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N-terminal brain natriuretic peptide in children with different forms of primary hypertension

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Background. *The serum level of NT-proBNP plays a significant role in the regulation of intravascular volume and vascular tone. Current study includes children with primary hypertension (PAH).*
Aims. The aim of the study is to investigate the level of serum NT-proBNP in children with various forms of primary hypertension (PAH) and prognostic significance for the development of myocardial dysfunction in children depending on the form of PAH.
Objectives. The study involved 71 children at the age of 9–17 years old, among them — 53 with PAH and 18 — with normal blood pressure.
Methods. *All children underwent general clinical examination, ambulatory blood pressure monitoring (ABPM), echocardiography, determination of NT-proBNP in serum by ELISA.*
Results. *The serum NT-proBNP level in children with degree II PAH was 31,23±9,32 fmol/ml, with degree I PAH — 59,48±20,73 fmol/ml, which was higher than in control group (12,48±2,18 fmol/ml, p<0,05). Among the 7 children with EF less than 55% only one child's NT-proBNP level was higher than 300 fmol/ml. Concentric LV remodeling was observed in 32,3±8,4% of children with stable PAH and 22,7±8,9% of labile PAH. The NT-proBNP increase in serum of females occurs at stage II PAH, in males - already at stage I PAH; systolic dysfunction in children with PAH is rare and it is accompanied with increased levels of NT-proBNP above 300 fmol/ml.*
Key words: *NT-proBNP; Children; Primary hypertension.*

Introduction

Natriuretic peptides play an important role in the regulation of intra-vascular blood volume and vascular tone and their increase is an important compensatory mechanism that reduces the activity of the sympathoadrenal and renin-angiotensin-aldosterone system [1,4,19].

Brain natriuretic peptides — BNP and NT-proBNP — have the greatest clinical significance. With systolic or diastolic dysfunction, NT-proBNP level increases significantly. It is proved that the level of NT-proBNP is directly correlated with the severity of heart failure, the size of the left ventricle (LV) and the thickness of its walls in dilated and hypertrophic cardiomyopathy [9] and other diseases in children [5,6].

Research in adult patients with primary hypertension (PAH) showed that the increase in plasma natriuretic peptides level associated with left ventricular hypertrophy2 may precede the development of such hypertrophy and it is a reliable marker for the presence of diastolic dysfunction or high risk of its development [10]. Determination of NT-proBNP has a great prognostic value in PAH adults. Its increase is assessed as one of the risk factors for hypertension in non-hypertensive patients [7], as well as an unfavorable prognostic factor in already formed PAH [12].

In children with PAH, similar investigations are not available. Therefore, further study of the levels of NT-proBNP is relevant today to improve diagnosis and clarify the pathogenic heart disease mechanisms in children and adolescents with PAH.

Aim: to investigate the serum level of NT-proBNP in children with various forms of PAH and its prognostic significance for the development of myocardial dysfunction in children depending on the form of PAH.

Methods. 71 children aged 9–17 years participated in the research. The main group consisted of 53 children with PAH. The diagnosis was established on the basis of blood pressure measurement and daily monitoring of blood pressure (ABPM). Based on ABPM results, several subgroups were allocated: the first one — children with stable degree II PAH (systolic blood pressure (SBP) load more than 80%), the second group — children with stable degree I PAH (SBP load — 50–80%), the third group — children with labile PAH (SBP load — 25–50%). The control group consisted of 18 healthy children with normal blood pressure.

The study didn't include children with symptomatic hypertension, heart disease, carditis, kidney disease.

All children underwent general clinical examination, ABPM, echocardiography, determination of NT-proBNP in serum by ELISA.

The following values were determined by the echocardiography: left ventricular diastolic diameter (LVDD); left ventricular systolic diameter (LVSD); LV ejection fraction (EF); LV myocardial mass (LVM); left ventricular mass index (LVMI); LV posterior wall thickness (LVPW); interventricular septum thickness (IVS); left ventricular systolic and diastolic volumes (LVSV and LVDV); relative wall thickness (RWT).

