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MICROCIRCULATORY PREDICTORS
OF THE FORMATION OF PRIMARY
ARTERIAL HYPERTENSION
IN CHILDHOOD

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Summary

Introduction. *The problem of early diagnosis of arterial hypertension in children is extremely urgent. According to some foreign scientists, the prevalence of this disease among school-age children in the world has been increasing over the past ten years. Children of prepubertal and pubertal age are most prone to the development of arterial hypertension, which is largely determined by vegetative dysfunctions and microcirculation disorders characteristic of these periods of childhood.*

It has been proven that changes in microcirculation are determined by the variant of arterial hypertension and are a fairly early marker of the degree of damage to target organs.

The aim of the study is to study microcirculatory predictors of the formation of primary arterial hypertension in childhood.

Material and methods.

113 school-age children from the residents of Chernivtsi region and Chernivtsi were examined. The examined children were divided into two groups: the main group consisted of 30 children with arterial hypertension and the control group - 83 children with a normal level of blood pressure.

Blood pressure was measured with automatic pressure gauge with removable cuffs, in the morning on both arms, three times with an interval of 2 minutes. Results were evaluated according to percentile tables for age, sex, and height.

The recommendations of the American Academy of Pediatrics (AAP) were used to diagnose hypertension in children.

Capillaroscopic examination of the nail bed was used to assess the state of peripheral microcirculation in the examined children. Quantitative and qualitative parameters of microcirculation were evaluated.

The research was carried out in compliance with the "Rules of Ethical Principles of Conducting Scientific Medical Research with Human Participation" approved by the Declaration of Helsinki (1964-2013), ICH GCP (1996), EU Directive No. 609 (from 24.11.1986), orders of the Ministry of Health of Ukraine No. 690 from 23.09.2009, No. 944 from 14.12.2009, No. 616 from 03.08.2012.

Statistical processing of the data was performed using nonparametric methods of evaluation. Mathematical processing of the data was performed using Microsoft Office Excel and Statistica 10.0.

The work was performed within the framework of the planned research work of the Department of Pediatrics, Neonatology and Perinatal Medicine of Bukovynian State Medical University: Chronobiological and adaptation aspects and features of autonomic regulation in pathological conditions in children of different age groups, (№ 0122U002245, term of execution 2022 - 2026).

Results. *When comparing the quantitative capillaroscopic indicators of the nail bed between the groups, it was found that the children from the main group showed probable differences in individual indicators (reduced linear density, greater distance between capillaries, 2 times less number of anastomoses, change in the shape of capillaries) compared to the control group, which indicates on changes in peripheral microcirculation in children with elevated blood pressure.*

After conducting a correlation analysis of the obtained data, we found correlations between changes in the microcirculation of the nail bed and indicators of the functional state of the cardiovascular system in the form of changes in the linear density of capillaries and the distance between them, the presence of increased tortuosity of capillaries and "sweetening". Thus, the linear density of capillaries had high correlations with the level of systolic blood pressure ($r=0.73$, $p<0.05$) and the level of diastolic blood pressure ($r=0.69$, $p<0.05$).

When conducting a multifactorial analysis, a clear relationship between changes in the indicators of the state of the cardiovascular system, on the one hand, and the capillaries of the nail bed, on the other, can be traced.

Conclusions. *1. Microcirculatory disorders in the capillaries of the nail bed reflect the changes in central hemodynamics and may be early signs of arterial hypertension in children.*

2. According to the results of the epidemiological analysis, the presence of predictors of the development of primary arterial hypertension in children was established. These factors are a reduced number of capillaries per unit area (OR = 2.54; RR = 2.12; 95% CI 2.06-4.98) and their pathological tortuosity (OR = 1.75; RR = 1.44; 95% CI 1.18-2.63).

