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ЭПИДЕРМАЛЬНЫЙ ФАКТОР РОСТА, ЕГО ДИАГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ У ДЕТЕЙ С АТОПИЧЕСКИМ ДЕРМАТИТОМ, ИНФИЦИРОВАННЫХ ВИРУСОМ ПРОСТОГО ГЕРПЕСА

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РЕЗЮМЕ. ***Введение.*** Проводятся исследования, касающиеся физиологической активности эпидермального фактора роста (EGF, Epidermal Growth Factor), его влияния на клеточный и гуморальный иммунитеты, исследуются состояния и факторы, провоцирующие и отягощающие течение патологических процессов. Работы, направленные на выявление клинико-диагностических значений ростовых факторов для повышения эффективности оказания медицинской помощи пациентам различных профилей и снижения степени тяжести заболеваний, показывают необходимость и актуальность их реализации. ***Цель исследования*** — установить клинико-диагностическое значение уровня эпидермального фактора роста у детей с атопическим дерматитом (АтД) на фоне инфицирования вирусом простого герпеса. ***Материалы и методы.*** Проведено комплексное обследование 140 пациентов с АтД в возрасте от 2 до 12 лет, распределенных на 2 группы: с установленным диагнозом АтД и с диагнозом «атопический дерматит», инфицированных вирусом простого герпеса (АтД+ГВИ). Контрольную группу составили 70 здоровых пациентов. Специальное лабораторное обследование включало определение специфических антител классов IgM и/или IgG к антигенам вируса простого герпеса 1–2-го типа методом иммуноферментного анализа (ИФА); определение ДНК исследуемых герпесвирусов в образцах крови методом полимеразной цепной реакции; определение эпидермального фактора роста в плазме крови больных методом ИФА. Статистическая обработка результатов выполнялась с использованием пакета программ STATISTICA 12.0 (Stat Soft, США) и SPSS-16. ***Результаты и выводы.*** Установлено статистически значимое ($p < 0{,}001$) повышение уровня эпидермального фактора роста в сыворотке крови у детей с АтД по сравнению с контрольной группой. На фоне инфицирования вирусом простого герпеса выявлено увеличение уровня эпидермального фактора роста в сыворотке крови по сравнению с пациентами с АтД ($p < 0{,}001$). Также было выявлено статистически значимое увеличение уровня EGF в сыворотке крови у пациентов с АтД ($p < 0{,}001$) и АтД+ГВИ ($p < 0{,}001$) с увеличением степени тяжести АтД. Присоединение герпесвирусной инфекции к АтД ухудшает клиническую симптоматику данного заболевания.

КЛЮЧЕВЫЕ СЛОВА: ангиогенез, эпидермальный фактор роста, атопический дерматит

EPIDERMAL GROWTH FACTOR AND ITS DIAGNOSTIC VALUE IN CHILDREN WITH ATOPIC DERMATITIS INFECTED WITH HERPES SIMPLEX VIRUS

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ABSTRACT. ***Introduction.*** Studies are being conducted on the physiological activity of epidermal growth factor (EGF), its effect on cellular and humoral immunity, and conditions and factors that provoke and aggravate the course of pathological processes. Work aimed at identifying the clinical, diagnostic and prognostic values of growth factors to improve the effectiveness of medical care for patients of various profiles and reduce the severity of diseases, show the need and relevance of their implementation. ***Objective.*** To establish the clinical and diagnostic significance of the level of epidermal growth factor in children with atopic dermatitis (AtD) on the background of infection with the herpes simplex virus. ***Materials and methods.*** A comprehensive examination of 140 patients was conducted with AtD aged from 2 to 12 years, distributed into 2 groups: with established diagnosis of AtD and with diagnosis of atopic dermatitis, infected with herpes simplex virus (AtD+HSV). The control group consisted of 70 healthy patients. Special laboratory examination included determination of specific antibodies of IgM and/or IgG classes to the antigens of herpes simplex virus type 1–2 by enzyme-linked immunosorbent assay (ELISA); determination of DNA of the studied herpesviruses in blood samples by polymerase chain reaction; determination of epidermal growth factor in blood plasma of patients by ELISA. Statistical processing of the results was performed using the STATISTICA 12.0 (Stat Soft, USA) and SPSS-16 program packages. ***The results and conclusions.*** A statistically significant ($p < 0.001$) increase in the level of epidermal growth factor in serum of children with AtD compared to the control group was found. On the background of herpes simplex virus infection, an increase in the level of epidermal growth factor in blood serum was found compared to patients with atopic dermatitis ($p < 0.001$). A statistically significant increase in serum EGF levels was also found in patients with AtD ($p < 0.001$) and AtD+HSV ($p < 0.001$) with increasing severity of AtD. Accession of herpesvirus infection to AtD worsens the clinical symptomatology of this disease.