LVM was determined according to R.B. Devereux et al. (1986) formula:

$$LVM\ (g)=0.80(1.04(IVS+LVED+LVPW)^3-(LVED)^3)+0.6$$

LVMI is calculated by the formula:

$$LVMI=\frac{LVM}{(height)^{2.7}}$$

Characteristic value of LVMI was taken for 95-percentile value depending on the age and gender (Philip R., 2009).

Based on the type of ventricular remodeling, R.M. Lang et all. (2005) suggested a classification to the American Society of Echocardiography and the European Association of Echocardiography according to which the following types of remodeling were established: normal LV geometry (LVMI is not increased, RWT<0,42); concentric LV remodeling (LVMI is not increased, RWT>0,42); concentric hypertrophy (LVMI is increased, RWT>0,42); eccentric hypertrophy (LVMI is increased, RWT<0,42).

Table 1

Serum NT-proBNP level in children with various forms of PAH

Groups	NT-proBNP, fmol/ml
1. Degree II stable PAH, n=16	31.23±9.32*1-4; 1-3
2. Degree I stable PAH, n=15	59.48±20.73*2-4; 2-3
3. Labile PAH, n=22	5.98±1.51*3-4
4. Control group, n=18	12.48±2.18

Note: * — $p < 0.05$

Table 2

Serum NT-proBNP in children with various forms of PAH by gender

Groups	Gender	NT-proBNP
1. Degree II stable PAH	boys, n=8	35.55±15.0
	girls, n= 8	22.58±2.95*1-4
2. Degree I stable PAH	boys, n=10	79.11±29.06*2-4
	girls, n=5	15.3±5.16#
3. Labile PAH	boys, n=12	4.08±1.01*3-4; 1-3; 2-3
	girls, n=10	7.89±2.81
4. Control group	boys, n=10	13.15±3.0
	girls, n=8	11.9±3.70

Note: * — $p < 0.05$ between groups; # — $p < 0.05$ between boys and girls in groups

Mean daytime and nighttime systolic blood pressure (SBP), diastolic blood pressure (DBP), SBP and DBP load, SBP and DBP dipping, blood pressure variation coefficient (BPVC) were determined by ABPM. BPVC was calculated by the formula: BPSDx100/SBP or DBP, respectively, for SBP and DBP, where BPSD is standard deviation for blood pressure.

For the evaluation of results, generally accepted methods of mathematical statistics were used. Univariate analyses for group comparisons of continuous variables were performed using Student's t-test. The relationship of these hemodynamic parameters was determined as the Pearson correlation coefficient. A *p* value <0,05 was considered to be statistically significant.

Results. Determination of the serum NT-proBNP level in children with various forms of PAH showed higher levels of NT-proBNP in children with stable PAH compared with the control group (Table 1).

Boys were characterized by higher levels of NT-proBNP compared to girls in stable PAH. As provided in Table 2, they experienced a significant increase in NT-proBNP at the stage of degree I stable PAH, girls — at the stage of degree II stable PAH (Table 2).

In previous studies, we found that in healthy children at the age of 9–17 years old, serum NT-proBNP is less than 28 fmol/ml. This study demonstrated that 9.1±6.1% of children with labile PAH had levels of NT-proBNP above 28 fmol/ml, whereas among children with degree II stable PAH and degree I stable PAH, this number was 32.3±11.6% and 40.0±12.6%, respectively.

In 4 children with stable PAH, NT-proBNP level was more than 100 fmol/ml. All of them were males and differed from other children by higher mass and growth rates and had a longer history of hypertension (Table 3).

ABPM results in surveyed children presented in Table 3 indicate higher values of SBP, SBP load and variability of blood pressure in children with high levels of NT-proBNP. In children with levels of NT-proBNP above 100 fmol/ml, echocardiographic data found higher ($p<0.05$) LVM, LVPW and IVS values. Left ventricular cavity dimensions and RWT were characterized by tendency to greater values compared to those in children with lower NT-proBNP.

Low levels of NT-proBNP compared with the control group were found mainly in boys with labile PAH (Table 2), indicating a lack of activation of regulatory processes in these patients.

The most significant correlation of NT-proBNP with studied parameters are presented in Figure 1.