Keywords: *Blood Pressure; Arterial Hypertension; Children; Microcirculation; Microcirculatory Disorders.*

Introduction

Arterial hypertension (AH) is a disease characterized by an increase in systolic or diastolic blood pressure (BP), occurs on the background of excessive activity of the sympathoadrenal or renin-angiotensin-aldosterone systems, endothelial dysfunction and leads to hypertensive damage to target organs (heart, kidneys, cerebral vessels and retina) [1-4, 19].

The continuation of adult hypertension begins in childhood, which makes early diagnosis of hypertension important when blood pressure does not yet reach high levels [5-9]. The problem of early diagnosis of hypertension in children is of utmost importance. Therefore, the most thorough approach to determining the criteria for high blood pressure is a screening examination of the pediatric population [5, 10, 11, 21].

According to some foreign scientists, the prevalence of hypertension in school-age children has been increasing worldwide over the past ten years [3, 6, 12-14]. Over the past 10 years, systolic blood pressure in children has increased by an average of 1.4 mm Hg and diastolic blood pressure by 3.1 mm Hg [6, 14, 22].

In Ukraine, 32.2% of the adult population has high blood pressure [7]. The prevalence of hypertension in children, according to various authors, ranges from 1% to 14%, among schoolchildren - 12-18% [2, 4, 8]. In children of the first year of life, as well as early and preschool age, hypertension develops extremely rarely, and in most cases, it has a secondary symptomatic character [5]. Children of prepubertal and pubertal age are most susceptible to the development of hypertension, which is largely determined by autonomic dysfunctions and microcirculatory disorders (MC) inherent in these periods of childhood [4, 5, 23].

The microcirculatory link is a subsystem of the vascular bed, which, as a result, ensures transcapillary metabolism and its response to the influence of environmental and internal factors [15, 16]. It is obvious that changes in the blood MC system closely correlate with changes in central hemodynamics, which allows them to be used as criteria for assessing the health status of the examined individuals [15, 17]. The study of the MC is of great importance in modern pediatrics, since it is at this level of the circulatory system that oxygen, energy and plastic substrates are delivered to cells, carbon dioxide and other decay products are removed from tissues [16, 18, 24]. The MC responds quickly to various pathological factors, so its disorders can be early signs, and with prolonged exposure - persistent, and often the only signs of the disease. It has been proven that changes in MC are determined by the variant of hypertension and are a fairly early marker of the degree of target organ damage [16, 17, 18, 25].

Therefore, the aim of our study was to investigate microcirculatory predictors of primary arterial hypertension in childhood.

Material and Methods

113 school-age children of Chernivtsi region and Chernivtsi city were examined. The examined children were divided into the following groups: the main group consisted of 30 children with arterial hypertension and the control group consisted of 83 children with normal blood pressure. The ratio of girls to boys was 1:1. The average age of children was 14.3 ± 0.12 years.

We used the following research methods: anthropometric, clinical, laboratory, instrumental and statistical.

Blood pressure was measured by automatic blood pressure monitors with interchangeable cuffs in the morning on both arms, three times, with an interval of 2 minutes. The results were evaluated according to percentile tables for age, gender, and height.

For the diagnosis of hypertension in children, the recommendations of the American Academy of Pediatrics (AAP) were used, according to which, for children from 1 to 13 years of age, blood pressure is considered normal if its level is <90th percentile;

high blood pressure - a level from ≥ 90 th to <95th percentile, or 120/80 mm Hg to <95th percentile; hypertension of the first degree of severity - from ≥ 95 th to <95th percentile +12 mm Hg, or 130/80 to 139/89 mm Hg; AH of the second degree of severity - from ≥ 95 th percentile +12 mm Hg, or $\geq 140/90$ mm Hg. For children over 13 years of age, the simplest interpretation of blood pressure values, close to adults, is proposed [4].

To assess the state of peripheral microcirculation in the examined children, capillaroscopic examination of the nail bed was used. The examination was carried out using a digital USB microscope Digital Microscope, Cam-04 with a maximum magnification of 400x under direct transmitted illumination with LED lamps. The obtained images were registered and recorded using the above-mentioned microscope on a personal computer in JPG format and evaluated by the Micro-Measure program. The state of microcirculation was studied on the 4th and 5th fingers, as these fingers showed the highest and best skin transparency.