KEYWORDS: angiogenesis, epidermal growth factor, atopic dermatitis

INTRODUCTION

Over the past few decades, the understanding of the pathogenesis of AtD has changed significantly. This pathology is a complex disorder in the development of which a role is played by a violation of the epithelial barrier of the skin and allergic inflammation in the skin of a patient whose genetic background predisposes to atopy.

Genetically determined or acquired, once developed, skin inflammation and a defect in the skin barrier in AtD, subsequently allow allergens to penetrate, which cause an immune response and can lead to the development of IgE-mediated allergy. The fact that in many cases AtD is the first manifestation of atopy and probably plays a key role in the development and progression of the atopic march makes it an important target for treatment. By influencing the development of AtD, we can potentially modify the process of development of further manifestations of atopy [1, 4, 5].

Angiogenesis of allergic skin lesions is characterized by significant vasodilation and increased vascular permeability due to the presence of a single- or multilayer basement membrane and fenestrated endothelium. Chronic hypoxia is considered the main trigger of angiogenesis, which activates angiogenic impulses through a number of cytokines and growth factors, the main action of which is directed at endothelial

cells, as a result of which they migrate beyond the basement membrane and take direct part in the formation of vascular tubes [6, 7].

In recent years, there have been active studies of the physiological activity of epidermal growth factor (EGF), and of particular interest is the study of its role in the skin. EGF is widely expressed in normal skin tissues, such as the epidermis, sebaceous and eccrine glands, and dendritic cells [2, 3]. However, in the literature available to us, there are no data indicating the nature of the influence of epidermal growth factor on the progression of atopic dermatitis and herpesvirus infection. Thus, it is advisable to conduct a study of the blood serum of children with atopic dermatitis and atopic dermatitis against the background of herpesvirus infection in order to determine the level of EGF, establish its diagnostic value depending on the severity and duration of the disease, and identify its prognostic indicators.

OBJECTIVE OF THE STUDY

To establish the clinical and diagnostic value of the EGF level in the blood plasma of children with AtD against the background of HSV infection and parasitic invasion.

MATERIALS AND METHODS

A study of the EGF content in blood plasma was conducted using enzyme-linked immunosorbent assay in 140 patients with AtD aged 2 to 12 years. The following groups were formed: 70 children with an established diagnosis of AtD; 70 children with an AtD diagnosis infected with the herpes simplex virus (AtD+HSV). The control group consisted of 70 healthy children. In the group of patients with AtD: moderate severity — 62 children, severe severity — 8 children; in the group of patients with AtD+HSV: moderate severity — 49 children, severe severity — 21 children. Both study groups included patients with AtD in childhood, with children with a widespread process predominating.

Determination of epidermal growth factor in the blood plasma of patients was carried out by the ELISA method using highly sensitive HEA560Hu reagent kits from Cloud-Clone Corp., China.

No gender differences were found in either the group with AtD (χ^2=0.95; df=1; p=0.329) or the group of patients with AtD+HSV (χ^2=3.11; df=1; p=0.078).

The proportion of children on artificial or mixed feeding in the group of children with AtD was statistically insignificantly higher than that of children on natural feeding (χ^2=3.75; df=1; p=0.053). In the group of patients with AtD+HSV, the number of children on artificial or mixed feeding was statistically significantly higher (χ^2=17.5; df=1; p <0.001).

