15. Loy J. What should a radiation regulator do about naturally occurring radioactive material? // Annals of the ICRP : Proceedings of the Second International Symposium on the System of Radiological Protection. 2015. – Vol.44, – №.1S. – P. 197-201.
16. Ярмошенко И.В., Малиновский Г.П., Васильев А.В., Жуковский М.В. Обзор рекомендаций МАГАТЭ по защите от облучения радоном в жилищах // АНРИ. 2015. – №4 (83). – С.22-28.
17. Киселев С.М., Жуковский М.В., Стамат И.П., Ярмошенко И.В. Радон: От фундаментальных исследований к практике регулирования / М.: ФГБУ ГНЦ ФМБЦ им. А.И. Бурназяна ФМБА России, 2016. – 432 с.
18. Киселев С.М., Жуковский М.В. Современные подходы к обеспечению защиты населения от радона. Международный опыт регулирования // Радиационная гигиена. 2014. – Т.7, – №4. – С. 48-52.
19. Васильев А.В., Ярмошенко И.В., Жуковский М.В. Радоновая безопасность современных многоэтажных зданий // Биосферная совместимость: человек, регион, технологии. 2014. – №3(7). – С.19-25.
20. Ярмошенко И.В., Малиновский Г.П., Васильев А.В., Жуковский М.В. Обзор рекомендаций МАГАТЭ по защите от облучения радоном в жилищах // АНРИ. 2015. – №4(83). – С.22-28.
21. Павленко Т.О., Аксьонов М.В., Фризюк М.А., Турос О.І., Герман О.О. Методи протирадонового захисту будівель (огляд літератури) // Гігієна населених місць : Зб. наук. праць. 2012. – №60. – С. 218-222.

КОНЦЕПТУАЛЬНЫЕ ОСНОВЫ СОЗДАНИЯ ПЛАНА ДЕЙСТВИЙ ПО ЗАЩИТЕ НАСЕЛЕНИЯ ОТ РАДОНА (обзор международных требований)

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Статья содержит обзор международных требований относительно структуры и основных положений плана действий по защите населения от радона.

CONCEPTUAL BASICS OF ACTION PLAN CREATION TO PROTECT POPULATION FROM RADON (review of international requirements)

N.V. Aksenov, M.A. Fryziuk, O.Y. Tarasiuk

Review of international requirements on the structure and key provisions of action plan to protect population from radon is given in this article.

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ASSOCIATIONS BETWEEN THYROID HORMONES AND HOMOCYSTEINE IN CHILDREN LIVING IN AREAS AFFECTED BY THE CHERNOBYL NUCLEAR POWER PLANT ACCIDENT

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Relevance of the problem. 30 years after the Chernobyl nuclear power plant accident, children living in areas contaminated with radioactive substances have been reported to have metabolic abnormalities associated with sulphur-containing amino acids methionine and homocysteine [1-3]. From a scientific and practical point of view, it is important to determine the role of these abnormalities in the occurrence of thyroid diseases.

The aim of this paper is to identify associations between homocysteine and thyroid hormones in children with different physical growth levels living in areas affected by the Chernobyl nuclear power plant accident.

Material and methods. The research 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). We performed a laboratory and instrumental examination of 178 children from Ivankov district, which according to data of dosimetry certification of settlements, has remained contaminated with radioactive substances after the Chernobyl accident until the present day and has a ^{137}Cs soil contamination density of 0.17 up to 1.9 Cu/km^2 [4]. The average age of the children 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 the parents. We measured blood levels of pituitary thyroid-stimulating hormone (TSH), free triiodothyronine (T_3), free thyroxine (T_4), homocysteine (Hc), and vitamins B_6, B_9 and B_{12}, and assessed the state of the folate metabolism (FM) genetic system.

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

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

Vitamin B_6 concentrations were determined using a high-performance liquid chromatography (HPLC) assay method. An analyser and a test system: HPLC-System 1100, Agilent with fluorescence detection; Recipe complet Kit (Germany).

Vitamin B_9 (folacin) levels were measured using an electrochemiluminescent immunoassay method (ECLIA). An analyser and a test system: Cobas e411; Roche Diagnostics (Switzerland).

