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ДИАГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ СОДЕРЖАНИЯ ВАЗОЭНДОТЕЛИАЛЬНОГО ФАКТОРА РОСТА В ЗАВИСИМОСТИ ОТ СТЕПЕНИ ТЯЖЕСТИ И ДЛИТЕЛЬНОСТИ АТОПИЧЕСКОГО ДЕРМАТИТА, А ТАКЖЕ С УЧЕТОМ НАЛИЧИЯ МАРКЕРОВ ГЕРПЕСВИРУСНОЙ ИНФЕКЦИИ

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Diagnostic Significance Vasoendothelial Growth Factor Depending on the Severity and Duration of Atopic Dermatitis, as Well as Taking into Account the Presence of Markers of Herpes Virus Infection

Резюме

В настоящее время остро стоит проблема диагностики и лечения заболеваний, связанных с нарушениями процесса ангиогенеза, а также регенераторных процессов. Факторы, регулирующие процессы ангиогенеза при аллергических заболеваниях, в том числе при атопическом дерматите играют ключевую роль в поддержании хронического воспаления и могут оказывать значительное влияние на течение заболевания. **Материалы и методы.** Исследование аналитическое поперечное и представлено комплексным обследованием 140 пациентов с АтД в возрасте от 2 до 12 лет (медиана возраста 4,2 года), распределенных на 2 группы: 70 детей с установленным диагнозом АтД; 70 детей с диагнозом атопический дерматит, инфицированных вирусом простого герпеса (АтД+ГВИ). Группу контроля составили 70 соматически здоровых детей. Специальное лабораторное обследование включало определение специфических антител классов IgM и/или IgG к антигенам вируса простого герпеса 1-2 типа методом иммуноферментного анализа (ИФА); определение ДНК исследуемых герпесвирусов в образцах крови методом полимеразной цепной реакции; определение фактора роста эндотелия сосудов А (VEGF-A) в плазме крови пациентов методом ИФА. **Результаты собственных исследований.** Было установлено статистически значимое ($p<0,001$) повышение уровня фактора роста эндотелия сосудов А в сыворотке крови у детей с АтД по сравнению с контрольной группой. На фоне инфицирования вирусом простого герпеса выявлено увеличение уровня фактора роста эндотелия сосудов А в сыворотке крови по сравнению с пациентами с атопическим дерматитом ($p<0,001$).Также было выявлено статистически значимое увеличение уровня VEGF-A в сыворотке крови у пациентов с АтД ($p<0,001$) и АтД+ГВИ ($p<0,001$) с увеличением степени тяжести АтД. Это подтверждалось результатами корреляционного анализа, выявившего взаимосвязи между уровнем VEGF-A и выраженностью клинических симптомов заболевания. Присоединение герпесвирусной инфекции к АтД ухудшает клиническую симптоматику данного заболевания.

Ключевые слова: *ангиогенез, вазоэндотелиальный фактор роста, атопический дерматит*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract
Currently, the problem of diagnosis and treatment of diseases associated with disorders of the angiogenesis process, as well as regenerative processes, is acute. Factors regulating the processes of angiogenesis in allergic diseases, including atopic dermatitis, play a key role in maintaining chronic inflammation and can have a significant impact on the course of the disease. **Materials and methods:** The study is analytical cross-sectional and presented by a comprehensive examination of 140 patients with AtD aged 2 to 12 years (median age 4.2 years), divided into 2 groups: 70 children with an established diagnosis of AtD; 70 children with atopic dermatitis infected with herpes simplex virus (AtD+HVI). The control group consisted of 70 somatically healthy children. A special laboratory examination included the determination of specific IgM and/or IgG class antibodies to herpes simplex virus type 1-2 antigens by enzyme immunoassay (ELISA); determination of the DNA of the studied herpesviruses in blood samples by polymerase chain reaction; determination of vascular endothelial growth factor A (VEGF-A) in the blood plasma of patients by ELISA. **The results of our own research:** A statistically significant (p <0.001) increase in the level of vascular endothelial growth factor A in blood serum was found in children with AtD compared with the control group. Against the background of infection with the herpes simplex virus, an increase in the level of vascular endothelial growth factor A in blood serum was revealed compared with patients with atopic dermatitis (p <0.001). There was also a statistically significant increase in serum VEGF-A levels in patients with AtD (p <0.001) and AtD+HVI (p <0.001) with an increase in the severity of AtD. This was confirmed by the results of a correlation analysis that revealed the relationship between the level of VEGF-A and the severity of clinical symptoms of the disease.The addition of herpesvirus infection to AtD worsens the clinical symptoms of this disease.