Quantitative and qualitative parameters of MC were evaluated. When assessing quantitative parameters, the following indicators were analyzed: the number of functioning capillaries in the field of view, the number of anastomoses, capillary diameter (d) and length (l), capillary spacing, linear density (capillary/mm), shape changes, and the presence of abnormal capillaries. Among the qualitative parameters were evaluated: (perivascular changes, vascular and intravascular changes in venules, arterioles and capillaries).

Statistical processing of the data was performed using nonparametric methods of evaluation. Mathematical processing of the data was performed using Microsoft Office Excel and Statistica 10.0.

The study was performed in compliance with the "Rules for Ethical Principles for Scientific Medical Research Involving Human Subjects" approved by the Declaration of Helsinki (1964-2013), ICH GCP (1996), EEC Directive 609 (24.11.1986), orders of the Ministry of Health of Ukraine No. 690 of 23.09.2009, No. 944 of 14.12.2009, No. 616 of 03.08.2012.

An informed consent form was prepared for each patient, which reflects basic ethical principles, such as respect for the child's personality, assessment of the risk of benefits and harms of examinations for the child, anonymity of the study results and participation in the study, and parental information and consent. This form was approved by the Bioethics Committee of Bukovinian State Medical University.

The work was performed within the framework of the planned research work of the Department of Pediatrics, Neonatology and Perinatal Medicine of Bukovinian State Medical University: Chronobiological and adaptation aspects and features of autonomic regulation in pathological conditions in children of different age groups, (№ 0122U002245, term of execution 2022 - 2026).

Results of the study and their discussion

We compared the capillaroscopic parameters of the nail bed in children of the main and control groups.

In most of the examined children, the capillaries had a regular structure, with parallel loops in several rows, a standard U-shaped shape, with a symmetrical distribution and the same diameter of vessels and uniform blood flow in them. The perivascular area of the nail bed in children was mostly pink in color.

In 4 (13.3%) of the study group and 2 children (2.4%) of the control group, the capillaries of the nail bed had an abnormal shape (bifurcation, dilation, giant and microloops, tangles). According to some foreign researchers (Y. Sheng 2013), atypical capillary morphology, including abnormal capillary shape, can occur in 9-17% of cases in healthy children [18].

Pathologic tortuosity of capillaries was detected in 6 children (20.0%) of the main group and in 2 children (2.4%) of the control group. Localized

precapillary spasm was detected in 9 children (24.3%) of the study group and 4 children (6.0%) of the control group. The phenomenon of "sludging" in capillaries was detected in 5 (16.7%) children from the main group, compared to 2 (2.4%) children in the control group, indicating more pronounced disorders of capillary blood flow in children with high blood pressure.

We evaluated and compared quantitative biomicroscopic parameters between the groups (Table 1).

Thus, in children from the main group, there were significant differences in certain parameters (reduced linear density, greater distance between capillaries, 2 times fewer anastomoses, changes in capillary shape) compared with the control group, indicating changes in peripheral MC in children with high blood pressure.

Table 1

Main capillaroscopic parameters in children from the study groups

Indicators	Group of respondents	
	Main group (M±m) n=30	Control group (M±m) n=83
Perivascular zone, microns	102,2±2,1	102,6±2,8
Distance between capillaries, microns	109,8±7,3*	105,2±7,2
Capillary length, microns	176,4±5,4	175,4±5,2
Capillary width, microns	41,0±1,7	40,5±1,9
Number of anastomoses (per 10 capillaries)	1,2±0,3*	2,5±0,3
Linear density, capillary/mm	4,8±0,4*	8,2±0,4
Changing the shape of the capillary (per 10 capillaries)	2,7±0,2*	1,0±0,2

Note. * - significant difference with the control group ($p < 0,05$)

On the basis of the data obtained, a correlation analysis was performed, which showed the presence of correlations between the indicators of MC of the nail bed capillaries. The most significant sign can be considered increased tortuosity of capillaries, since they most reflect the MC in microvessels. Correlations were found between the degree of tortuosity of venules and changes in their caliber ($r=0.79$, $p<0.05$); precapillary spasmodicity and capillary tortuosity ($r=0.84$, $p<0.05$); linear density of capillaries and distance between them ($r=0.69$, $p<0.05$); number of functioning capillary loops and the phenomenon of "sliding" in capillaries ($r=0.58$, $p<0.05$).