Vitamin B_{12} (holotranscobalamin, active vitamin B_{12}) concentrations were measured using a chemiluminescent immunoassay method (CLIA). An analyser and a test system: Architect 1000 (ABBOT Diagnostics (USA)).

The allelic variants 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) were identified during genetic analysis of folate metabolism. A real-time PCR method was used. An analyser and a test system: the 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) – calculated by dividing weight in kilograms by the cubic of height in meters – was used as a criterion for assessment of physical growth and metabolism in children.

This measure allows to estimate the degree of weight and height conformity of an individual. Normal PG is diagnosed at the RI values of 10.7 to 13.7 kg/m^3, children's abnormal PG with insufficient body weight is diagnosed at the RI values of less than 10.7 kg/m^3, and children's abnormal PG with excessive body weight is diagnosed at the RI values of 13.7 kg/m^3. Three subgroups were identified in the group of children from Ivankov district according to the 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.

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 (a Kolmogorov-Smirnov test) was tested. All the parameters under study did not conform to the normal distribution law, thus, a non-parametric U Mann-Whitney 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, and the T_3/T_4 coefficient 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. An inverse association was reported between TSH and free T_4 values in the total group of children, which should be viewed as a physiological interaction between the pituitary system and the thyroid gland. At the same time, a direct association was observed between TSH and T_3 levels (table 1). In our opinion, it is formed because TSH has a stimulating effect on the deiodinase enzyme, which converts T_4 to T_3 [8]. Thus, the higher the TSH, the higher T_3. It is proved by a direct association between TSH and the T_3/T_4 coefficient values (table 1).

Weak direct associations were found between homocysteine and TSH values, and homocysteine and free T_3 values in this group of children (table 1).

Table 1. Results of correlation analysis of metabolic variables in a total group of children from Ivankov district.

Parameter	Correlation coefficient	Parameter			
		Hc	TSH	T_3	T_4
Hc	Spearman's	1.000	0.206**	0.157*	0.095
	Sign. (2-tailed), p	.	**0.006**	**0.037**	0.207
	N	178	178	178	178
TSH	Spearman's	0.206**	1.000	0.236**	-0.149*
	Sign. (2-tailed), p	**0.006**	.	**0.001**	**0.047**
	N	178	178	178	178
T_3	Spearman's	0.157*	0.236*	1.000	-0.010
	Sign. (2-tailed), p	**0.037**	**0.001**	.	0.890
	N	178	178	178	178
T_4	Spearman's	0.095	-0.149*	-0.010	1.000
	Sign. (2-tailed), p	0.207	**0.047**	0.890	.
	N	178	178	178	178
T_3/T_4	Spearman's	-0.002	0.272**	-	-
	Sign. (2-tailed), p	0.981	**0.0001**	-	-
	N	178	178	-	-

Note. * – correlation is significant at the 0.05 level (2-tailed);
** – correlation is significant at the 0.01 level (2-tailed);
Hc – homocysteine;
TSH – thyroid-stimulating hormone;
T_3 – triiodothyronine;
T_4 – thyroxine.

The association between homocysteine and TSH values was stronger (r_{xy}=0.502, p=0.029, n=19) in the subgroup of children with insufficient body weight. In this subgroup, blood homocysteine levels were higher than in the children with normal PG, and free T_4 levels were lower than in the children with excessive body weight (tables 2,3).

Table 2. Levels of metabolic variables of school children with different physical growth levels from Ivankov district.

Variable	A group of children from Ivankov district					
	Subgroup 1 (n=19)		Subgroup 2 (n=127)		Subgroup 3 (n=32)	
	Me	IR	Me	IR	Me	IR
Hc, µmol/L	12.6	11.6-17.3	11.4	9.5-13.3	11.9	10.9-13.8
TSH, µIU/mL	1.9	1.47-2.5	1.8	1.3-2.4	1.9	1.3-2.7
T_3, pg/mL	4.3	3.9-4.9	4.4	4.0-4.8	4.4	4.0-4.6
T_4, ng/dL	1.2	1.1-1.3	1.2	1.1-1.3	1.3	1.2-1.3
T_3/T_4	3,5	3.2-4.3	3.6	3.2-4.0	3.3	2.9-3.8
B_9, ng/mL	6.0	4.7-8.0	6.6	5.1-8.0	5.7	4.7-6.8
B_{12}, pg/mL	283.6	261.1-344.6	313.4	255.0-422.5	332.5	258.3-454.6
B_6, µg/L	19.9	16.1-25.2	18.6	15.3-22.3	16.0	13.5-21.4