It should be noted that these links were observed only in patients with stable PAH unlike in those with labile PAH, and they had certain differences in children with various degrees of stable PAH. Thus, the level of NT-proBNP, regardless of the degree of stable hypertension, had a positive correlation with the average daily level of blood pressure variability and blood pressure parameters according to the ABPM data, with

Table 3

The research results in children with PAH at different values of NT-proBNP

Indicator	NT-proBNP		
	less than 28 fmol/ml	28-100 fmol/ml	more than 100 fmol/ml
Weight, kg	62.20±2.46	65.5±3.11	92.25±7.89*1-3;2-3
Height, cm	165.62±1.64	164.25±1.84	185.0±4.61*1-3;2-3
The duration of hypertension, years	1.98±0.10	2.23±0.11	3.25±0.37*1-3;2-3
SBP, mmHg	131.26±1.63	136.4±5.28	145.75±2.29*1-3
DBP, mmHg	71.38±1.10	76.80±4.85	74.50±1.50
SBP load, %	52.91±3.79	65.26±10.62	75.65±7.83*1-3
DBP load, %	22.15±3.12	42.16±10.97	29.32±11.21
SBP dipping, %	3.32±1.04	0.69±1.13	2.91±3.08
DBP dipping, %	9.25±1.37	8.34±3.85	7.75±4.70
Day time systolic BPVC, %	8.56±0.32	7.69±0.58	10.14±0.71*1-3;2-3
Day time diastolic BPVC, %	11.89±0.46	10.27±1.69	13.86±3.01
Night time systolic BPVC, %	10.22±0.68	7.56±1.08	11.42±1.43*2-3
Night time diastolic BPVC, %	13.60±0.80	8.81±1.33	16.54±1.29*2-3
LVDD, cm	4.36±0.10	4.20±0.09	4.85±0.43
LVSD, cm	2.82±0.09	2.55±0.15	3.15±0.40
EF, %	64.38±1.36	69.17±4.93	64.24±6.13
LVM, g	115.41±6.68	106.88±10.59	180.78±23.92*1-3;2-3
LVMI, g/m^{2,7}	29.09±1.37	28.16±2.83	34.21±4.25
LVPW, cm	0.84±0.02	0.90±0.05	1.05±0.03*1-3;2-3
IVS, cm	0.78±0.02	0.73±0.04	0.96±0.11*2-3
RWT	0.39±0.01	0.43±0.02	0.45±0.05