Key words: *angiogenesis, vascular endothelial growth factor,atopic dermatitis*

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AtD — atopic dermatitis, ALT — alanine aminotransferase, AST — aspartate aminotransferase, HVI — herpes virus infection, RTK — tyrosine-protein kinase, VEGF-A — vascular endothelial growth factor A, ELISA — enzyme-linked immunosorbent assay

Introduction

Currently, the problem of the diagnosis and therapy of diseases associated with impaired angiogenesis and regeneration processes is very relevant. Alongside the known ethiopathogenetic factors, the study of clinical and diagnostic criteria of the course of these diseases is of great interest. Usually, the main diagnostic laboratory parameters are clinical blood assay and blood biochemistry; however, the exploratory value for the practical medicine lies in the study of various molecular peptide factors contributing to the development of angiogenic and endothelial disorders [1,2].

Angiogenesis of allergic skin disorders is characterised by marked vasodilation and higher vascular permeability, which is caused by the presence of singe-layer or multilayer basal membrane and fenestrated endothelium [3].

However, available literature does not contain any evidence of the nature of the impact of vascular endothelial growth factor A (VEGF-A) on the progression of atopic dermatitis (AtD) and herpes virus infection (HVI) [the link is irrelevant, since these are original data].

Some aspects of physiology and angiogenesis

It has been shown that physiological angiogenesis is a result of a balanced activity of its stimulators (vascular endothelial growth factor (VEGF), angiogenesis factor, interleukin 8, etc.) and inhibitors (endostatin, thrombospondin, angiostatin, vascular endothelial growth factor receptor 1 (VEGF-R1), vasostatin, etc.) [3,12]. The key trigger of angiogenesis is chronic hypoxia, which activates angiogenic impulses via a number of cytokines and growth factors, the main target of which are endothelial cells; as a result, they migrate outside the basal membrane and take direct part in formation of vascular tubes [4,13].

It has been shown that the key role in formation and development of new blood microvessels is played by angioblasts, the functional activity of which manifests

under the impact of vascular endothelial growth factor (VEGF), acting as a chemoattractant. It has been proven that VEGF is produced by various cells (macrophages, fibroblasts, lymphocytes, osteoblasts, keratinocytes, etc.). The main function of endothelial factor is to induce mitosis of vascular epithelial cells, micro- and macrovascular cells of blood and lymph vessels [5-7].

There are several isoforms of VEGF: VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placenta growth factor, which have proven biological activity spectrum. For instance, at early stages of body development, VEGF-A acts as a stimulator of proliferation and migration of endothelial cells, a key angiogenesis regulator, which inhibits endothelial cell apoptosis and contributes to regulation of vascular wall permeability, thus acting as an angioprotector [7,8]. The angiogenic role of VEGF-B has been proven for the vascular tree of the myocardium; however, large volumes of this variant of endothelial factor are synthesised in nervous tissue, preventing neuron apoptosis and having neuroprotective effect (this ligand is being studied for the possible use in the management of Alzheimer's disease) [9]. It has been shown that the function of VEGF-C and VEGF-D consists in the regulation of foetal lymphogenesis in pulmonary tissue. The functional activity of a VEGF isoform depends on the type of tyrosine-protein kinases (RTK) of receptors ((VEGFR) -1, -2 and -3.). There is some evidence that, by interacting with various VEGF-R, each ligand can cause opposite physiological effects [9,10].

Together with a physiological role in processes of angiogenesis, the endothelial factor has one of the leading roles in the development of various diseases, pathogenesis of which is associated with pathological angiogenesis. One of the most striking examples is retinopathy, atopic dermatitis, rheumatoid arthritis, malignancies, psoriasis, etc., which are associated with more intense angiogenesis [11].