Note. Me – median;
IR – interquartile range;
Hc – homocysteine;
TSH – thyroid-stimulating hormone;
T_3 – triiodothyronine;
T_4 – thyroxine.
Subgroup number: 1 – abnormal (low) PG (RI<10.7);
2 – normal PG (RI within the range≤13.7 and≥10.7);
3 – abnormal (high) PG (RI>13.7).

Table 3. Results of quantitative comparison of metabolic variables (non-parametric analysis) in a group of children from Ivankov district.

Variable	Subgroup number	Ivankov district		
		Number of cases	Average rank	U Mann-Whitney test, statistical significance, p
Hc, µmol/L	1	19	93.87	U=819.5, p=0.024
	2	127	70.45	
T_4, ng/dL	1	19	19.66	U=183.5, p=0.019
	3	32	29.77	
T_4, ng/dL	2	127	75.16	U=1417.5, p=0.008
	3	32	99.20	
T_3/T_4	2	127	84.54	U=1455.0, p=0.013
	3	32	61.97	

Note. Hc – homocysteine;
T_3 – triiodothyronine;
T_4 – thyroxine.
Subgroup number: 1 – abnormal (low) PG (RI<10.7);
2 – normal PG (RI within the range ≤13.7 and ≥10.7);
3 – abnormal (high) PG (RI>13.7).

A direct association was reported between TSH and homocysteine levels (r_{xy}=0.224, p=0.011, n=127), and a direct association was found between TSH and T_3 levels (r_{xy}=0.211, p=0.017, n=127) in the subgroup of children with normal PG.

Unlike the subgroups of children with normal PG and insufficient body weight, no association was observed between TSH and homocysteine levels in the subgroup of children with excessive body weight. A moderate direct association was found between TSH and T_3 concentrations (r_{xy}=0.382, p=0.031, n=32). The T_3/T_4 coefficient values were statistically significantly lower in this subgroup than in the subgroup of children with normal PG (tables 2,3).

Vitamins B_9, B_6 and B_{12} values did not differ statistically in the subgroups under study (tables 2,3).

In the subgroup of children with normal PG, the proportion of variants with the MTHFR:677CC genotype was statistically significantly lower, and the proportion of variants with the MTHFR:677CT genotype was higher than in the subgroup of children with abnormal (high) PG (tables 4,5).

Table 4. Percentage of polymorphic alleles of folate metabolism genes among children with abnormal (high) physical growth from Ivankov district (n=32).

Gene, polymorphism	“Neutral genotype” allele		“Heterozygous genotype” risk allele		“Homozygous genotype” risk allele	
	Abs. number	Percen-tage, %	Abs. number	Percen-tage, %	Abs. number	Percen-tage, %
MTR:A2756G	23	71.9±8.0	9	28.1±8.0	0	0
MTHFR:A1298C	18	56.3±8.8	14	43.8±8.8	0	0
MTHFR:C677T	22	68.8[1]±8.2	9	28.1[2]±8.0	1	3.1±3.1
MTRR:A66G	3	9.4±5.2	15	46.9±8.8	14	43.8±8.8

Table 5. Percentage of polymorphic alleles of folate metabolism genes among children with normal physical growth from Ivankov district (n=127).

Gene, polymorphism	“Neutral genotype” allele		“Heterozygous genotype” risk allele		“Homozygous genotype” risk allele	
	Abs. number	Percen-tage, %	Abs. number	Percen-tage, %	Abs. number	Percen-tage, %
MTR:A2756G	72	56.7±4.4	45	35.4±4.2	10	7.9±2.4
MTHFR:A1298C	62	48.8±4.4	58	45.7±4.4	7	5.5±2.0
MTHFR:C677T	48	37.8±4.3	68	53.5±4.4	11	8.7±2.5
MTRR:A66G	22	17.3±3.4	67	52.8±4.4	38	29.9±4.1

Note. 1 – statistical differences between subgroups of children with normal and abnormal (high) PG with respect to MTHFR:677CC genotype: t=3.35; p=0.001347;
2 – statistical differences between subgroups of children with normal and abnormal (high) PG with respect to MTHFR:677CT genotype: t=2.79; p=0.006662.