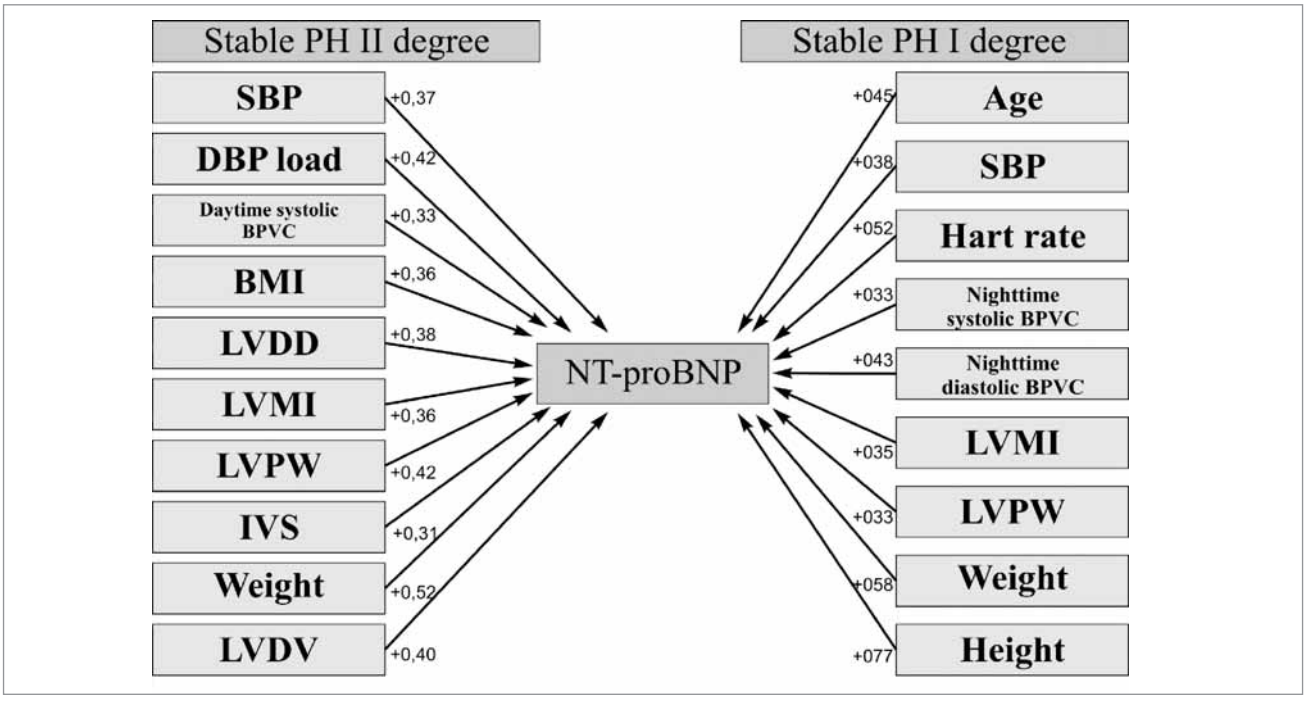

Fig. 1. The most significant correlative relationship of NT-proBNP with anthropometric data, echocardiography results and ABPM in children with stable hypertension (BMI — body mass index)

the magnitude of weight gain in children, as well as LVPW according to echocardiography. In addition, positive correlation with LVDD, LVDV, IVS, and consequently, with LVMI were observed in degree II PAH. In degree I stable PAH, such a clear connection with the above mentioned heart parameters were not found. These data may indicate that at the stage of degree I stable PAH endocrine system of the heart is just beginning to be involved in the pathogenic processes in the body in PAH and its high activity in children is formed at the stage of degree II stable PAH.

The connection of the NT-proBNP level with the body mass index (BMI) is clearly observed only at the stage of degree II stable PAH. In degree I stable PAH, the level of NT-proBNP is correlated with both the weight and height of children, resulting in the loss of connections with BMI.

Based on echocardiographic data, left ventricular hypertrophy was met in 7 out of 31 (22.6±7.5%) children with stable PAH (in 6.5±4.4% — concentric and in 12.9±6.0% — eccentric) and in 1 child (4.5±4.4%) with labile PAH (eccentric). Concentric left ventricular remodeling was observed more frequently — in 32.3±8.4% of children with stable PAH and 22.7±8.9% — with labile PAH.

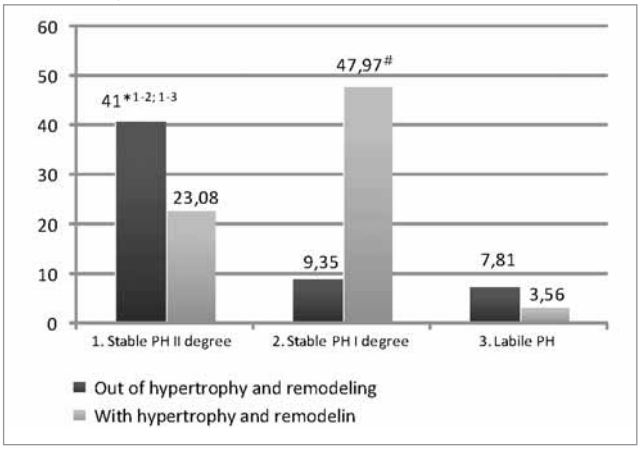

Fig. 2. Level of NT-proBNP (fmol/ml) depending on the presence of myocardial remodeling in children with various forms of PH
* — p <0,05 between groups;
# — p <0,05 between children with signs and with no signs of LVH)

The diagrams demonstrate that children without hypertrophy and remodeling show relatively high levels of NT-proBNP formed at the stage of degree II stable PAH, and in hypertrophy and remodeling — at an earlier stage of hypertension stabilization (Figure 2).

