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Endothelial dysfunction in children with SARS-CoV-2-associated pneumonia and its dependence on the activity of the infectious-inflammatory process

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One of the key pathogenetic mechanisms of COVID- 19 is endothelial dysfunction, which enhances prothrombotic phenomena, endotheliitis, and multiorgan immunothrombosis. The mechanisms of endothelial damage in children remain insufficiently studied.
Aim: to determine the levels of endothelial dysfunction in children with SARS-CoV-2-associated pneumonia and to analyze its relationships with clinical and laboratory indicators of the activity of the infectious and inflammatory process.
Materials and methods. The Main group consisted of 160 children with SARS-CoV-2-associated pneumonia and 40 healthy children (Control group). The Main group was divided depending on gender, age, disease severity, levels of C-reactive protein (CRP), and procalcitonin. To assess endothelial dysfunction, the level of endothelin-1 and vascular endothelial growth factor (VEGF) in blood serum was determined.
Results. The values of VEGF and endothelin-1 were the highest in patients with severe pneumonia. The values of laboratory markers of endothelial dysfunction were significantly higher with higher levels of CRP in children of the Main group by 31.95% and 33.14% for endothelin-1 and VEGF, respectively. A positive medium-strength relationship was established between the values of fibrinogen and CRP with VEGF levels; a weak positive relationship between the levels of VEGF and procalcitonin; fibrinogen and endothelin-1 levels. A probable medium-strength positive relationship was established between the values of endothelin-1 and VEGF, with the levels of interleukins (IL) 1, 6.
Conclusions Children of the Main group have endothelial dysfunction, as evidenced by increased levels of endothelin-1 and VEGF. These values were associated with disease severity, CRP levels, and gender. VEGF levels were highest in patients with severe pneumonia. There was a moderate positive association between laboratory markers of endothelial dysfunction, such as endothelin-1 and VEGF, and IL-1 and IL-6 levels.
Keywords: endothelial dysfunction, SARS-CoV-2, pneumonia, children, endothelin-1, VEGF, C-reactive protein.

Особливості ендотеліальної дисфункції в дітей із SARS-CoV-2 асоційованою пневмонією та її зв'язок із активністю інфекційно-запального процесу

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Одним із ключових патогенетичних механізмів під час COVID-19 є ендотеліальна дисфункція, яка посилює протромботичні явища, ендотеліїт та поліорганний імунотромбоз. Механізми ураження ендотелію в дітей залишаються недостатньо вивченими.
Мета: визначити рівні ендотеліальної дисфункції в дітей із SARS-CoV-2, асоційованою з пневмонією, та проаналізувати її взаємозв'язки з клініко-лабораторними показниками активності інфекційно-запального процесу.
Матеріали та методи. Основну групу становлять 160 дітей із SARS-CoV-2, асоційованою з пневмонією, та 40 здорових дітей (контрольна група). Основна група була поділена залежно від статі, віку, тяжкості перебігу хвороби, рівнів С-реактивного білка та прокальцитоніну. Для оцінки ендотеліальної дисфункції визначали рівень ендотеліну-1 та ендотеліального фактора росту судин (VEGF) у сироватці крові.
Результати. Значення VEGF та ендотеліну-1 були найвищими в пацієнтів із тяжким перебігом пневмонії. Вірогідно вищими є значення лабораторних маркерів ендотеліальної дисфункції при вищих рівнях СРБ у дітей основної групи на 31,95% та 33,14% для ендотеліну-1 та VEGF відповідно. Встановлено наявність позитивного середньої сили взаємозв'язку між значенням фібриногену та СРБ із рівнями VEGF; слабкого позитивного зв'язку між рівнем VEGF та прокальцитоніну; рівнем фібриногену та ендотеліну-1. Виявлено вірогідний позитивний взаємозв'язок середньої сили між значеннями ендотеліну-1 та VEGF, із рівнями інтерлейкінів 1, 6.
Висновки. У дітей основної групи простежується ендотеліальна дисфункція, яка проявляється підвищенням рівнів ендотеліну-1 та VEGF. Зафіксовано залежність цих показників від тяжкості захворювання, рівня СРБ та статі пацієнтів. Значення VEGF були найвищими в пацієнтів із тяжким перебігом пневмонії. Існує вірогідний позитивний зв'язок середньої сили між значеннями таких лабораторних маркерів ендотеліальної дисфункції, як ендотелін-1 та VEGF, із рівнями ІЛ-1 та ІЛ-6.
Ключові слова: ендотеліальна дисфункція, SARS-CoV-2, пневмонія, діти, ендотелін-1, VEGF, С-реактивний білок.