Despite the availability of numerous molecular-genetic and immunological studies of the role of VEGF in the development of various pathological processes, a number of aspects of the influence of this factor require further elaboration in order to target the pathological process more precisely.

At the same time, determination of the vascular endothelial growth factor levels in patients with atopic dermatitis can be promising both for detailing pathogenic mechanisms of inflammation in this disease, including type I and II HSV, and for forecasting disease progression and justified personalised approach in paediatric patients with AtD.

The purpose of the study is to determine the clinical and diagnostic significance of plasma levels of vascular endothelial growth factor in children with atopic dermatitis, who have herpes simplex virus and parasitic invasion.

Materials and Methods

This analytical cross-sectional study is a comprehensive examination of 140 patients with AtD aged 2 to 12 years old (median age: 4.2 years old), who were undergoing inpatient treatment in the State Budgetary Healthcare Institution of the Astrakhan Region N. N. Silischeva Regional Children Clinical Hospital in 2020–2022.

All subjects were divided into groups: 70 infants and children with confirmed AtD; 70 children with atopic dermatitis and herpes simplex virus (AtD + HSV). The control group included 70 healthy children.

In study groups, subjects were distributed depending on severity of their AtD. AtD group: moderate disease — 62 children, severe disease — 8 children; AtD + HSV group: moderate disease — 49 children, severe disease — 21 children.

Table 1. *Initial characteristics of patients*

Clinical symptoms	Children with AtD	Children with AtD+HVI	p
Age	4,1 [2,3; 6,5]	4,3 [2,6; 6,9]	0,365
Moderate severity	n=62	n=49	0,080
Severe severity	n=8	n=21	0,146
Common lesion process	n=67	n=63	0,072
Diffuse lesion process	n=3	n=7	0,230
Gender differences	girls n=40 boys n=30	girls n=44 boys n=26	0,135 0,074
Children on artificial/mixed feeding	n=42	n=56	0,310
Naturallyfed children	n=28	n=14	0,186.
Children with food allergies	n=25	n=29	0,055
Children with household allergies	n=10	n=31	0,240
Children with pollen allergies	n=7	n=11	0,780

Note: n — a quantitative characteristic accepted in mathematics.

Both study groups included patients with AtD during childhood, and children with widespread process prevailed.

There were no gender differences both in AtD group (χ^2 = 0.95; df = 1; p = 0.329) and AtD + HSV group (χ^2 = 3.11; df = 1; p = 0.078).

A share of children on formula and mixed feeding in AtD group was statistically insignificantly higher vs. breastfeeding (χ^2 = 3.75; df = 1; p = 0.053). In AtD + HSV group, the number of children on formula or mixed feeding was statistically higher (χ^2 = 17.5; df = 1; p < 0.001).

According to the history of allergies, there were no statistically significant differences in the incidence of food allergy (χ^2 = 0.021; df = 1; p = 0.644) and domestic allergy (χ^2 = 0.78; df = 1; p = 0.374). At the same time, AtD + HSV patients had pollen allergy more often (χ^2 = 9.0; df = 1; p = 0.003) [Table 1].

The study was approved by the Local Ethics Committee (LEC) at the Federal State Budgetary Educational Institution of Higher Education Astrakhan State Medical University of the Ministry of Health of the Russian Federation, excerpt from minutes No. 6 of the LEC meeting dated December 28, 2022. There were no amendments to the initial protocol.

Diagnostic criteria and therapy complied with the Clinical Guidelines on Atopic Dermatitis (2021-2022-2023) approved by the Ministry of Health of the Russian Federation on August 26, 2021 [15].

In addition to complaints and history taking, patient assessment included physical examination of organs and systems; routine laboratory tests (clinical blood assay, blood biochemistry); imaging (electrocardiography, ultrasonic examination).

Specialised laboratory tests:

- Enzyme-linked immunosorbent assay (ELISA) for identification of specific anti-HSV-1/2 IgM and/or IgG antibodies, using Vektor-Best reagent kit (Novosibirsk, Russia);
- Polymerase chain reaction (PCR) for identification of herpesvirus DNA in blood samples, using test systems developed by the Federal Budgetary Scientific Institution Central Research Institute of Epidemiology of the Russian Agency for Health and Consumer Rights (Moscow);
- ELISA for identification of vascular endothelial growth factor A (VEGF-A) in plasma samples, using high-sensitivity reagent kits HEA143Hu (CloudCloneCorp.). Reference values: 1.0–98.6 pg/mL.

