аварии на Чернобыльской атомной электростанции, сопровождается рядом существенных особенностей обмена веществ их организма.
Уровень гомоцистеина в крови детей – носителей аллели Т генетического полиморфизма MTHFR:C677T статистически выше, а индекс физического развития ниже, чем в крови детей, лишенных данной аллели.
Выявлены корреляционные взаимоотношения между гомоцистеином и гормонами гипоталамо-гипофизарно-тиреоидной оси, в частности тиреотропного гормона гипофиза, тироксина и трийодтиронина при различных вариантах носительства генетических полиморфизмов фолатного цикла.
Определена роль миссенс-мутации (замена цитозина на тимин) в позиции 677 гена MTHFR в возникновении корреляционных связей между серосодержащей аминокислотой гомоцистеином, тиреотропным гормоном гипофиза и трийодтиронином.
Носительство аллели Т генетического полиморфизма MTHFR:C677T предопределяет к возникновению прямой корреляционной связи между содержанием в сыворотке крови гомоцистеина и тиреотропного гормона гипофиза.
При отсутствии мутации в позиции 677 гена MTHFR в прямой корреляционной связи находятся показатели, отражающие содержание в сыворотке крови гомоцистеина и трийодтиронина.
Полученные результаты могут быть использованы при разработке мероприятий по профилактике патологических состояний, связанных с нарушением функционирования жизненно

важных систем у населения, проживающего на территории, загрязненной радиоактивными элементами в результате аварии на Чернобыльской атомной электростанции.
Ключевые слова: корреляционная связь, гомоцистеин, тиреотропный гормон гипофиза, трийодтиронин, тироксин, фолатный цикл, генетический полиморфизм, физическое развитие, радиоактивно загрязненная территория.

■ INTRODUCTION

The problem of thyroid pathologies is acute in raions affected by the Chernobyl nuclear power plant accident [1].

Studies conducted within projects of the European Commission and the Rhône-Alpes Regional Council (France) have shown that there is a large number of cases of abnormal methionine metabolism among children living in raions contaminated with radionuclides [2, 3]. The findings call for clarification of associations between folate metabolism and the hypothalamic-pituitary-thyroid axis.

The state of folate metabolism is determined by its genome and serum homocysteine levels. The physical growth of children reflects the state of metabolic processes in vital organs, including the thyroid gland.

■ PURPOSE OF THE STUDY

Determine associations between thyroid and pituitary hormones, the state of folate metabolism and physical growth in children living in a raion contaminated with radioactive substances as a result of the Chernobyl nuclear power plant accident.

■ MATERIALS AND METHODS

The study was carried out within the projects of the European Commission in Ukraine "Health and ecological programmes around the Chernobyl Exclusion Zone: Development, training and coordination of health-related projects" and the Rhône-Alpes Regional Council (France). 178 children from Ivankovsky raion, which according to data of dosimetry certification of settlements has remained contaminated with radioactive substances after the Chernobyl accident until the present day (^{137}Cs soil contamination density of 0.17 up to 1.9 curie/sq.km), were subjected to laboratory and instrumental examination [4]. The children's average age was 13.6±0.1 years (95% CI 13.4–13.8 years).

All the children who attended school had blood drawn from the ulnar vein on an empty stomach in the morning. The blood samples were analysed at a laboratory certified under quality standards with the agreement of parents. We assessed blood levels of thyroid-stimulating hormone of the pituitary gland (TSH), free triiodothyronine (T_3), free thyroxine (T_4), homocysteine (Hc), and the state of the folate metabolism (FM) genetic system.

TSH, T_3 and T_4 concentrations were determined using an electrochemiluminescent immunoassay (ECLIA) method. Analyser and test kit: Cobas 6000; Roche Diagnostics (Switzerland).

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.

The following allelic variants were identified during genetic analysis of folate metabolism: 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).

Anthropometric measuring techniques standardised in Ukraine [5] were used to assess physical growth (PG) in the children. Rules of bioethics were also observed and informed consents were signed by the parents of each subject [6, 7]. The Rohrer's weight/height index (RI), being independent of age and sex and calculated by dividing weight in kilograms by the cubic of height in meters, was chosen as a criterion for assessment of PG and metabolism in a child.