According to the allergological anamnesis data, no statistically significant differences were found in the study groups for the frequency of food allergy (χ^2=0.021; df=1; p=0.644) and household allergy (χ^2=0.78; df=1; p=0.374). At the same time, in the group of patients with AtD+HSV, pollen allergy was detected more often (χ^2=9.0; df=1; p=0.003) (Tables 1, 2).

Statistical processing of the results was performed using the STATISTICA 12.0 (Stat Soft, USA) and SPSS-16 applied statistical software package.

In each group, the median (Me), the values of the 1st and 3rd quartiles (Q1; Q3), the 5th and 95th percentiles were calculated for the numerical indicators; the absolute number and percentage share are indicated for each categorical variable in the group. To test statistical hypotheses when comparing quantitative indicators in two independent groups, the Mann–Whitney test (U) was used. When comparing categorical variables in groups, the Pearson chi-square test (χ^2) was used. To compare more than two groups of quantitative data, the Kruskal–Wallis test was used; in the presence of statistically significant dif-

Table 1

The level of epidermal growth factor in children with atopic dermatitis and atopic dermatitis on the background of herpesvirus infection [Q1–Q3]

Indicator/Group	Median	Lower and upper quartile	5 and 95 percentile
Control group	1.10	[0.84; 1.26]	[0.64; 1.66]
Children with atopic dermatitis	1.47 p_1 <0.001	[0.88; 1.7]	[0.73; 2.12]
Children with atopic dermatitis + herpes simplex virus	2.26 p_1 <0.001 p_2 <0.001	[1.89; 3.00]	[0.62; 5.12]

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 atopic dermatitis infection.

Table 2

The level of epidermal growth factor in children with atopic dermatitis and atopic dermatitis on the background of herpesvirus infection, depending on the severity [Q1–Q3]

Indicator/Group	Median	Lower and upper quartile	5 and 95 percentile
Control group	1.10	[0.84; 1.26]	[0.64; 1.66]
Children with moderate atopic dermatitis	1.21 p_1=0.041	[0.88; 1.31]	[0.73; 1.76]
Children with severe atopic dermatitis	1.5 p_1 <0.001 p_3=0.004	[1.12; 2.0]	[0.98; 2.12]
Children with atopic dermatitis + herpes simplex virus of moderate severity	2.10 p_1 <0.001 p_2 <0.001	[1.73; 2.94]	[0.62; 3.12]
Children with severe atopic dermatitis + herpes simplex virus	2.6 p_1 <0.001 p_2 <0.001 p_3=0.003	[1.92; 4.89]	[2.23; 5.12]

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 atopic dermatitis in the corresponding subgroup; p_3 — stat level, significance of differences with moderate severity in the corresponding subgroup.

ferences, the Mann–Whitney test was used for pairwise comparisons. The critical level of statistical significance when comparing more than two independent groups was calculated using the formula p=1–0.95 1/n, where n is the number of comparisons.

The study of the relationships between features was carried out by calculating the Spearman rank correlation coefficient (r). Correlations were considered statistically significant at p <0.05. The strength of the correlation was assessed qualitatively: at r from 0.0 to 0.3 — as absent or weak correlation; at r from 0.4 to 0.7 — as moderate; at r over 0.70 — as strong.

RESULTS AND DISCUSSION

Most patients with AtD, regardless of the clinical form and severity of the process, showed an increase in the level of epidermal growth factor in the blood serum, which is presented in the tables below (Tables 3, 4, 5, 6).

In the control group, the median and interquartile range of the epidermal growth factor level was 1.10 [0.84; 1.26] ng/ml. In the group of patients with atopic dermatitis, the EGF level was 1.47 [0.88; 1.7] ng/ml, which was statistically significantly higher (p_1 <0.001) compared to the control group. In the group of patients with atopic dermatitis against the background of herpesvirus infection, the EGF level was 2.26 [1.89; 3.00] ng/ml, which was statistically significantly higher than this indicator in the control group (p_1 <0.001) and statistically significantly higher than in the group of patients with atopic dermatitis against the background of herpesvirus infection (p_2 <0.001).