Introduction

The SARS-CoV-2 pandemic remains a pressing issue for humanity due to its human-to-human transmission and the potential for infection across all age groups. The majority of patients are older adults; however, recent trends indicate a rise in the incidence of this condition among children [7]. Numerous reports describe a predominantly mild course of coronavirus infection in children and a high percentage of asymptomatic cases [2], which does not exclude the possibility of long-term consequences, not to mention severe disease progression requiring hospitalization and the development of complications [1].

The influence of various factors on the severity of the disease is being studied [5], including the development of endothelial dysfunction, which exacer-

Table 1

Characteristics of the examined children of the Main group by age and gender (n=160)

Main group (n=160)					Control group (n=40)				
age of the respondents	boys (n=89)		girls (n=71)		age of respondents	boys (n=20)		girls (n=20)	
	abs.	%	abs.	%		abs.	%	abs.	%
0–1 years (n=41)	22	13.75	19	11.87	0–1 years (n=5)	2	5.0	3	7.5
1–4 years (n=37)	20	12.5	17	10.63	1–4 years (n=12)	9	22.5	3	7.5
5–14 years (n=40)	23	14.37	17	10.63	5–14 years (n=21)	8	20.0	13	32.5
15–17 years (n=42)	24	15.00	18	11.25	15–17 years (n=2)	1	2.5	1	2.5
Всього (n=160)	89	55.63	71	44.37	Всього (n=40)	20	50.0	20	50.0

Note: no statistically significant difference was found.

bates prothrombotic phenomena, endotheliitis, and multiorgan thrombosis. The inflammatory process in endothelial cells stimulates procoagulant, prothrombotic, and antifibrinolytic factors, adversely affecting the blood coagulation process. Additionally, excessive synthesis of vasoconstrictive factors, activated by the endothelium, contributes to hypercoagulable states in the body. Literature sources point to the possibility of both direct damage to vascular endothelial cells by coronaviruses and indirect damage mediated by immune cells, cytokines, and free radicals, leading to the development of endothelial dysfunction. This, in turn, increases the risk of earlier onset of long-term cardiovascular complications in convalescent patients [8]. Disruptions in microcirculation and vasoconstriction provoke the development of organ ischemia, inflammation, tissue edema, and coagulation abnormalities. Vascular endothelial damage also contributes to systemic background inflammation in the post-COVID period, laying the foundation for complications, primarily affecting the cardiovascular, urinary, and endocrine systems, among others [6]. In adult patients, endothelial damage following COVID-19 infection increases the risk of thromboembolism, arrhythmias, and myocardial ischemia by 22-25% [4].

The mechanisms of endothelial damage have been studied primarily in adult patients, while the specifics of this process in children remain insufficiently explored. This underscores the need for the development of highly sensitive methods to ensure timely diagnosis and treatment of endothelial dysfunction in patients who have experienced coronavirus infection.

The aim of the study is to assess the presence of endothelial dysfunction in children with SARS-CoV-2-associated pneumonia and its relationship with clinical and laboratory indicators of infectious-inflammatory process activity.

Materials and methods of the study

To achieve the study's objective, we conducted a comprehensive examination of 160 children (71 (44.37%) girls and 89 (55.63%) boys) with SARS-CoV-2-associated pneumonia (Main group) aged from 1 month to 18 years (average age 10.50±8.30) during 2022-2023.

For the purpose of conducting a comparative analysis of the examination results of patients the Main group, a Control group of 40 practically healthy children aged 1 month to 18 years was examined (average age 10.50±8.30). This group included 20 (50.0%) boys and 20 (50.0%) girls. All children in the Control group had normal results in clinical, laboratory, and instrumental examinations. The distribution of the examined subjects of the Main and Control groups by age and gender is given in Table 1.

According to the data in Table 1, the patients of the Main and Control groups included in the study did not differ significantly in age and gender. It should be noted that both groups of patients were comparable in age, the ratio of girls and boys was approximately 1:1.

To achieve the objective, all children of the Main group underwent an assessment of C-reactive protein (CRP), procalcitonin, and fibrinogen levels upon hospitalization. We evaluated the activity of the inflammatory process and endothelial function in children with SARS-CoV-2-associated pneumonia by measuring the levels of interleukins (IL) 1 and 6, endothelin-1, and vascular endothelial growth factor (VEGF) using enzyme-linked immunosorbent assay (ELISA).