The RI allows to estimate the degree of weight and height conformity of an individual. Normal PG is defined at RI values of 10.7 to 13.7 kg/m^3, abnormal PG in children with insufficient body weight is defined at RI values of less than 10.7 kg/m^3, and abnormal PG in children with excessive body weight is defined at RI values of 13.7 kg/m^3. Three subgroups were identified in the group of children from Ivankovsky raion according to RI values: 1 – abnormal (low) PG, RI values are <10.7; 2 – normal PG, RI values lie within the range ≤13.7 and ≥10.7; 3 – abnormal (high) PG, RI values are >13.7.

During the study, we compared above metabolic variables in groups of children in the context of carriership and absence of risk alleles of the genetic polymorphisms analysed.

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 percentiles 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 blood Hc, TSH, T_3 and T_4 levels were identified with the help of the Spearman's rank correlation coefficient (r_{xy}). The strength of correlation 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

There were no statistical differences between serum levels of Hc, TSH, T_3, T_4 and RI between groups of children who were carriers of risk and neutral alleles of the MTHFR:A1298C, MTR:A2756G and MTRR:A66G genetic polymorphisms.

However, serum Hc values in the group of children who were carriers of T allele of the MTHFR:C677T genetic polymorphism (MTHFR:677 C/T and T/T genotypes) were statistically significantly higher than that in the group of children with the MTHFR:677 C/C genotype. At the same time, an inverse association was detected with respect to RI. The mean values of this variable were higher in the group of children who were carriers of the MTHFR:677 C/C genotype compared with the group of children who were carriers of the MTHFR:677 C/T and T/T genotypes (Tab. 1, 2). This is due to the high percentage of children with abnormal high physical growth (Tab. 3).

A direct association was observed between Hc and TSH values in the groups of children who were carriers of a risk allele of the MTHFR:C677T, MTR:A2756G and MTRR:A66G polymorphisms, and in the group of carriers of only A neutral allele of the MTHFR:A1298C polymorphism (Tab. 4).

A direct association was reported between Hc and T_3 in the groups of children who were carriers of genotypes, which included only neutral alleles - MTHFR:677 C/C, MTHFR:A1298C A/A and MTRR:A66G A/A (Tab. 5).

There was an association between TSH and T_3 in all the genetic groups studied, except for the group of children who were carriers of the MTHFR:1298 C/C genotype. The strongest association was found in the groups of carriers of the MTHFR:1298 A/A and MTRR:66 A/A genotypes (Tab. 6).

Weak inverse associations were detected between TSH and T_4 (r=–0.278*, p=0.012, n=80), RI and T_3 (r=–0.227*, p=0.043, n=80) in the group of children who were carriers of the MTHFR:677 C/C genotype. The analyses carried out showed that blood levels of homocysteine were higher in the group of children who were carriers of the T allele of the MTHFR:C677T polymorphism than in the group of children who were not carriers of the allele. In this group, a direct association was reported between Hc and TSH.

Table 1
Statistical characteristics of metabolic and physical growth variables of the children examined

Variables	A group of children with MTHFR:677 C/C genotype			A group of children with MTHFR:677 C/T + T/T genotypes		
	n	Me	IR	n	Me	IR
Hc, μmol/L	80	11.36	9.4–13.0	98	11.82	10.04–14.85
TSH, μIU/mL	80	1.76	1.29–2.89	98	1.84	1.31–2.46
T_3, pg/mL	80	4.44	4.08–4.81	98	4.33	3.96–4.68
T_4, ng/dL	80	1.24	1.12–1.31	98	1.22	1.14–1.30
RI	80	12.2	11.2–14.0	98	11.8	11.0–13.0

Table 2
Results of statistically significant differences when comparing metabolic and physical growth variables in the children examined

Variables	Comparison groups	Comparison group size	Average rank	Mann–Whitney U test, significance level, p
Hc, μmol/L	1	80	80.71	U=3217.000; p=0.040
	2	98	96.67	
RI	1	80	98.64	U=3188.500; p=0.032
	2	98	82.4	

Note: group 1 – a group of children with MTHFR:677 C/C genotype; 2 – a group of children with MTHFR:677 C/T+T/T genotypes.