Results were statistically processed with the help of STATISTICA 12.0, StatSoft, Inc. and SPSS-16.

In each group, the median (Me), 1st and 3rd quartiles (Q1; Q3), 5th and 95th percentiles were calculated for quantitative parameters; each category variable in a group is assigned an absolute value and percent. Mann — Whitney U test was used to test statistical hypotheses when comparing quantitative parameters in two independent groups. Pearson's chi-squared test (χ^2) was used for the comparison of category variables in groups. For the comparison of more than two groups of category variables, Kruskal — Wallis test was used; if there were statistically significant differences, Mann — Whitney U test was used for paired comparison. For the comparison of more than two independent groups, the critical statistical significance was calculated using the formula: p = 1–0.95 1/n, where n is the number of comparisons. The normality of data distribution was assessed using the Lilliefors-adjusted Kolmogorov — Smirnov test (at n > 50 in a group) and Shapiro — Wilk test (at n < 50 in a group). Levene's test was used to check the hypotheses on the general dispersion homogeneity. Relationships between attributes were studied using Spearman correlation analysis (r). Correlations were statistically significant at p < 0.05. The correlation strength was assessed in qualitative terms: at r of 0.0–0.3 — absence or loose correlation; at r of 0.4–0.7 — moderate; and at r over 0.70 — strong.

Results

The majority of patients with AtD, irrespective of the clinical form of their disease and process severity, usually had higher serum levels of vascular endothelial growth factor A (see tables below).

In control, the median value and interquartile ranges of vascular endothelial growth factor were 9.59 [9.05; 10.78] ng/mL. In AtD group, VEGF levels were 15.27 [12.60; 18.66] ng/mL, that is statistically higher (p_1 < 0.001) vs. controls. In AtD + HSV group, VEGF levels were 22.20 [14.89; 30.00] ng/mL, that is statistically higher than in controls (p_1< 0.001) and statistically higher than in AtD group (p_2< 0.001).

Higher VEGF values in children with AtD evidence more active processes of angiogenesis and vascular permeability.

At the same time, significantly increased VEGF levels in children with AtD + HSV are of interest, since they indicate that herpes simplex virus stimulates VEGF production [Table 2].

In control, the median value and interquartile ranges of vascular endothelial growth factor were 9.59 [9.05; 10.78] ng/mL. In the group of patients with moderate AtD, VEGF levels were 13.1 [12.6; 16.2] ng/mL, which was statistically significantly higher (p_1< 0.001) vs. controls. In the group of patients with severe AtD, VEGF levels were 18.4 [15.71; 19.31] ng/mL, that is statistically much higher (p_1< 0.001) vs. controls and statistically significantly higher (p_3< 0.001) vs. patients with moderate atopic dermatitis.

In the group of patients with moderate AtD + HSV, VEGF values were 16.7 [14.1; 21.3] ng/mL, that is statistically significantly higher than in controls (p_1 < 0.001) and in the group of patients with moderate AtD (p_2= 0.004).

Table 2. *The level of vasoendothelial growth factor in children with atopic dermatitis and atopic dermatitis on the background of herpesvirus infection*

Indicator/Group	Median	Lower and upper quartile	5 and 95 percentile
Control group	9,59	[9,05; 10,78]	[2,10; 11,75]
Children with ATD	15,27 p_1<0,001	[12,60; 18,66]	[10,10; 20,35]
Children with AtD+HVI	20,20 p_1<0,001 p_2<0,001	[14,89; 30,00]	[11,62; 91,12]

Note: the calculated critical level of statistical significance is p=0.017;
- p_1 — stat level. significance of differences with the control group;
- p_2 — stat level. significance of differences with a group of children with AtD

Table 3. *The level of vasoendothelial growth factor in children with atopic dermatitis atopic dermatitis on the background of herpesvirus infection, depending on the severity*