The results were subjected to statistical analysis using the SPSS Statistics 12.0 software package, employing both parametric and non-parametric methods for evaluating the obtained data. The arithmetic

Table 2

Levels of laboratory markers of endothelial dysfunction in the blood serum of children the Main group by sex (M±m)

Marker	Main group		Control group n=40
	boys, n=89	girls, n=71	
Endothelin-1 (pg/ml)	9.77±0.68*	12.72±0.84*,**	2.25±0.13
VEGF, (pg/ml)	52.99±2.79*	55.88±2.86*	23.53±1.23

Notes: * – significant difference compared to the healthy children (p≤0.05); ** – significant difference compared to children of the opposite sex (p≤0.05).

Table 3

Levels of laboratory markers of endothelial dysfunction in the blood serum of children the Main group by severity (M±m)

Marker	Main group			Control group, n=40
	average score (n=160)	severity		
		non-severe (n=62)	severe (n=98)	
Endothelin-1 (pg/ml)	11.08±0.54*	8.58±0.69	12.66±0.72**	2.25±0.13
VEGF, (pg/ml)	54.27±2.00*	38.59±1,99	64.19±2.56**	23.53±1.23

Notes: * – significant difference compared to the Control group (p<0.001); ** – significant difference compared to patients with non-severe disease (p≤0.05).

Table 4

Levels of laboratory markers of endothelial dysfunction in children of the Main group by CRP levels (M±m)

CRP level quartile (mg/l)	Endothelin-1 level (pg/ml)	VEGF level (pg/ml)
I Quartile (less than 9.3), n=40	9.76±0.99	43.66±3.11
II Quartile (9.3–13.99), n=40	10.86±1.04	50.17±4.01
III Quartile (14.00–23.99), n=40	11.37±1.16	58.13±3.83*
IV Quartile (more than 24), n=40	14.33±1.13*	65.13±4.27*

Note: * – significant difference compared to levels in the I and II quartiles (p≤0.05).

mean (M) and standard error (m) of the indicators were determined. For qualitative variables, the frequency of occurrence (%) and its standard error (m%) were calculated. The distribution's conformity to the Gauss's law was tested using the Shapiro–Wilk criterion. The significance of differences between independent quantitative variables with a normal distribution was assessed using the Student's t-test for independent samples. For percentage data, Fisher's exact test was used, and in other cases, the Mann–Whitney U-test was applied. Values of $P<0.05$ were considered statistically significant. To determine the strength and direction of the relationship between the indicators in the studied groups, correlation analysis was used (with a parametric data distribution – Pearson's pairwise correlation, and with a nonparametric distribution of features – Spearman's rank correlation). The strength of the relationship was determined by the value of the correlation coefficient: strong, or dense, with a correlation coefficient of $r>0.70$; medium at $0.50<r<0.69$; moderate at $0.30<r<0.49$; weak at $0.20<r<0.29$; very weak at $r<0.19$.

The study was conducted in accordance with the ethical principles of scientific research involving human subjects (Declaration of Helsinki) and the guidelines of Good Clinical Practice (GCP). The informed consent was obtained from the parents of the patients. The informed consent text was developed by the Local independent Ethics Committee based on a bioethical review. The study design was approved by the Ethics Committee of Vinnytsia National Pirogov Memorial Medical University (protocol No. 4, dated May 18, 2023).

Results of the study and discussion

Analyzing the laboratory markers of endothelial dysfunction in the blood serum of children in the Main group, depending on sex, revealed a significant difference compared to children of the Control group. Notably, girls exhibited a significantly higher endothelin-1 level by 30.19% (Table 2). There was no significant difference in endothelin-1 levels by gender in the Control group.

The analysis of endothelin-1 and VEGF levels depending on the severity of SARS-CoV-2-associated

Table 5

Levels of laboratory markers of endothelial dysfunction in children of the Main group by procalcitonin levels (M±m)

Procalcitonin level quartile (ng/ml)	Endothelin-1 level (pg/ml)	VEGF level (pg/ml)
I Quartile (less than 0.89), n=40	9.92±0.84	48.19±2.62
II Quartile (0.90–1.02), n=40	10.39±1.25	51.13±3.78
III Quartile (1.03–1.29), n=40	11.41±1.10	56.90±3.77
IV Quartile (more than 1.3), n=40	12.61±1.09	60.86±3.61*

Note: * – significant difference compared to levels in other quartiles (p≤0.05).

