PEDIATRICS

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Mechanisms of myocardial remodeling in adolescents with hypothalamic syndrome of the puberty and arterial hypertension.

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Abstract: The study deals with the assessment of patterns of left ventricular myocardial remodeling in adolescents with hypothalamic syndrome of puberty and arterial hypertension depending on endothelial nitric oxide synthase gene polymorphism in intron 4 (4b, 4a) and blood serum homocysteine level.

Key Words: gene polymorphism, endothelial NO-synthase, homocysteine, adolescents, myocardial remodeling, arterial hypertension.

INTRODUCTION

An increase in the number of younger patients with arterial hypertension (AH), which ranks high in the incidence and remains a significant medical and social challenge, has been observed recently [1-3]. Leading experts emphasize that determination of abnormal tendencies to the development of hypertension in adolescents, early diagnosis and correction of cardiovascular disorders exert a positive impact on the health of adults [4-8].

Hereditary factors have lately acquired certain significance among the causes of risk factors for hypertension and its complications. Mapped candidate genes, namely: angiotensin gene (AGT), angiotensin-converting enzyme gene (ACE) and endothelial nitric oxide synthase gene (eNOS) have become a prime focus for experts.AGT gene polymorphismis associated with high blood pressure in adults and left ventricular hypertrophy [9].

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Particular attention has recently been given to the study of complications resulting from hypertension, particularly impairment of the target organs (heart, blood vessels; potential risk factors for cardiovascular complications presently include hyperhomocysteinemia [10, 11].

The mechanisms of hypertension development in overweight adults are well understood. Adaptation and subsequent chronic compensatory hypofunction of the myocardium in patients with obesity leads to an increase in myocardial mass, which can enlarge due to hypertrophy of myocardiocytes. At the same time, the increase of the heart mass in patients with obesity can be associated with the increase in itscontent of fibrous tissue. Activation of myocardial fibrosis promotes an increase in the rigidity of the walls of the left ventricle reducing myocardial ability to relax, which triggers the development of diastolic dysfunction. Besides, myocardial fibrosis results in depletion of the vascular bed of the coronary arteries and a gradual decrease in myocardial contractility, remodeling of the left ventricle with subsequent development of circulatory failure [12,14].

Development of hypertension in adolescents has been actively studied [13]. Hypothalamic syndrome of puberty (HSP) is one of the diseases occurring in most patients with hypertension. This syndrome basically involves impairment

of the system hypothalamus-hypophysis-peripheral endocrine organs with the development of insulin resistance with lipid metabolism shifts and progression of obesity. HSP is not a rare abnormality, but it is rarely diagnosed, therefore it is appropriate to study pathophysiological mechanisms underlying the formation of arterial hypertension in adolescents with HSP, presentation of metabolic disorders and methods of early diagnosis.

In view of the above, early identification of changes in the cardiovascular system in adolescents with HSP is relevant in childhood, when the groundwork for disease development or preservation of health in adults isformed [10, 11].

2 PURPOSES, SUBJECTS AND METHODS:

101 adolescents with HSP aged 14 to 17 years (average age 15.8±0.66 years) were examined at Communal Health Protection Institution "Regional Children's Clinical Hospital" and Department of Pediatrics No.1 and Neonatology due to past history of high blood pressure episodes.

The study involved assessment of case histories and presentation, physical development with waist measurement (WM), hip measurement (HM), abdominal obesity (WM/HM ratio), and body mass index (BMI). The diagnosis was specified by 24-hour blood pressure monitoring (ABPM) using MD plus unit (Russia, Novosibirsk). The state of cardiovascular system was evaluated by Doppler echocardiography with standard technique recommended by the Association of Echocardiography [1].

Polymorphism of endothelial nitric oxide synthase gene was studied by polymerase chain reaction. Homocysteine level inblood serum in patients with different genotype was evaluated by immunoenzyme assay (ELISA). Statistical data processing was carried out using STATISTICA-6 software with parametric and nonparametric methods.

Conflict of interests

There is no conflict of interests.

3 RESULTS AND DISCUSSION

The examination of 101 adolescents with hypothalamic syndrome of puberty showed the following genotypes: genotype 4b4b in 47 (46.53±4.99%) children, genotype 4b4a in 43 (42.57±4.95%) adolescents and genotype 4a4a in 11 (10.89±3.12%) teenagers.

The relation of certain biochemical indices to patient's genotype was assessed by a dispersive analysis version, namely Kruskall-Wallis test.