The increase in the EGF level detected in children with AtD indicates the possibility of its stimulating effect on cell growth and differentiation, including epidermal cells, which can lead to dysfunction of the epidermal skin barrier. At the same time, a significant increase in the EGF level in children with AtD+HSV is of interest, since it indicates stimulation of EGF production by the herpes virus, which can be the cause of excessive keratinization of the epidermis in AtD in herpesvirus-infected patients, and be the cause of lichenification and thickening of the stratum corneum.

In the control group, the median and interquartile range of the epidermal growth factor level was 1.10 [0.84; 1.26] ng/ml.

In the group of patients with moderate AtD, the EGF level was 1.21 [0.88; 1.31] ng/ml, which was statistically insignificantly higher (p_1=0.041) compared to the control group.

In the group of patients with severe AtD, the EGF level was 1.5 [1.12; 2.0] ng/ml, which was statistically significantly higher (p_1 <0.001) compared to the control group and statistically significantly higher (p_3=0.004) compared to the group of patients with moderate atopic dermatitis.

In the group of patients with moderate AtD+HSV, the EGF level was 2.10 [1.73; 2.94] ng/ml, which was statistically significantly higher than this indicator in the control group (p_1 <0.001) and in the group of patients with moderate AtD (p_2 <0.001).

In the group of patients with AtD+HSV of severe severity, the EGF level was 2.6 [1.92; 4.89] ng/ml, which was statistically significantly higher than this indicator in the control group (p_1 <0.001) and in the group of patients with AtD+HSV of moderate severity (p_3=0.003) and in the group of patients with severe AtD (p_2 <0.001).

An increase in EGF in patients with AtD and AtD+HSV with an increase in the severity of atopic dermatitis reflects an increase in the pathological effect of this factor on keratinization processes and the functional state of the epidermal barrier with an increase in the severity of AtD. At the same time, a higher level of EGF in the subgroups of patients with AtD+HSV corresponding to the severity of the disease confirms the stimulating effect of HSV on EGF production.

Low-power correlations were found between the presence of erythema and the level of epidermal growth factor in children with AtD (r=0.2; p=0.615) and AtD+HSV (r=0.31; p=0.311), but a significant level of correlation coefficients between these indicators was not achieved.

The presence of positive statistically significant correlations of medium strength between such clinical indicators as lichenification/flaking (r=0.57; p=0.024), dry skin (r=0.51; p=0.037) and the level of epidermal growth factor in the group of patients with AtD indicate the influence of this growth factor on keratinization, which is due to its stimulating effect on the proliferation of keratinocytes and an increase in the severity of these symptoms. In the group of children with AtD+HSV, more pronounced statistically significant correlation relationships of medium strength between the indicators of lichenification/flaking (r=0.71; p <0.001), dry skin (r=0.68; p <0.001) and the level of epidermal growth factor — on the potentiating effect of herpes virus infection on the clinical course of the disease, the severity of these symptoms, involving different pathogenetic mechanisms.

The revealed correlation relationships between the presence of edema/papular elements and the level of epidermal growth factor in children with AtD (r=0.15; p=0.721) and AtD+HSV (r=0.24; p=0.587) are considered very weak, which indicates the absence of a significant level of correlation coefficients between these indicators. This is also observed when studying the correlation relationships in the group of patients with AtD between such clinical symptoms as crusts/oozing (r=0.28; p=0.511), excoriations (r=0.3; p=0.413) and the level of epidermal growth factor, where the identified relationship is assessed by us as a weak positive relationship.

When working with children with AtD+HSV, a slight increase in the value of the correlation coefficient was noted and was assessed as a weak relationship between such indicators as crusts/oozing (r=0.3; p=0.413), excoriations (r=0.42; p=0.045) and the level of epidermal growth factor, which is a natural reflection of inflammatory activation in these patients, more pronounced when infected with herpesvirus infection.

Very weak correlation relationships were revealed in the studied groups of patients with AtD between the level of epidermal growth factor and a number of concomitant diseases, such as: bronchial asthma (r=0.11; p=0.812), allergic rhinitis (r=0.2; p=0.023), allergic rhinoconjunctivitis (r=0.19; p=0.705), biliary dyskinesia (r=0.05; p=0.911), gastritis/gastroduodenitis (r=0.21; p=0.611), reactive pancreatitis (r=0.24; p=0.556), reactive hepatomegaly (r=0.15; p=0.712), hepatosplenomegaly (r=0.09; p=0.934), giardiasis (r=0.27; p=0.505), amebiasis (r=0.25; p=0.501), helminthic infestations (r=0.29; p=0.578).