Indicator/Group	Median	Lower and upper quartile	5 and 95 percentile
Control group	9,59	[9,05; 10,78]	[2,10; 11,75]
Children with AtD of moderate severity	13,1 p_1<0,001	[12,6; 16,2]	[10,1; 17,3]
Children with severe AtD	18,4 p_1<0,001 p_3<0,001	[15,71; 19,31]	[14,5;20,35]
Children with AtD+HVI of moderate severity	16,7 p_1<0,001 p_2=0,004	[14,1; 21,3]	[11,57; 22,8]
Children with severe AtD+HVI	28,2 p_1<0,001 p_2<0,001 p_3<0,001	[19,2; 31,2]	[18,6; 91,2]

Note: the calculated critical level of statistical significance p=0.006
- p_1 is the level of statistical significance of differences with the control group
- p_2 — stat level. significance of differences with the group of children with AtD in the corresponding subgroup
- p_3 — stat level. significance of differences with moderate severity in the corresponding subgroup

In the group of patients with severe AtD + HSV, VEGF levels were 28.2 [19.2; 31.2] ng/mL, that is statistically much higher than in controls ($p_1 < 0.001$), in the group of patients with moderate AtD + HSV ($p_3 < 0.001$) and in the group of patients with severe AtD ($p_2 < 0.001$).

The more severe the process, the higher VEGF levels observed both in children with AtD and AtD + HSV; this stimulates angiogenesis, increases vascular permeability and aggravates due to herpes viral infection [Table 4].

Identified correlations between clinical manifestations, such as lichenification/peeling (r = 0.39; p = 0.045), dry skin (r = 0.23; p = 0.068) and vascular endothelial growth factor levels in patients with AtD are weak; the same situation is observed in the group of children with AtD + HSV between lichenification/peeling (r = 0.46; p = 0.031), dry skin (r = 0.38; p = 0.051) and vascular endothelial growth factor levels.

Table 4. *Correlations between the main clinical symptoms of atopic dermatitis and the level of endothelial growth factor A in children with atopic dermatitis topical dermatitis on the background of herpesvirus infection*

Clinical symptoms	AtD	AtD+HVI
Erythema	r=0,61 p<0,001	r=0,87 p<0,001
Edema/papular elements	r=0,59 p=0,011	r=0,83 p<0,001
Crust /wetness	r=0,54 p=0,021	r=0,78 p<0,001
Excoriation	r=0,42 p=0,039	r=0,51 p=0,026
Lichenification/peeling	r=0,39 p=0,045	r=0,46 p=0,031
Dry skin	r=0,23 p=0,068	r=0,38 p=0,051

Note: p — is the level of statistical significance of correlation coefficients

There are statistically significant weak correlations between excoriation and vascular endothelial growth factor levels in AtD patients (r = 0.42; p = 0.039) and statistically significant moderate correlations in children with AtD + HSV (r = 0.51; p = 0.026), indicating higher intensity of skin receptor irritation by inflammatory agents, with more marked increase in vascular endothelial growth factor levels and vascular permeability in HSV.

Table 5. *Correlations between the presence of concomitant somatic diseases and the level of vasoendothelial growth factor in children with atopic dermatitis and atopic dermatitis on the background of herpesvirus infection*

Concomitant diseases	AtD	AtD+HVI
Bronchial asthma	r=0,35 p=0,115	r=0,38 p=0,056
Allergic rhinitis	r=0,41 p=0,021	r=0,59 p=0,001
Allergic rhinoconjunctivitis	r=0,38 p=0,045	r=0,56 p=0,002
Biliarydyskinesia	r=0,11 p=0,812	r=0,13 p=0,773
Gastritis, gastroduodenitis	r=0,15 p=0,756	r=0,18 p=0,731
Reactive pancreatitis	r=0,29 p=0,318	r=0,37 p=0,057
Reactive hepatomegaly	r=0,23 p=0,405	r=0,35 p=0,115
Hepatosplenomegaly	r=0,15 p=0,756	r=0,19 p=0,758
Giardiasis	r=0,29 p=0,318	r=0,31 p=0,262
Amoebiasis	r=0,27 p=0,379	r=0,3 p=0,281
Worm infestations	r=0,31 p=0,262	r=0,34 p=0,112

Note: p — is the level of statistical significance of correlation coefficients

Table 6. *Correlations between the indicators of the general blood test of patients with atopic dermatitis and the level of vasoendothelial growth factor in children with atopic dermatitis and atopic dermatitis on the background of herpesvirus infection*