High correlations were observed between "sliding" in venules, arterioles and in the entire capillary bed, which can be attributed to the fact that in case of MC disorders in one of these sections, disorders occur in other parts of the vessels.

The state of the microcirculatory bed of the nail bed reflected changes in central hemodynamics. We have found correlations between changes in the nail bed MC and indicators of the functional state of the cardiovascular system (CVS) in the form of changes in the linear density of capillaries and the distance between them, the presence of increased capillary tortuosity and "sludging". Thus, linear capillary density had high correlations with systolic blood pressure (SBP) ($r=0.73$, $p<0.05$) and diastolic blood pressure (DBP) ($r=0.69$, $p<0.05$).

Perhaps all these changes are related to common mechanisms of blood flow regulation, caused by the state

of central hemodynamics and the condition, integrity, size and diameter of capillaries regulated by the autonomic nervous system. The presence of increased tortuosity correlated with changes in the caliber of the nail bed capillaries ($r=0.47$, $p<0.05$), which can be regarded as the occurrence of stagnation in the microvasculature.

Thus, it can be said that microcirculatory disorders in the nail bed capillaries reflect the changes in central hemodynamics and may be early signs of hypertension in children.

In order to find the relationship between the indicators of nail bed microcirculation and indicators of CVD in children, we used multivariate analysis.

To select the number of factors that describe the symptoms inherent in the pathology under study and the methods of examination, a preliminary analysis was performed. We have identified 3 factors: the eigenvalue of the 1st factor is 21.8, the 2nd - 8.5, and the 3rd - 5.7. The first factor most fully describes the changes identified in the survey, the second and third factors are somewhat less important, but also significant (Fig. 1). Factors 4, 5 and the following ones have insufficient depth of description of the main changes, which is why we stopped at selecting 3 main factors.

We can analyze all the factors by importance. The first factor is multicomponent, has the highest value, larger share and greater influence. It consists of 5 components: SBP level (0.90), DBP level (0.85), capillary distance (0.82), linear capillary density (0.78),

and capillary shape change (0.71). The second factor is half as important as the first in terms of personal value. It consists of three components that are close to each other: the phenomenon of "sliding" in the capillaries

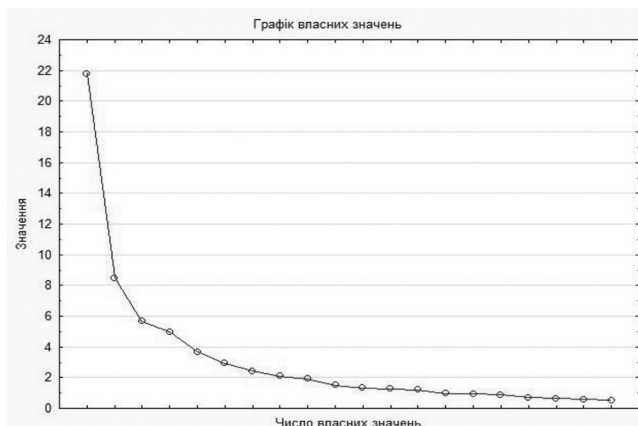


Fig. 1. Multifactorial analysis of microcirculatory parameters

(0.80), increased tortuosity of the capillaries (0.79), and the number of anastomoses (0.71). The third factor has only one component - local capillary spasm (0.71).

Indicators of the above factors are presented in more detail in Table 2.