Similar statistically significant weak relationships were found in children with AtD+HSV between the level of epidermal growth factor and the following concomitant diseases: bronchial asthma (r=0.15; p=0.771), allergic rhinitis (r=0.29; p=0.615), allergic rhinoconjunctivitis (r=0.27;

Table 3

Correlations between the main clinical symptoms of atopic dermatitis and the level of epidermal growth factor in children with atopic dermatitis and atopic dermatitis on the background of herpesvirus infection [Q1–Q3]

Clinical symptoms	Atopic dermatitis		Atopic dermatitis + herpes simplex virus	
of erythema	r=0.2	p=0.615	r=0.31	p=0.311
edema/papular elements	r=0.15	p=0.721	r=0.24	p=0.587
crust/wetness	r=0.28	p=0.511	r=0.3	p=0.413
excoriation	r=0.34	p=0.289	r=0.42	p=0.045
lichenification/peeling	r=0.57	p=0.024	r=0.71	p<0.001
dry skin	r=0.51	p=0.037	r=0.68	p<0.001

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

Table 4

Correlations between the presence of concomitant somatic diseases and the level of epidermal growth factor in children with atopic dermatitis and atopic dermatitis on the background of herpesvirus infection [Q1–Q3]

Concomitant diseases	Atopic dermatitis		Atopic dermatitis + herpes simplex virus	
Bronchial asthma	r=0.11	p=0.812	r=0.15	p=0.771
Allergic rhinitis	r=0.2	p=0.023	r=0.29	p=0.615
Allergic rhinoconjunctivitis	r=0.19	p=0.705	r=0.27	p=0.682
Biliary dyskinesia	r=0.05	p=0.911	r=0.11	p=0.813
Gastritis, gastroduodenitis	r=0.21	p=0.611	r=0.19	p=0.712
Reactive pancreatitis	r=0.24	p=0.556	r=0.15	p=0.783
Reactive hepatomegaly	r=0.15	p=0.712	r=0.21	p=0.635
Hepatosplenomegaly	r=0.09	p=0.934	r=0.13	p=0.801
Giardiasis	r=0.27	p=0.505	r=0.29	p=0.512
Amoebiasis	r=0.25	p=0.501	r=0.27	p=0.505
Worm infestations	r=0.29	p=0.578	r=0.3	p=0.213

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

Table 5

Correlations between the indicators of the general blood test of patients with atopic dermatitis and the level of epidermal growth factor in children with atopic dermatitis and atopic dermatitis on the background of herpesvirus infection [Q1–Q3]

Complete Blood Count Parameters	Atopic dermatitis		Atopic dermatitis + herpes simplex virus	
Red blood cells	r=–0.11	p=0.721	r=–0.15	p=0.678
Hemoglobin	r=–0.05	p=0.812	r=–0.04	p=0.844
White blood cells	r=0.35	p=0.045	r=0.39	p=0.034

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

p=0.682), biliary dyskinesia (r=0.11; p=0.813), gastritis/gastroduodenitis (r=0.19; p=0.712), reactive pancreatitis (r=0.15; p=0.783), reactive hepatomegaly (r=0.21; p=0.635), hepatosplenomegaly (r=0.13; p=0.801), giardiasis (r=0.29; p=0.512), amebiasis (r=0.27; p=0.505), helminthic invasions (r=0.3; p=0.213).

No statistically significant correlation relationships were found between the presence of concomitant somatic diseases and the level of epidermal growth factor in children with AtD and AtD+HSV, which is due to the fact that this factor does not have obvious common pathogenetic links with the development of these diseases.

Very weak correlation relationships were revealed in the studied groups of patients with AtD between the general blood test parameters: hemoglobin (r=–0.05; p=0.812), erythrocytes (r=–0.11; p=0.721) and the level of epidermal growth factor; and weak strength between the level of leukocytes (r=0.35; p=0.045) and the level of epidermal growth factor.