	AtD	AtD+HVI
Red blood cells	r=-0,34 p=0,045	r=-0,41 p=0,022
Hemoglobin	r=-0,36 p=0,041	r=-0,43 p=0,019
White blood cells	r=0,12 p=0,701	r=0,16 p=0,638

Note: p — is the level of statistical significance of correlation coefficients

Positive statistically significant moderate correlations between clinical manifestations, such as oedema/papular eruptions (r = 0.59; p = 0.011), crust/oozing lesions (r = 0.54; p < 0.021) and vascular endothelial growth factor levels in patients with AtD indicate that this growth factor impacts exudative symptoms, since vascular endothelial growth factor can boost vascular permeability and angiogenesis. Paediatric patients with AtD + HSV have statistically more significant strong correlations between oedema/papular eruptions (r = 0.83; p < 0.001), crust/oozing lesions (r = 0.78; p < 0.001) and vascular endothelial growth factor levels, confirming the stimulatory effect of HSV on the clinical course of the disease and intensity of exudative symptoms [Table 5].

Positive statistically significant moderate correlations between comorbidities, such as allergic rhinitis (r = 0.59; p = 0.001), allergic rhinoconjunctivitis (r = 0.56; p = 0.002) and vascular endothelial growth factor levels in patients with AtD + HSV indicate that this growth factor affects exudative symptoms, since vascular endothelial growth factor can boost vascular permeability. It also shows that herpes simplex virus infection has potentiating effect (as an inflammatory agent) on various pathogenic mechanisms of these diseases: changes in the nature of blood circulation in blood vessels, marked vascularisation, causing nasal congestion and exudation, which is regulated by various nervous paths, mediated by muscarinic and cholinergic receptors.

Children with AtD have less marked statistically significant strong correlations between such diseases as allergic rhinitis (r = 0.41; p = 0.021), allergic rhinoconjunctivitis (r = 0.38; p = 0.045) and vascular endothelial growth factor levels.

Analysis of the number of patients with comorbidities in the study groups showed that a combination of HSV and AtD not only aggravates clinical symptoms, but also facilitates manifestation of other atopic diseases, such as allergic rhinitis and rhinoconjunctivitis [Table 5].

The group of patients with AtD had moderate correlations between vascular endothelial growth factor and disease severity (r = 0.58; p = 0.001), similar to patients with AtD + HSV (r = 0.64; p < 0.001).

There are similar statistically significant moderate correlations between vascular endothelial growth factor levels and disease severity both in children with AtD (r = 0.67; p < 0.001) and with AtD + HSV (r = 0.73; p < 0.001).

These correlations indicate that this growth factors contribute to pathogenetic links; this can be explained by higher severity of atopic dermatitis in herpes viral infection, associated with higher values of vascular endothelial growth factor.

Statistically significant moderate correlations have been found between Hb levels (r = -0.43; p = 0.019), RBC values (r = -0.41; p = 0.022) and vascular endothelial growth factor levels in the group of patients with AtD + HSV (Table 6).

Table 7. *Correlations between the biochemical parameters of the blood of patients with atopic dermatitis and the level of vasoendothelial growth factor in children with atopic dermatitis and atopic dermatitis on the background of herpesvirus infection*

	AtD	AtD+HVI
Total protein	r=-0,08 p=0,861	r=-0,1 p=0,915
Albumin	r=-0,09 p=0,962	r=-0,12 p=0,813
Globulin	r=0,11 p=0,859	r=-0,09 p=0,962
Total bilirubin	r=-0,1 p=0,915	r=-0,12 p=0,813
ALT	r=0,01 p=0,969	r=0,03 p=0,901
AST	r=0,02 p=0,813	r=0,05 p=0,913
Glucose	r=0,04 p=0,829	r=0,01 p=0,969

Note: p — is the level of statistical significance of correlation coefficients

Weak correlations have been established between RBC count (r = -0.34; p = 0.045), Hb (r = -0.36; p = 0.041) and vascular endothelial growth factor levels in patients with AtD.