Table 6

Levels of laboratory markers of endothelial dysfunction in children of the Main group by fibrinogen levels (M±m)

Fibrinogen levels (g/l)	Endothelin levels -1 (pg/ml)	VEGF levels (pg/ml)
I Quartile (less than 8.23), n=40	9.09±0.90	38.96±2.49
II Quartile (8.24–9.82), n=40	9.33±1.02	48.73±3.85
III Quartile (9.83–11.25), n=40	12.47±1.17	63.84±4.38*
IV Quartile (більше 11.26), n=40	13.43±1.08*	65.56±3.56*

Note: * – significant difference compared to levels in the I and II quartiles (p≤0.05).

Table 7

Levels of laboratory markers of endothelial dysfunction in children of the Main group by IL-1 levels (M±m)

IL-1 level quartile (pg/ml)	Endothelin-1 level (pg/ml)	VEGF level (pg/ml)
I Quartile (less than 26.43), n=40	8.96±0.93	37.43±2.65
II Quartile (26.44–34.11), n=40	10.37±1.04	51.57±4.32
III Quartile (34.12–44.57), n=40	10.88±0.92	59.25±3.61
IV Quartile (more than 44.58), n=40	14.10±1.25**	68.81±3.60*

Notes: * – significant difference compared to levels in the I quartile (p≤0.05); ** – significant difference compared to levels in the I and II quartiles (p≤0.05).

pneumonia showed a significant difference between patients with severe and non-severe courses by 44.55% and 66.34%, respectively (Table 3).

Significantly higher levels of laboratory markers of endothelial dysfunction were observed in children of the Main group who had elevated CRP levels, showing increases of 31.95% and 33.14% for endothelin-1 and VEGF, respectively (Table 4).

When comparing the levels of endothelin-1 and VEGF based on procalcitonin levels, no significant differences in endothelin-1 levels were observed. However, VEGF levels were significantly higher, by 26.29%, in patients with serum procalcitonin levels in the IV quartile (Table 5).

When comparing endothelin-1 levels based on fibrinogen levels, significantly higher values (by 47.74%) were observed in patients with fibrinogen levels in the IV quartile. VEGF levels also significantly varied according to fibrinogen levels, particularly in patients with levels in the III and IV quartiles, showing increases of 63.86% and 34.49%, respectively (Table 6).

A moderate positive correlation was established between fibrinogen and CRP levels with VEGF levels (rxy=0.400; p=0.0001 and rxy=0.315; p=0.0001, respectively). Additionally, a weak positive correlation was noted between VEGF and procalcitonin levels (rxy=0.191; p=0.015) and between fibrinogen and endothelin-1 levels (rxy=0.277; p=0.0001). Depending on IL-1 levels, as one of the pro-inflammatory cytokines, significantly higher VEGF and endothelin-1 levels were observed – by 33.43% and 35.96%, respectively – compared to children of the Main group who had IL-1 levels in the I and/or II quartiles (Table 7).

When comparing the levels of endothelin-1 and VEGF in the blood serum in children of the Main group based on IL-6 levels, significantly higher values of these laboratory markers of endothelial dysfunction were observed in patients with IL-6 levels in the III and IV quartiles, increasing by 2.36 and 2.34 times, respectively (Table 8).

We identified a significant moderate positive correlation between the levels of endothelial dysfunction markers, such as endothelin-1 and VEGF, and the levels of IL-1 and IL-6. Children of the Main group had significantly higher levels of endothelin-1 and VEGF compared to children of the Control

Table 8

Levels of laboratory markers of endothelial dysfunction in children of the Main group by IL-6 levels (M±m)

IL-6 level quartile (pg/ml)	Endothelin-1 level (pg/ml)	VEGF level (pg/ml)
I Quartile (less than 14.80), n=40	5.97±0.60	30.58±2.35
II Quartile (14.81–23.32), n=40	10.66±0.93	52.01±3.43
III Quartile (23.33–31.12), n=40	13.57±1.05*	62.91±4.07*
IV Quartile (more than 31.13), n=40	14.11±1.16*	71.57±2.69*

Note: * – significant difference compared to levels in the I quartile (p≤0.05).

group (p⩽0.05). These markers were found to depend on disease severity, CRP levels, and the sex of the patients. In girls, endothelin-1 levels were 30.19% higher than in boys (p⩽0.05). VEGF levels were highest in patients with severe pneumonia, showing an increase of 66.34% compared to those with non-severe disease.