Similar statistically insignificant relationships were found in children with AtD+HSV between the level of epidermal growth factor and the number of erythrocytes (r=–0.15; p=0.678), the level of hemoglobin (r=–0.04; p=0.844) and the level of leukocytes (r=0.39; p=0.034).

No significant level of correlation coefficients between the level of epidermal growth factor and the number of erythrocytes, as well as the level of hemoglobin in the examined groups of patients with AtD and AtD+HSV were found, while statistically significant relationships with the level of leukocytes were found, which may indicate an association of inflammatory activation and expression of epidermal growth factor and keratinization processes.

The detected correlation relationships between the levels of such biochemical parameters as total protein (r=–0.34; p=0.045), albumin (r=–0.31; p=0.051), globulin (r=0.32; p=0.049) and the level of epidermal growth factor in the group of patients with AtD are assessed as weak, which is also observed in the group of children with AtD+HSV between the parameters total protein (r=–0.38; p=0.039), albumin (r=–0.36; p=0.042), globulin (r=–0.24; p=0.163) and the level of epidermal growth factor.

Table 6

Correlations between the biochemical parameters of the blood of patients with atopic dermatitis and the level of epidermal growth factor in children with atopic dermatitis and atopic dermatitis on the background of herpesvirus infection [Q1–Q3]

Biochemical Blood Parameters	Atopic dermatitis		Atopic dermatitis + herpes simplex virus	
Total protein	–r=0.34	p=0.045	–r=0.38	p=0.039
Albumin	–r=0.31	p=0.051	–r=0.36	p=0.042
Globulin	r=0.32	p=0.049	–r=0.24	p=0.163
Total bilirubin	–r=0.29	p=0.071	–r=0.37	p=0.041
Alanine Transaminase	r=0.05	p=0.913	r=0.06	p=0.903
Aspartate Transaminase	r=0.01	p=0.969	r=0.04	p=0.928
Glucose	r=0.03	p=0.901	r=0.02	p=0.813

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

The common pathogenetic link in the weak correlations found between the level of total protein, albumin, globulin and the level of epidermal growth factor in the group of patients with AtD and AtD+HSV is possibly the influence of toxins, oxidative stress, which inhibit the production of proteins and indirectly stimulate the production of epidermal growth factor.

CONCLUSIONS

The following conclusions were obtained during the study:

1. A statistically significant ($p < 0.001$) increase in the level of epidermal growth factor in the blood plasma was found in children with atopic dermatitis compared to the control group. Against the background of infection with the herpes simplex virus, an increase in the level of epidermal growth factor in the blood plasma was found compared to patients with atopic dermatitis ($p < 0.001$).

2. A statistically significant increase in the level of epidermal growth factor in the blood plasma was found in patients with atopic dermatitis ($p < 0.001$) and atopic dermatitis against the background of infection with the herpes simplex virus ($p < 0.001$) with an increase in the severity of atopic dermatitis.

3. The addition of herpesvirus infection to AtD worsens the clinical symptoms of this disease, which is manifested in a statistically significant increase in the number of erythematous elements, edema and papules, crusts, excoriations and oozing, which indicates that HSV is an aggravating factor that supports the inflammatory process in this nosology, which is also reflected in a statistically significant increase in the number of patients with high intensity of clinical signs in the group of children with AtD+HSV.

4. Significant ($p < 0.001$) correlations were found between EGF and the severity of the disease, the severity of clinical symptoms and the presence of concomitant diseases both in the group of children with atopic dermatitis and in the group of children with atopic dermatitis infected with the herpes simplex virus.

5. The identified relationships allow us to recommend using the value of the epidermal growth factor content in the blood serum of healthy children as control values in children with various pathologies and studying the level of epidermal growth factor in children with AtD and AtD+HSV to form a risk group for severe disease and prognosis of the development of the atopic march.

6. The obtained data on changes in the epidermal growth factor in children with atopic dermatitis with HSV markers expand our understanding of the pathogenesis of the disease and can be used in dermatovenereological practice to improve the quality of diagnosis, therapy and prevention of atopic dermatitis.

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Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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