The study revealed statistically reliable differences in a number of indices in patients with various genotypes, particularly insulin ($p<0.05$), homocysteine ($p<0.001$), triglycerides (TG) ($p<0.05$),very low density lipoproteins(VLDL) ($p<0.05$), average systolic blood pressure during the night(ASPP(n)) ($p<0.05$), increase in the thickness of the posterior wall of the left ventricle in percent (%PWLV) ($p<0.05$), glomerular filtration rate (GFR) ($p<0.05$) (Table 1).

Table 1

The metabolic and structurally functional indicators depending on the genotype.

Parameters	genotype 4a4a (n=11)			genotype 4b4a (n=43)			genotype4b4b (n=47)			P
	Me	LQ	UQ	Me	LQ	UQ	Me	LQ	UQ	
Insulin, ulU/ml	33,2	16,52	40,08	14,68	10,4	19,9	16,2	12,8	22,46	<0,05*
Homocysteine, mcmole/l	2,9	2,5	4,6	12,2	7,9	19,3	11,8	6,9	17,3	<0,001*
TG, mmol /l	1,41	1,18	1,64	1,02	0,65	1,24	0,94	0,71	1,22	<0,05*
VLDL, mcmole /l	0,28	0,23	0,33	0,2	0,13	0,25	0,08	0,14	0,24	<0,05*
ASBP(n), mm Hg	116	106	119	119	112	126	121	109	126	<0,05*
GFR ,ml / min	123	117,2	146,02	123,2	110,2	144	116,3	110,7	140,35	<0,05*
% PWLV %	50	33	99	6 63,0	40	100	39	22	71	<0,05*

(*Note:Me- median, LQ- lower quartile, UQ- upper quartile; TG-, triglycerides, VLDL- very low density lipoproteins; ASBP(n)- average systolic blood pressure during the night; GFR- glomerular filtration rate. P- between groups of the genotypes 4a4a, 4b4b.)*

Thus, patients with genotype 4a4a were found to have the highest level of insulin in blood serum and dyslipidemia; besides, patients-carriers of allele a were more frequently diagnosed with signs of myocardial remodeling with involvement of the posterior wall of the left ventricle.

Patients with genotype 4b4b were shown to have the highest indices of average systolic blood pressure during the night. Genotype 4b4a is perhaps an average version between the previous two genotypes.

Thus, it is possible to assume that allele influence and, in particular, the most "unfavorable" genotype 4a4a, is mediated through a number of metabolic disorders, resulting in the progression of atherosclerosis, endothelial dysfunction and myocardial remodeling of the left ventricle.

Interesting data were obtained in the analysis of homocysteine levels in blood serum of patients with different genotype. The study showed the following findings: in patients with genotype 4b4b its level amounted Me = 11.8 [6.9; 17.3] mcmole/l. In children with genotype 4b4a it comprised Me = 12.2 [7.9; 19.3] mcmole/l. In the group of adolescents with genotype 4a4a the level of homocysteine was Me = 2.9 [2.5; 4.6] mcmole/l.

Thereafter, the patients were divided into 4 groups according tocluster 1, 2, 3 or 4, that is by the level of homocysteine in blood serum (Table2).

Table 2.

The level of homocysteine in the blood serum of patients carried to different, clusters mcmole / l.

Cluster	Abs.	%	Mean	Min.	Max.	S.D.	Me	LQ	UQ
1	11	10,9	2,43	1,7	2,9	0,31	2,5	2,3	2,6
2	34	33,7	6,65	3,1	9,8	1,94	6,8	4,9	8,5
3	38	37,6	13,68	10,4	19,3	2,46	13,1	11,5	15,3
4	18	17,8	29,56	21	47,7	8,42	25,9	23,5	37

Note:
Me- median, LQ- lower quartile, UQ- upper quartile.

Thus, the first cluster included 11 adolescents with the lowest content of homocysteine in blood (2.43 ± 0.31 μmol/l). The second cluster (n = 34) comprised patients with the level of homocysteine corresponding to normal indices (6.65 ± 1.94 μmol/l). The third cluster involved 38 patients with the increased level of homocysteine in blood serum (13.68 ± 2.45 μmol/l). The fourth cluster consisted of 18 children with high level of homocysteine (29.56 ± 8.42 μmol/l).