It should be noted that these links were observed only in patients with stable PAH unlike in those with labile PAH, and they had certain differences in children with various degrees of stable PAH. Thus, the level of NT-proBNP, regardless of the degree of stable hypertension, had a positive correlation with the average daily level of blood pressure variability and blood pressure parameters according to the ABPM data, with the magnitude of weight gain in children, as well as LVPW according to echocardiography. In addition, positive correlation with LVDD, LVDV, IVS, and consequently, with LVMI were observed in degree II PAH. In degree I stable PAH, such a clear connection with the above mentioned heart parameters were not found. These data may indicate that at the stage of degree I stable PAH endocrine system of the heart is just beginning to be involved in the pathogenic processes in the body in PAH and its high activity in children is formed at the stage of degree II stable PAH.

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The value of left ventricular ejection fraction less than 55% was observed in 6 of 31 (9.7±5.3%) children with stable PAH and in 1 of 22 (4.5±4.4%) child with labile PAH. However, only one child reported NT-proBNP values characteristic of systolic dysfunction (ejection fraction — 47%, NT-proBNP — 311.9 fmol/ml). In others, levels of NT-proBNP did not exceed 28 fmol/ml and ejection fraction was within 49–55%, indicating a relatively rare formation of systolic dysfunction in children with PAH.

Discussion. The ability to predict heart disease as a target organ in children with PAH depending on the level of NT-proBNP is a key issue, but works devoted to solving this problem are not enough and some are not clear. In particular, there are several reports regarding the impact of overweight on NT-proBNP level in children with hypertension. According to some authors, this relationship is found regardless of a child's gender [18], others have reported higher levels of NT-proBNP in boys with PAH and obesity, and lack of NT-proBNP correlation with body weight, systolic and diastolic blood pressure in girls with PAH [15]. Some studies, however, show a lack of clear links of natriuretic peptides with weight and blood pressure in children [11].

Today, the issue of low levels of NT-proBNP in certain categories of patients is also unclear [8].

This study points to possible causes for different results by other authors. We believe that one of these reasons is that labile and stable hypertension in children is formed under different conditions: for children with labile PAH, low NT-proBNP is typical, for children with stable PAH — high NT-proBNP. In conducted studies, no results are evaluated depending on the form of hypertension. Based on our data, we can assume that in children with stable PAH, increase in NT-proBNP is a necessary compensatory mechanism that balances the activity of sympathoadrenal system. In children with labile hypertension, activation system which includes NT-proBNP is inadequate and that causes sharp fluctuations of pressure.

According to our data, the level of NT-proBNP above 28 fmol/ml is the criterion of increased hormonal activity of the heart in children of 9–17 years old. These data were first received in the previous study [11]. At the examination of children with different levels of exercise tolerance, we found that children with high relative maximum oxygen consumption and normal myocardium reserve capacity had of NT-proBNP level ranged from 2.12 fmol/ml to 27.88 fmol/ml. In children with reduced exercise tolerance, however, average NT-proBNP values were 4.2 times higher. Our data go back to the studies by other authors. For example, according to one study, the hypertensive heart disease with preserved systolic function in adults is diagnosed with NT-proBNP levels over 21.67 fmol/ml [13].

Our study demonstrates that girls had lower blood NT-proBNP values as well as the study of Pervanidou P.et al. [15]. Their average level of NT-proBNP, even in degree II stable PAH, doesn`t exceed 28 fmol/ml. This may be due to better compensatory mechanisms in females aimed at normalizing blood pressure in comparison with males. It is known that stable PAH in girls occurs less frequently compared to boys and blood pressure is not as high as in boys even in stable PAH [17,20]. It also should be considered that the neuroendocrine system of the heart is closely related to other hormones. Proof of this is the close relationship of NT-proBNP levels with testosterone in adolescents16 which correlates with the stage of puberty [14]. But NT-proBNP is one of the components of a complex and multi-adaptive system that participates in the body adjustment to fluctuations of blood pressure.

Prospects for the development of scientific research are further investigations of the links between the neuroendocrine system of the heart in children with PAH and the levels of hormones that regulate vascular tone, endotelial factors vasoconstriction and vasodilation, the effect of different treatment regimens on the level of NT-proBNP and myocardial remodeling in children with PAH.