Discussion of the results obtained

Coronavirus disease remains one of the most severe in the world. The percentage of severe and fatal cases among children is lower than in adults. The search for biomarkers that indicate the severity of the disease is ongoing. Endothelial dysfunction is a systemic condition in which the endothelium loses its physiological properties. The mechanism of endothelium's participation in the occurrence and development of various pathological conditions is multifaceted and is associated not only with the regulation of vascular tone but also with participation in the process of thrombus formation, and protection of the integrity of the vascular wall. The endothelium plays a key role in maintaining normal vascular tone and structure, local homeostasis, and proliferation processes of vascular wall cells. The function of the endothelium and its role in the normal functioning of the cardiovascular system in children has been known for a long time. The regulatory functions of the endothelium are numerous, including maintaining the tone and structure of the vascular walls, vascular remodeling, regulation of thrombus formation and fibrinolytic functions, participation in inflammatory and immune reactions, regulation of leukocyte and platelet adhesion to its surface, regulation of vascular wall permeability. Endothelial dysfunction is believed to be one of the elements of the pathogenesis of SARS-CoV-2 infection and leads to the activation of thrombus formation processes and impaired vascular tone. Moreover, endothelial dysfunction is exacerbated by excessive synthesis of pro-inflammatory cytokines.

Endothelial cell dysfunction is accompanied by an increase in D-dimer levels, which are a breakdown product of fibrin and fibrinogen. This suggests that the essence of coagulopathies in COVID infection is increased fibrin formation, and not prolonged prothrombin and activated partial thromboplastin time, decreased antithrombin and platelets, which are observed in sepsis and disseminated intravascular coagulation syndrome [3].

Activation of endothelin-1 synthesis is probably a response to damage to endothelial cells by toxins during the onset of the inflammatory process in the lungs. An increase in this indicator can also be associated with a compensatory response to the hyperproduction of nitric oxide. As a result of a decrease in the elimination of endothelin during damage to lung tissue and inactivation of nitric oxide during its interaction with free radicals (formation of peroxynitrite, etc.), an imbalance occurs between vasoconstrictors and vasodilators in the direction of vasoconstriction. A high content of endothelin-1 in the blood can lead to a predominance of the vasoconstrictor effect, impaired microcirculation, and the development of hypoxia of peripheral tissues, which can cause a more severe course of community-acquired pneumonia and the development of complications. It is natural that in children in the group with a mild course of pneumonia, in whom inflammatory phenomena are less pronounced, the level of endothelin-1 in the blood is minimal. Elevated levels of endothelin-1 and VEGF, which are associated with disease severity and systemic inflammation, indicate the need to consider these markers in predicting the course of the disease. High levels of VEGF in severe disease indicate activation of vascular inflammation, which requires further study.

SARS-CoV-2 infection promotes the development of endotheliitis in various organs as a consequence of viral damage. It is the presence of COVID-19-induced endotheliitis that can explain the systemic microcirculatory impairment in various vascular beds and their clinical consequences.

Conclusions

Endothelial dysfunction plays a significant role in the pathogenesis of SARS-CoV-2-associated pneumonia in children, as evidenced by an increase in endothelin-1 and VEGF levels by 4.92 and 2.31 times, respectively, compared to the Control group ($p<0.001$). Additionally, the levels of endothelin-1 and VEGF in the blood serum of children with severe SARS-CoV-2-associated pneumonia were 1.47 and 1.62 times higher, respectively, than in patients with non-severe disease.

The levels of laboratory markers of endothelial dysfunction were also influenced by indicators of the inflammatory process. Specifically, at CRP, procalcitonin, and fibrinogen levels within the IV quartile, the levels of endothelin-1 and VEGF were 1.26–1.68 times higher, respectively, than in patients with pro-inflammatory marker levels in the I quartile. Moreover, a significant ($p=0.0001$) positive correlation was identified between the levels of endothelin-1 and VEGF and IL-1 and IL-6. For IL-1, the correlation coefficients were $rxy=0.318$ and $rxy=0.493$, respectively, and for IL-6, they were $rxy=0.491$ and $rxy=0.614$, respectively.

Prospects for further research. Given the development of endothelial dysfunction and the potential for thrombosis in children with coronavirus infection, future research should focus on evaluating blood coagulation system parameters.

The authors declare no conflict of interest.

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