A moderate direct association was reported between homocysteine and thyroid-stimulating hormone values (r_{xy}=0.343, p=0.001, n=98) in the group of children with the T allele of the MTHFR:C677T polymorphism. No association was found between homocysteine and thyroid-stimulating hormone values in the group of children without the T allele of the MTHFR:C677T polymorphism (n=80).

The studies conducted show that there exists a relationship between metabolism of sulphur-containing amino acids methionine and homocysteine, and the production of thyroid hormones in the children living in the area affected by the Chernobyl nuclear power plant accident.

Blood homocysteine levels directly correlated with increased thyroid-stimulating hormone levels in the total group of children from Ivankov district.

The association between these metabolic variables was the strongest in the subgroup of children with insufficient body weight. At the same time, there was no association between thyroid-stimulating hormone and triiodothyronine concentrations.

Alternatively, there was no association between homocysteine and thyroid-stimulating hormone levels in the subgroup of children with excessive body weight.

At the same time, there was an association between thyroid-stimulating hormone and triiodothyronine concentrations. Both associations between homocysteine and thyroid-stimulating hormone, and thyroid-stimulating hormone and triiodothyronine levels were reported in the subgroup of children with normal PG. The presence of the T allele of the MTHFR:C677T polymorphism contributed to establishing an association between homocysteine and thyroid-stimulating hormone levels. It should be noted that there was a decrease in the production of triiodothyronine in the subgroup of children with abnormal PG associated with increased body weight compared with the subgroup of children with normal PG.

Thus, there is a disturbed relationship between methionine metabolism cycles and hormonogenesis of the thyroid gland in the children with excessive body weight living in the area contaminated with radionuclides as a result of the Chernobyl nuclear power plant accident. The results obtained allow to assess associations between metabolic variables of children with different PG levels.

Conclusions

1. Direct associations were found between thyroid-stimulating hormone and triiodothyronine concentrations, and homocysteine and thyroid-stimulating hormone concentrations, and homocysteine and triiodothyronine concentrations, and an inverse association was observed between thyroxine and thyroid-stimulating hormone levels in the group of children living in the area affected by the Chernobyl nuclear power plant accident.
2. Plasma homocysteine levels correlated with thyroid-stimulating hormone levels in the subgroup of children with abnormal (low) physical growth.
3. Blood thyroid-stimulating hormone levels correlated with triiodothyronine levels in the subgroup of children with abnormal (high) physical growth.
4. Both associations between homocysteine and thyroid-stimulating hormone concentrations, and thyroid-stimulating hormone and triiodothyronine concentrations were present in the subgroup of children with normal physical growth.
5. The production of triiodothyronine is decreased in the subgroup of children with abnormal (high) physical growth compared with the subgroup of children with normal physical growth.
6. The dependence of the correlation between homocysteine and thyroid-stimulating hormone levels on the T allele of the MTHFR:C677T polymorphism was established.
7. The results of the research can be used in assessing the effects of chronic radiation exposure on metabolic processes in human body.

REFERENCES

1. Bandazhevskiy Yu.I. Hyperhomocysteinemia and Vitamin B12 and Folate Deficiency in Children Living in an Area Contaminated with Radionuclides due to the Chernobyl Nuclear PowerPlant Accident / Yu.I. Bandazhevskiy, N.F. Dubovaya // Pediatriya. Vostochnaya Evropa. 2017. – Том 5, – №1. – P. 25-32.
2. Bandazhevsky Yu.I. Comparative assessment of metabolic processes in children living in the areas affected by the Chernobyl Nuclear Power plant accident / Yu.I. Bandazhevsky, N.F. Dubova // Environment&Health. 2017. – №4. – С. 27-30.