Table 3
Number of children with different physical growth comprising groups with a certain folate metabolism genotype

Subgroups of physical growth	A group of children with MTHFR:677 C/C genotype, n=80		A group of children with MTHFR:677 C/T + T/T genotypes, n=98	
	Absolute number	%	Absolute number	%
Abnormal low	10	12.5	9	9.2*
Normal	48	60.0	79	80.6**
Abnormal high	22	27.5	10	10.2***

Notes:
* statistical differences between groups with MTHFR:677 C/C and MTHFR:677 C/T+T/T genotypes (t=0.73; p=0.478313);
** statistical differences between groups with MTHFR:677 C/C and MTHFR:677 C/T+T/T genotypes (t=3.03; p=0.002985);
*** statistical differences between groups with MTHFR:677 C/C and MTHFR:677 C/T+T/T genotypes, (t=2.94; p=0.006373)

Table 4
Results of correlation analysis between Hc and TSH values in groups of children with different polymorphisms

Genotype	Correlation coefficient	Parameters
		Hc and TSH
MTR:2756 A/G + MTR:2756 G/G	**Spearman's**	0.266*
	Sign. (2-tailed), p	0.024
	N	72
MTR:2756 A/A	**Spearman's**	0.140
	Sign. (2-tailed), p	0.152
	N	106
MTHFR:1298 A/C + MTHFR:1298 C/C	**Spearman's**	0.108
	Sign. (2-tailed), p	0.313
	N	89
MTHFR:1298 A/A	**Spearman's**	0.288**
	Sign. (2-tailed), p	0.006
	N	89
MTHFR:677 C/T + MTHFR:677 T/T	**Spearman's**	0.343**
	Sign. (2-tailed), p	0.001
	N	98
MTHFR:677 C/C	**Spearman's**	0.023
	Sign. (2-tailed), p	0.838
	N	80
MTRR:66 A/G + MTRR:66 G/G	**Spearman's**	0.229**
	Sign. (2-tailed), p	0.005
	N	151
MTRR:66 A/A	**Spearman's**	0.108
	Sign. (2-tailed), p	0.592
	N	27

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

In other groups divided according to the principle of carriership of risk and neutral alleles of folate metabolism polymorphisms, a smaller number of subjects have T allele in their genome. As a result, the strength of association between Hc and TSH is weaker. The extreme case is 100 per cent absence of the allele in the children with the MTHFR:677 C/C genotype, and there is no correlation between Hc and TSH.

Thus, in subjects with homozygous and heterozygous variants of the T allele of the MTHFR gene C677T polymorphism, there is a high probability of elevated blood homocysteine levels, which may be a stimulus for excessive production of thyroid-stimulating hormone by the pituitary gland.

The excessive production of TSH by the pituitary gland may facilitate hyperplasia of cells of the thyroid gland [8].

There was an association between blood levels of Hc and T_3 in the groups of children who were carriers of genotypes that included only neutral alleles of the polymorphisms under study: MTHFR:677 C/C, MTHFR:1298 A/A

Table 5
Results of correlation analysis between Hc and T3 values in groups of children with different polymorphisms

Genotype	Correlation coefficient	Parameters
		Hc and T_3
MTR:2756 A/G + MTR:2756 G/G	**Spearman's**	0.147
	Sign. (2-tailed), p	0.218
	N	72
MTR:2756 A/A	**Spearman's**	0.171
	Sign. (2-tailed), p	0.080
	N	106
MTHFR:1298 A/C + MTHFR:1298 C/C	**Spearman's**	–0.027
	Sign. (2-tailed), p	0.801
	N	89
MTHFR:1298 A/A	**Spearman's**	0.299**
	Sign. (2-tailed), p	0.004
	N	89
MTHFR:677 C/T + MTHFR:677 T/T	**Spearman's**	0.113
	Sign. (2-tailed), p	0.270
	N	98
MTHFR:677 C/C	**Spearman's**	0.256*
	Sign. (2-tailed), p	0.022
	N	80
MTRR:66 A/G + MTRR:66 G/G	**Spearman's**	0.092
	Sign. (2-tailed), p	0.263
	N	151
MTRR:66 A/A	**Spearman's**	0.502**
	Sign. (2-tailed), p	0.008
	N	27

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

Table 6
Results of correlation analysis between TSH and T_3 values in groups of children with different polymorphisms