Assessment of the heart remodeling variants according to the level of homocysteine showed that in the group of children with normal and increased homocysteine level the myocardial mass index of the left ventricle (LV) was within the normal range, while the relative thickness of LV wall tended to increase.The patients with the highest level of homocysteine were found to have a significantly reliable enlargement of the relative thickness of LV wall ($p < 0.05$) and an increase in the myocardial mass index of the left ventricle ($p < 0.05$).

The study showed that progression of hyperhomocysteinemia was accompanied by an increase in the incidence of restrictive diastolic LV dysfunction as compared to adolescents with normal blood serum homocysteine level ($p < 0.05$).

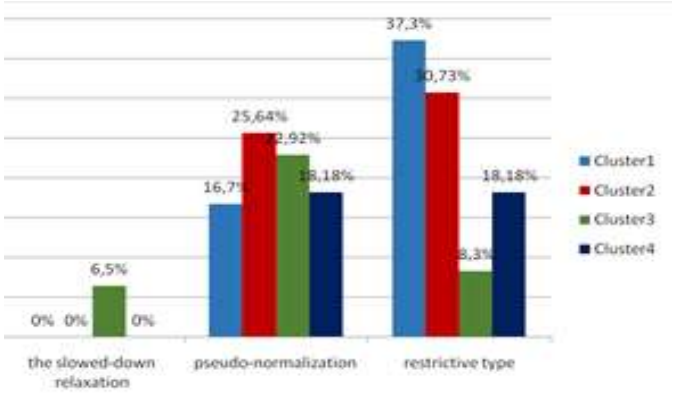

Fig. 1.The frequency of diastolic dysfunction in children with different levels of homocysteine in the serum.

Thus, an increase in blood serum homocysteine level influences the development of LV myocardial remodeling. In normal homocysteine level myocardial geometry is within normal range, whereas an increase in homocysteine level results in the development of concentric remodeling andconcentric hypertrophy of LV myocardium in children with the highest level of homocysteine, which reflects regularities of LV myocardium remodeling.

We investigated blood serum homocysteine level in adoles-

cents with different ENOS genotype. The most obvious differences between the indices of homocysteine in blood serum were observed between patients with 4a4a and 4b4b genotypes.

The nature of these distinctions was clarified by identification of alleles a and b as a sign of "GROUP" sample stratification, as well as by regression analysis in the subgroup of patients with allele a (hereafter - Group A) separately and in the subgroup of patients with allele b (hereafter- Group B).

Thus, the study showed that patients-carriers of allele b with the growth of body mass and progression of abdominal obesity (WM/HM ratio) were more likely to have an increase in the level of homocysteine in blood serum. It promoted progression of hypertension in this cohort of patients. Blood pressure stabilization was rather associated with the involvement of kidneys.The growth of body mass increased the volume of circulating blood and viscosity of blood. Moreover, fatty tissue might release angiotensinogen which resulted in dysfunction of kidneys, responsible for the long-term regulation of blood pressure by changing the activity of RAAS and sodium-volume-dependent systems. Hyperhomocysteinemia itself, as was stated above, promoted myocardial remodeling of the left ventricle.

Thus, patients-carriers of allele b, were found to have a decreased cavity of LV myocardium (concentric remodeling). It was reflected by sphericity index rateswhich as well as the height of the left ventricle decreased in hyperhomocysteinemia progression.

The results for group A regression are shown in Fig. 2. Indices of average diastolic blood pressure during the day and night and average systolic blood pressure during the day and night should be considered the most influential in prognosis of homocysteine level in blood serum for allele a carriers.

Progression of arterial hypertension in this cohort of patients was associated with a change of vascular tone.As was mentioned above, destabilization of vascular wall in genotype 4a4a was influencedby the altered levels of triglycerides, lipoproteins of very low density and hyperinsulinemia.

	regression results for a dependent variable: HOMO (tabl_natali_HOMOx3.sta) R= .64386623 R2= .41456372 Correct. R2= .37348048 F(8.114)=10.091 p<.00000 Standart error of estimate: 8.7864					
	beta	SE,B	B	SE, B	t(114)	p-level
			-38,113	13,491	-2,825	0,006
SADD	-0,564	0,174	-0,629	0,194	-3,248	0,002
DADD	0,706	0,139	1,021	0,201	5,070	0,000
SADN	0,586	0,166	0,651	0,185	3,519	0,001
DADN	-0,562	0,158	-0,748	0,211	-3,544	0,001

Fig. 2.**The summary table of model of linear regression for group A when calculating in statistical environment to the STATISTICA.**
Note: SADD- average systolic blood pressure during the day, DADD - the average diastolic blood pressure during the day, SADN - average systolic blood pressure during the night, DADN- the average diastolic blood pressure during the night, VrSD - variability of systolic blood pressure during the day, VrSN- variability in systolic blood pressure overnight, TZS2 - the thickness of the back wall of the left ventricle in diastole, OTS - relative wall thickness of the left ventricle.