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N-терминальный мозговой натрийуретический пептид у детей с различными формами первичной гипертензии

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Уровень N- терминального мозгового натрийуретического пептида (NT-proBNP) играет существенную роль в регуляции внутрисосудистого объема крови и сосудистого тонуса. В данном исследовании принимали участие дети с первичной артериальной гипертензией (ПАГ).

Цель. Исследовать уровень NT-proBNP в сыворотке крови у детей с различными формами первичной артериальной гипертензии, а так же его прогностическую значимость в развитии дисфункции миокарда у детей с разными формами первичной артериальной гипертензии.

Пациенты. В исследовании приняли участие 71 ребенок в возрасте 9–17 лет, из них — 53 пациента с ПАГ и 18 пациентов- с нормальным артериальным давлением.

Методы. Все дети прошли общее клиническое обследование, суточное мониторирование артериального давления (СМАД), эхокардиографию. Уровень NT-proBNP в сыворотке крови определяли с помощью иммуно-ферментного анализа.

Результаты. Уровень NT-proBNP в сыворотке крови у детей с первичной артериальной гипертензии второй степени был 31,23±9,32 фмоль/мл, с первичной артериальной гипертензией первой степени — 59,48±20,73 фмоль/мл, что указывало на более высокие показатели, по сравнению с группой контроля (12,48±2,18 фмоль/мл, $p<0,05$). Среди 7 детей с фракцией выброса менее 55% только у одного ребенка уровень NT-proBNP был выше, чем 300 фмоль/мл. Концентрическое ремоделирование левого желудочка наблюдалась у 32,3±8,4% детей со стабильной первичной артериальной гипертензии и 22,7±8,9% с лабильной артериальной гипертензии. Повышение уровня NT-proBNP в сыворотке крови у девочек происходит на вторичной стадии первичной артериальной гипертензии, у мальчиков — уже на первой; систолическая дисфункция у детей с ПАГ встречается редко и сопровождается повышением уровня NT-proBNP более 300 фмоль/мл.

Ключевые слова: NT-proBNP, дети, первичная гипертония.

N-термінальний мозковий натрійуретичний пептид у дітей із різними формами первинної гіпертензії

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Рівень N-термінального мозкового натрійуретичного пептиду (NT-proBNP) грає суттєву роль у регуляції внутрішньосудинного об'єму крові та судинного тонусу. В даному дослідженні брали участь діти з первинною артеріальною гіпертензією (ПАГ).

Мета. Дослідити рівень NT-proBNP у сироватці крові у дітей із різними формами первинної артеріальної гіпертензії, а також його прогностичну значимість у розвитку дисфункції міокарда у дітей із різними формами ПАГ.

Пацієнти. У дослідженні взяли участь 71 дитина у віці 9–17 років, із них — 53 пацієнти з ПАГ і 18 пацієнтів — із нормальним артеріальним тиском.

Методи. **Всі діти пройшли загальне клінічне обстеження, добове моніторирування артеріального тиску (ДМАТ), ехокардіографію. Рівень NT-proBNP** в сироватці крові визначали за допомогою імуноферментного аналізу.

Результати. Рівень NT-proBNP у сироватці крові у дітей із ПАГ другого ступеню був 31,23±9,32 фмоль/мл, із ПАГ першого ступеню — 59,48±20,73 фмоль/мл, що вказувало на більш високі показники порівняно з групою контролю (12,48±2,18 фмоль/мл, $p<0,05$). Серед 7 дітей із фракцією вибросу менше 55% тільки в одної дитини рівень NT-proBNP був вищим, ніж 300 фмоль/мл. Концентричне ремоделювання лівого шлуночка спостерігалось у 32,3±8,4% дітей зі стабільною ПАГ та у 22,7±8,9% — з лабільною артеріальною гіпертензією. Підвищення рівня NT-proBNP у сироватці крові у дівчаток відбувається на вторинній стадії ПАГ, у хлопчиків — уже на першій; систолічна дисфункція у дітей із ПАГ зустрічається рідко та супроводжується підвищенням рівня NT-proBNP більше 300 фмоль/мл.

Ключові слова: NT-proBNP, діти, первинна гіпертонія.

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