Genotype	Correlation coefficient	Parameters
		TSH and T_3
MTR:2756 A/G + MTR:2756 G/G	**Spearman's**	0.258*
	Sign. (2-tailed), p	0.029
	N	72
MTR:2756 A/A	**Spearman's**	0.240*
	Sign. (2-tailed), p	0.013
	N	106
MTHFR:1298 A/C + MTHFR:1298 C/C	**Spearman's**	0.134
	Sign. (2-tailed), p	0.210
	N	89
MTHFR:1298 A/A	**Spearman's**	0.325**
	Sign. (2-tailed), p	0.002
	N	89
MTHFR:677 C/T + MTHFR:677 T/T	**Spearman's**	0.222*
	Sign. (2-tailed), p	0.028
	N	98
MTHFR:677 C/C	**Spearman's**	0.264*
	Sign. (2-tailed), p	0.018
	N	80
MTRR:66 A/G + MTRR:66 G/G	**Spearman's**	0.186*
	Sign. (2-tailed), p	0.022
	N	151
MTRR:66 A/A	**Spearman's**	0.580**
	Sign. (2-tailed), p	0.002
	N	27

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

and MTRR:66 A/A. At the same time, an inverse association was observed between T_3 and RI in the group of carriers of the MTHFR:677 C/C genotype responsible for the synthesis of the methylenetetrahydrofolate reductase enzyme. Considering that RI had significantly higher values in this group than in the group of carriers of the T allele, mainly because of cases of abnormal high PG, it can be concluded that T_3 is produced inadequately, which can be one of the reasons for the increase in weight in adolescent children.

Both the direct association between TSH and T_3 reported in the majority of the groups studied, and the inverse association between TSH and T_4 detected in the group of carriers of the MTHFR:677 C/C genotype reflect the processes of physiological regulation in the pituitary-thyroid system.

Thus, as a result of the studies conducted, correlations were identified between homocysteine and hormones of the hypothalamic-pituitary-thyroid axis, in particular, thyroid-stimulating hormone of the pituitary

gland, thyroxine and triiodothyronine in the context of different variants of carriership of folate metabolism genetic polymorphisms.

The role of a missense mutation (replacement of cytosine with thymine) at position 677 in the MTHFR gene in the occurrence of associations between the sulphur-containing amino acid homocysteine, thyroid-stimulating hormone of the pituitary gland and triiodothyronine was determined.

In particular, carriership of the T allele of the MTHFR:C677T genetic polymorphism predetermines the occurrence of the direct association between serum concentrations of homocysteine and thyroid-stimulating hormone of the pituitary gland.

In the absence of the mutation at position 677 in the MTHFR gene, serum homocysteine correlates directly with serum triiodothyronine.

The findings can be used in the development of measures for the prevention of pathological conditions associated with abnormal functioning of vital systems in population living in areas contaminated with radioactive substances as a result of the Chernobyl nuclear power plant accident.

■ CONCLUSIONS

1. The studies conducted have shown that carriership of the T allele of the MTHFR:C677T genetic polymorphism in children living in raions affected by the Chernobyl nuclear power plant accident is accompanied by a number of significant peculiarities of their body's metabolism.
2. Blood homocysteine levels are statistically higher and physical growth index is lower in children who are carriers of the T allele of the MTHFR:C677T genetic polymorphism than in those who have no this allele.
3. There is a direct association between serum levels of homocysteine and thyroid-stimulating hormone of the pituitary gland in the group of children who are carriers of the T allele of the MTHFR:C677T polymorphism.
4. In subjects with the C677T mutation in the MTHFR gene responsible for the synthesis of methylenetetrahydrofolate reductase, there is a high probability of elevated blood homocysteine levels above physiological limits, which may be a stimulus for excessive production of thyroid-stimulating hormone by the pituitary gland.
5. There was a direct association between serum levels of Hc and T_3 in the groups of children who were carriers of genotypes that included only neutral alleles of the polymorphisms under study (MTHFR:677 C/C, MTHFR:1298 A/A and MTRR:66 A/A genotypes).
6. Mean values of RI are significantly higher in the group of children who do not carry the T allele (MTHFR:677 C/C genotype) than in the group of children who are carriers of the T allele due to cases of abnormal high PG. The inverse association between serum concentrations of T_3 and RI values shows that there is an inadequate hormonal regulation of metabolic processes in a developing body by the thyroid gland.
7. Direct associations between TSH and T_3 reported in the majority of the groups of children studied, and the inverse association between TSH and T_4 detected in the group of carriers of the MTHFR:677 C/C genotype reflect the processes of physiological regulation in the pituitary-thyroid system.

8. The identification of associations between methionine metabolism and the hypothalamic-pituitary-thyroid axis allows to mark out the ways of effective prevention of thyroid diseases in adults and children in areas affected by the Chernobyl nuclear power plant accident.

Authors declare no conflict of interest.

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