3. Bandazheuski Yu.I. Provision of vitamins that participate in the exchange of homocysteine in children from the areas affected by the accident at the Chernobyl nuclear power plant / Yu.I. Bandazheuski, N.F. Dubovaya // Pediatrics. Eastern Europe. 2018. – Vol.6, – №1. – P. 41-48.
4. General dosimetric certification and results of LU-monitoring in the settlements of Ukraine who suffered radioactive contamination after the Chernobyl disaster. Data for 2011 Collection 14. – K.: of MOZ of Ukraine, will TRAMPLE Ukraine, MINISTRY of emergency measures of Ukraine, DAZV, DU "NNCRM NAMN Ukraine", ND IRZ ATN Ukraine, 2012. – 99 p.
5. Standards for the Assessment of Physical Development of Schoolchildren (Issue 3) / Under the Soc. edited by acad. AMNU, MD, prof. Serdyuk A.M. – K.: LTD «Fairy-tale», 2010. – 60 p.
6. Baranov A.A. Methods for studying the physical development of children and adolescents in population monitoring: A guide for physicians / A.A. Baranov, V.R. Kuchma, Yu.A. Yampolskaya i dr. / Pod red. akad. RAMN A.A. Baranova i prof. V.R. Kuchmyi. – M.: Soyuz pediatrov Rossii, 1999. – 226 p.
7. Ivakhno O.P. Methods of estimation of physical development and health of children population: Textbook / O.P. Ivakhno, I.P. Kozyarin, Yu.V. Nemceva. – K.: NMAPO the name of P.L. Shupika, 2012. – 129 p.
8. Park So Y. Increases in Thyrotropin Are Associated with Increased Triiodothyronine /Thyroxine Ratio in the Korean Healthy Adult Group / So Young Parkhttp: //press.endocrine.org/doi/abs/10.1210/endo-meetings.2016.THPTA.2.SUN-269 – aff_1, Song Vogue Ahn, Hyun Seok Jin and al. // Endocrine Society's 98th Annual Meeting and Expo, April 1-4, 2016. – Boston, 2016. SUN-269.

ЗВ'ЯЗОК ГОРМОНІВ ЩИТОВИДНОЇ ЗАЛОЗИ І ГОМОЦИСТЕЇНУ У ДІТЕЙ, ЯКІ ПРОЖИВАЮТЬ В РАЙОНАХ, ЯКІ ПОСТРАЖДАЛИ ВІД АВАРІЇ НА ЧОРНОБИЛЬСЬКІЙ АТОМНІЙ ЕЛЕКТРОСТАНЦІЇ

Бандажевський Ю.І., Дубова Н.Ф.

Мета – визначення зв'язку гомоцистеїну і гормонів щитовидної залози у дітей з різним рівнем фізичного розвитку, які проживають в районах, постраждалих від аварії на Чорнобильській атомній електростанції.

Матеріали і методи дослідження. Проаналізовано показники фізичного розвитку, рівень гомоцистеїну, гормонів щитовидної залози, вітамінів B_6, B_9 і B_{12}, а також стан генетичної системи фолатного циклу у 178 сільських школярів, які проживають в радіоактивно забруднених населених пунктах Іванківського району Київської області. Середній вік дітей становив 13,6±0,1 років (95%ДІ 13,4-13,8 років).

В якості інтегрального показника фізичного розвитку й обміну речовин оцінювався масо-ростовий індекс Рорера, що не залежить від віку і статі. Статистична обробка отриманих результатів здійснювалася за допомогою програми IBM SPSS Statistics 22 (США).

Результати. На підставі оцінки індексу Рорера були визначені підгрупи дітей з різним фізичним розвитком. Проведено кореляційний аналіз між різними рівнями фізичного розвитку сільських школярів, показниками гормоногенезу щитовидної залози і функціонування фолатного циклу. Виявлено, що у дітей з підвищеною масою тіла, які постійно проживають на радіоактивно забрудненій території, спостерігається порушення зв'язку між метаболічними циклами обміну метіоніну і гормоногенезом щитовидної залози. Встановлена залежність зв'язку між гомоцистеїном і тиреотропним гормоном від аллелі Т поліморфізму MTHFR:C677T.

Висновки. Отримані результати досліджень можуть бути використані при оцінці наслідків хронічного радіаційного впливу на метаболічні процеси людського організму.

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