Reduced RBC count is likely to stimulate production of vascular endothelial growth factor, because lower RBC level can be a trigger of vascular endothelial growth factor production and angiogenesis activation, since low RBC count is associated with cell hypoxia. This mechanism is based on circulating VEGF protein binding with a receptor on endothelial surface, activation of tyrosine kinase action and angiogenesis initiation [10].

There are very weak correlations between vascular endothelial growth factor levels and blood biochemistry in the study groups of patients with AtD and AtD + HSV, but they are not statistically significant [Table 7].

Discussion

Higher VEGF-A values in children with AtD evidence more active processes of angiogenesis and vascular permeability. This correlates with works of I. L. Solovyeva, A. I. Kafarova [16] and A. A. Lebedenko, O. E. Semernik [17], where similar results were reported.

Excessive VEGF expression in patients with AtD and herpes viral infection due to activation of angiogenesis and higher vascular permeability can contribute to more marked exudative clinical symptoms, severe disease and persistent skin eruptions. Higher VEGF levels in AtD are described by A. A. Lebedenko, O. E. Semernik et al. [17]. Severe atopic dermatitis cases are associated with higher VEGF levels, observed both in children with AtD and with AtD + HSV. This conclusion correlates with the results obtained by T. V. Solomay, T. A. Semenenko, S. L. Vedunov et al. [18] and O. B. Tamrazov, T. A. Chebotarev et al. 2018 [19].

Statistically significant correlations have been found between clinical manifestations and vascular endothelial growth factor levels in patients with AtD + HSV, which are more pronounced in a combination with HSV, thus confirming a stimulatory impact of HSV on the clinical course of the disease and intensity of exudative symptoms via stimulatory effect on production of vascular endothelial growth factor with the help of various pathogenic mechanisms, including inflammatory mediator action.

Analysis of these patients with a comorbidity in the study groups demonstrated that AtD + HSV not only aggravates clinical symptoms, but also contributes to manifestation of other atopic conditions, for instance, allergic rhinitis and rhinoconjunctivitis, thus indicating potentiating impact of herpes simplex virus infection on the intensity of atopy manifestations and maintaining atopic inflammation in the body.

Identified correlations between vascular endothelial growth factor levels and severity of the disease reflect the contribution of these growth factors to pathogenic links of AtD, which is a result of AtD aggravation in HSV, associated with an increase in vascular endothelial growth factor values. Our observations correlate with results obtained by our foreign fellows [20].

The data on changes in vascular endothelial growth factor levels in children, patients with AtD with HSV markers, extend our idea on the pathogenesis of the disease and can be used in paediatrics for improvement of the quality of AtD diagnosis, therapy and prevention.

Predictors of severe atopic dermatitis are concurrent herpes simplex infection and parasitic invasion, higher VEGF-A levels, polyvalent sensitisation, etc. Paediatric patients in this group of risk require close follow-up and monitoring of the course and therapy of atopic dermatitis. An up-to-date management algorithm for this group of risk should include primary and secondary prevention of herpes simplex virus and therapeutic methods aimed at supporting the immune system of the child with atopic dermatitis to prevent secondary infections.

The results of the study emphasise the significance of VEGF-A in AtD pathogenesis, its role in persistent inflammation and development of clinical skin eruptions. Plasma levels of vascular endothelial growth factor A in healthy children can be used as reference values for children with various pathologies. VEGF-A level can indicate the source of AtD, including herpes viral infection, changes in initial symptoms, emergence of new symptoms and progression of all signs of the disease.

Conclusions

The following conclusions were made based on the study results:

1. Serum levels of vascular endothelial growth factor A in children with AtD are higher than in healthy children, while in patients with AtD and HSV this value is higher vs. non-infected patients with AtD. The rate of increase in this population is associated with AtD severity.

2. Concurrent HSV and AtD aggravate clinical symptoms of this disease: there is statistically significant increase in the number of erythematous elements, oedemas and papules, crusts, excoriations and oozing lesions.

3. In order to identify groups of risks of severe AtD, it is recommended to assess levels of vascular endothelial growth factor A in children with AtD and AtD + HSV.

Additional studies in this scientific area can help to form comprehensive and deep understanding of the mechanisms of atopic dermatitis, as well as facilitate development of new pathogenic-based therapies.

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