Literature data confirm that nitrogen oxide production is decreased in patients-carriers of allele a [15-17], triggering endothelial dysfunction. In progression of arterial hypertension and hyperhomocysteinemia these patients develop an increase in the thickness of left ventricular posterior wall and relative thickness of left ventricular wall – an integral indicator of myocardial LV remodeling, which is the most typical for concentric hypertrophy of LV myocardium.

Thus, hypothalamic syndrome of puberty is a disorder in children, which develops with arterial hypertension, abdominal type of obesity, disruption of lipid range of blood, hyperinsulinemia. Considering the metabolic essence of HSPas a "prototype" of metabolic syndrome in adults, it is possible to consider that patients with HSP in adulthood are likely to develop cardiovascular impairments. If metabolic disorders typical for HSP have a significant effect on vascular endothelium, in future it will ultimately result in endothelial dysfunction, myocardial LV remodeling, development of diastolic and systolic dysfunction.

4 CONCLUSIONS

1. The increased blood serum homocysteine level (≥10.40 μmol/l) and high homocysteine level (≥21.0 μmol/l) in adolescents is associated with hypothalamic syndrome of puberty with signs of myocardial remodeling and diastolic function of the left ventricle. Progression of hyperhomocysteinemia results in a decrease in indices of LV cavityсphericity.

2. Assessment of endothelial nitric oxide synthase (eNOS) gene polymorphism in adolescents with hypothalamic syndrome of puberty determined genotype 4b/4b in 47% of children, genotype 4b/4a in 43%, genotype 4a/4a in 11% of adolescents. Genotype 4a4a is unfavorable concerning the development of metabolic disorders and is characterized by the highest level of immunoreactive insulin in blood serum (33.2 (16.5; 40.1) uIU/mL), an increased level of triglycerides (1.41 (1.18; 1.64) mmol/l).

3. Adolescents with hypothalamic syndrome of puberty, accompanied by arterial hypertension with different eNOS genotypes, who carry allele b typically develop concentric remodeling ($p < 0.05$), whereascarriers of allele aundergo remodeling of a left ventricular myocardium by the type of concentric hypertrophy.

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РЕЗЮМЕ

Гончарь М.О., Коновалова Н.В., Муратов Г.Р.

МЕХАНІЗМИ РЕМОДЕЛЮВАННЯ МІОКАРДУ У ПІДЛІТКІВ З ГІПОТАЛАМІЧНИМ СИНДРОМОМ ПУБЕРТАТНОГО ПЕРІОДУ ТА АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ

Харківський національний медичний університет

Авторами вивчені моделі ремоделювання міокарда лівого шлуночка у підлітків із гіпоталамічним синдромом пубертатного періоду та артеріальною гіпертензією в залежності від поліморфізма гена ендотеліальної синтази оксиду азоту в інтроні 4 (4b,4a) та рівня гомоцистеїну сироватки крові.

Ключові слова: поліморфізм гена, ендотеліальна NO-синтаза, гомоцистеїн, підлітки, ремоделювання міокарда, артеріальна гіпертензія.

РЕЗЮМЕ

Гончарь М.О., Коновалова Н.В., Муратов Г.Р.

МЕХАНИЗМЫ РЕМОДЕЛИРОВАНИЯ МИОКАРДА У ПОДРОСТКОВ С ГИПОТАЛАМИЧЕСКИМ СИНДРОМОМ ПУБЕРТАТНОГО ПЕРИОДА И АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ

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Авторами изучены модели ремоделирования миокарда левого желудочка у подростков с гипоталамическим синдромом пубертатного периода и артериальной гипертензией в зависимости от полиморфизма гена эндотелиальной синтазы оксида азота в интроне 4 (4b,4a) и уровня гомоцистеина сыворотки крови.

Ключевые слова: полиморфизм гена, эндотелиальная NO-синтаза, гомоцистеин, подростки, ремоделирование миокарда, артериальная гипертензия.

Received: 23-Feb. – 2016
Accepted: 25-Mar. - 2016