Thus, based on the data obtained, there is a clear relationship between changes in CVD parameters on the one hand and nail bed capillaries on the other.

The next step was to conduct an epidemiologic analysis to assess the specificity and sensitivity, odds ratio, and relative risk of the main microcirculatory predictors. The factor of reduced capillary number was the most sensitive (Table 3).

The factor of reduced number of capillaries has a fairly high specificity (0.82) and is significant ($p < 0.05$). The lower limit of the 95% confidence interval is 2.06. That is, children with a reduced number of capillaries are 2.54 times more likely to develop hypertension than children with a normal number of capillaries. In addition, the relative risk of hypertension in these children is 2.12 times higher than in children with normal capillary density.

Table 2

Composition of the main factors according to the results of multivariate analysis

Factors	1 factor	2 factor	3 factor
SBP level	0,90	0,23	0,12
DAT level	0,85	0,15	0,12
The phenomenon of "sliding" in capillaries	0,23	0,80	0,38
Number of anastomoses	0,20	0,71	0,11
Changing the shape of the capillary	0,71	0,10	0,42
Increased capillary tortuosity	0,27	0,79	0,06
Linear capillary density	0,78	0,16	0,19
Localized spasm of capillaries	0,15	0,11	0,71
Distance between capillaries	0,82	0,10	0,10

Table 3

The effect of a reduced number of capillaries on systolic blood pressure

Statistical indicator	Value of the indicator	Lower bound	Upper limit 95% confidence interval
OR	2,54	2,06	4,98
RR	2,12	1,67	3,21
Sensitivity	0,40	0,32	0,48
Specificity	0,82	0,78	0,81

The factor of pathological tortuosity of capillaries was analyzed in a similar way (Table 4).

The factor also has a high specificity (0.81) and is significant ($p < 0.05$). The lower limit of the 95% confidence interval is 1.08. Thus, children with

pathologic tortuosity of capillaries are 1.75 times more likely to develop hypertension than children with normal capillaries, and their relative risk of hypertension is 1.44 times higher.

Thus, disorders of the microcirculatory system

Table 4

Effect of pathological tortuosity of capillaries on the level of systolic blood pressure

Statistical indicator	Value of the indicator	Lower bound 95% confidence interval	Upper limit 95% confidence interval
OR	1,75	1,18	2,63
RR	1,44	1,05	1,37
Sensitivity	0,30	0,23	0,29
Specificity	0,81	0,79	0,84

can be reliable predictors of the formation of primary arterial hypertension in childhood.

Conclusions

1. Microcirculatory disorders in the capillaries of the nail bed reflect the changes in central hemodynamics and may be early signs of arterial hypertension in children.

2. The results of the epidemiological analysis revealed the presence of predictors of primary arterial hypertension in children. These factors are a reduced number of capillaries per unit area (OR = 2.54; RR = 2.12; 95% CI 2.06-4.98) and their pathological tortuosity (OR = 1.75; RR = 1.44; 95% CI 1.18-2.63).

3. These factors are unmodifiable, genetically determined and can be regarded, to some extent, as indirect triggers of hypertension due to increased peripheral resistance.

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The prospect of further research is to study in more detail the relationship between microcirculation parameters and the formation of primary arterial hypertension in childhood.

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МІКРОЦИРКУЛЯЦІЙНІ ПРЕДИКТОРИ ФОРМУВАННЯ ПЕРВИННОЇ АРТЕРІАЛЬНОЇ ГІПЕРТЕНЗІЇ У ДИТЯЧОМУ ВІЦІ

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Резюме

Вступ. Проблема ранньої діагностики артеріальної гіпертензії у дітей має надзвичайну актуальність. За даними деяких закордонних науковців впродовж останніх десяти років відзначається зростання поширеності цього захворювання у дітей шкільного віку в світі. Найбільш схильні до розвитку артеріальної гіпертензії діти препубертатного і пубертатного віку, що багато в чому визначається властивими цим періодам дитинства вегетативними дисфункціями та розладами мікроциркуляції.

Доведено, що зміни мікроциркуляції визначаються варіантом артеріальної гіпертензії та є досить раннім маркером ступеня ураження органів-мішеней.

Мета дослідження – вивчити мікроциркуляційні предиктори формування первинної артеріальної гіпертензії у дитячому віці.

Матеріал та методи дослідження.

Обстежено 113 дітей шкільного віку жителів Чернівецької області та м. Чернівці. Обстежених дітей було розподілено на дві групи: основну групу склали 30 дітей із артеріальною гіпертензією та контрольну групу – 83 дитини з нормальним рівнем артеріального тиску.

Вимірювання рівня артеріального тиску проводилось автоматичними тонометрами зі змінними манжетами в ранковий час на обох руках, тричі, з інтервалом у 2 хвилини. Результати оцінювалися за перцентильними таблицями відносно віку, статі та зросту. Для діагностики артеріальної гіпертензії у дітей використовувались рекомендації Американської педіатричної академії (American Academy of Pediatrics, AAP). Для оцінки стану периферичної мікроциркуляції в обстежених дітей було застосовано капіляроскопічне дослідження нігтьового ложа. Оцінювалися кількісні та якісні параметри мікроциркуляції.

Дослідження виконані з дотриманням «Правил етичних принципів проведення наукових медичних досліджень за участю людини», затверджених Гельсінською декларацією (1964-2013 рр.), ICH GCP (1996 р.), Директиви ЄЕС № 609 (від 24.11.1986 р.), наказів МОЗ України № 690 від 23.09.2009 р., № 944 від 14.12.2009 р., № 616 від 03.08.2012 р.

Робота виконана в рамках планової науково-дослідної роботи кафедри педіатрії, неонатології та перинатальної медицини Буковинського державного медичного університету: Хронобіологічні й адаптаційні аспекти та особливості вегетативної регуляції при патологічних станах у дітей різних вікових груп, (№ 0122U002245, термін виконання 2022 – 2026 рр.).

Результати дослідження. При порівнянні кількісних капіляроскопічних показників нігтьового ложа між групами виявлено, що у дітей із основної групи спостерігалися вірогідні відмінності окремих показників (знижена лінійна щільність, більша відстань між капілярами, у 2 рази менша кількість анастомозів, зміна форми капілярів) у порівнянні з контрольною групою що вказує на зміни периферичної мікроциркуляції у дітей з підвищеним рівнем артеріального тиску.

Провівши кореляційний аналіз отриманих даних нами були виявлені кореляції між змінами мікроциркуляції нігтьового ложа та показниками функціонального стану серцево-судинної системи у вигляді змін лінійної щільності капілярів та відстані між ними, наявності підвищеної звивистості капілярів і «сладжуванням». Так, лінійна щільність капілярів мала високу кореляційні зв'язки із рівнем систолічного артеріального тиску ($r=0,73$, $p<0,05$) та рівнем діастолічного артеріального тиску ($r=0,69$, $p<0,05$).

При проведенні багатофакторного аналізу простежується чітка залежність між змінами показників стану серцево-судинної системи з одного боку та капілярів нігтьового ложа – з іншого.

Висновки.

1. Мікроциркуляторні розлади у капілярах нігтьового ложа є відображенням змін у центральній гемодинаміці та можуть бути ранніми ознаками артеріальної гіпертензії у дітей.

2. За результатами епідеміологічного аналізу було встановлено наявність предикторів розвитку первинної артеріальної гіпертензії у дітей. Цими факторами є зменшена кількість капілярів на одиницю площі (OR = 2,54; RR = 2,12; 95% ДІ 2,06 -4,98) та їх патологічна звивистість (OR = 1,75; RR = 1,44; 95% ДІ 1,18 -2,63).

Ключові слова: артеріальний тиск; артеріальна гіпертензія; діти; мікроциркуляція; мікроциркуляторні розлади.

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