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ПРОГНОЗИРОВАНИЕ РАЗВИТИЯ АТОПИЧЕСКОГО МАРША У ДЕТЕЙ С АТОПИЧЕСКИМ ДЕРМАТИТОМ, ИНФИЦИРОВАННЫХ ВИРУСОМ ПРОСТОГО ГЕРПЕСА

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РЕЗЮМЕ. ***Введение.*** В последние годы активно ведется поиск различных диагностических и прогностических маркёров при атопическом дерматите (АтД). Так, например, внимание исследователей привлекло изучение роли сигнальных белков, вырабатываемых клетками эндотелия сосудов, — вазоэндотелиальный фактор (VEGF) — регулирующих процессы ангиогенеза, рост и деление клеток эпидермиса как важных патогенетических механизмов воспаления. И поэтому была предпринята попытка оценить уровень VEGF у детей с АтД на фоне герпесвирусной инфекции (ГВИ) с целью прогнозирования дальнейшего течения болезни и обоснованного подхода к персонифицированной терапии у детей с АтД. ***Цель*** — разработать алгоритм индивидуального прогноза развития атопического марша у детей с АтД на фоне инфицирования вирусом простого герпеса. ***Материалы и методы.*** Комплексно обследовано 140 пациентов с АтД в возрасте от 2 до 12 лет и 70 здоровых пациентов аналогичного возраста. Статистическая обработка результатов выполнялась с использованием пакета программ STATISTICA 12.0 (Stat Soft Inc.) и SPSS-16. Для разработки математической модели прогнозирования вероятности развития атопического марша у детей с АтД на фоне ГВИ использовался метод бинарной логистической регрессии. Оценка качества разработанной модели проводилась при помощи ROC-анализа с расчетом площади под ROC-кривой (AUC). ***Результаты.*** Разработан алгоритм индивидуального прогноза развития ассоциированной атопической патологии у детей с АтД, инфицированных вирусом простого герпеса. Выявлено также пороговое значение уровня вазоэндотелиального фактора роста 19,15 нг/мл — «точка разделения» (cutoff), позволяющее рекомендовать его для прогноза развития атопического марша у детей с АтД, инфицированных вирусом простого герпеса. ***Заключение.*** Предложенный алгоритм позволяет спрогнозировать развитие атопического марша у детей с АтД, инфицированных вирусом простого герпеса, обладает высокой чувствительностью (82%), специфичностью (90%) и прогностической значимостью (90%), что дает возможность рекомендовать его использование в клинической практике.

КЛЮЧЕВЫЕ СЛОВА: атопический дерматит, атопический марш, алгоритм, диагностика

PREDICTION OF THE DEVELOPMENT OF ATOPIC MARCH IN CHILDREN WITH ATOPIC DERMATITIS INFECTED WITH HERPES SIMPLEX VIRUS

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ABSTRACT. ***Introduction.*** In recent years, there has been an active search for various diagnostic and prognostic markers for Atopic dermatitis (AtD). For example, the attention of researchers was drawn to the study of the role of signaling proteins produced by vascular endothelial cells — vasoendothelial factor (VEGF) — regulating angiogenesis, growth and division of epidermal cells as important pathogenetic mechanisms of inflammation. ***The aim of study*** — to develop an algorithm for an individual prognosis of the development of the atopic march in children with AtD against the background of infection with the herpes simplex virus. ***Materials and methods.*** The study is a comprehensive examination of 140 patients with AtD aged 2 to 12 years and 70 healthy patients of the same age. Statistical processing of the results was performed using the STATISTICA 12.0, (Stat Soft Inc.) and SPSS-16 software packages. To develop a mathematical model for predicting the probability of developing an atopic march in children with AtD against the background of HSV, the binary logistic regression method was used. The quality of the developed model was assessed using ROC analysis, with the calculation of the area under the ROC curve (AUC). ***Results.*** An algorithm for an individual prediction of the development of associated atopic pathology in children with ATD infected with the herpes simplex virus has been developed. A threshold value of vasoendothelial growth factor level of 19.15 ng/ml was also identified — the "cutoff point" (cutoff), which allows us to recommend it for predicting the development of the atopic march in children with AtD infected with the herpes simplex virus. ***Conclusion.*** The proposed algorithm allows predicting the development of the atopic march in children with ATD infected with the herpes simplex virus, has high sensitivity (82%), specificity (90%) and prognostic significance (90%), which allows us to recommend its use in clinical practice.

KEYWORDS: angiogenesis, epidermal growth factor, atopic dermatitis, diagnostics

INTRODUCTION

Atopic dermatitis (AtD) remains an important medical and social problem in childhood due to its high prevalence, early manifestation, polymorphism of clinical manifestations and tendency to recurrent course. Despite the successes achieved in the diagnosis and treatment of the disease, many pathogenetic mechanisms, including those in combination with an infection, remain unexplored. At the same time, contamination with bacterial, fungal, viral agents and parasitic invasions are not only triggers, but also promoters of complicated AtD [3].

The problem of AtD is important for medicine, in particular for pediatrics and pediatric allergology, dermatovenereology, as evidenced by the prevalence and steady growth of this disease among children all over the world. The onset of the disease is observed in early childhood and is observed in 60–70% of children in the first year of life. For many years, AtD retains its clinical signs, acquiring a chronic course [5].

The data available in the literature on the pathogenesis of AtD do not allow a more accurate assessment of the effect on the course of the disease of various disorders of the immunological status of the child's body, which can act as a cause of secondary skin infection. The frequency of complicated forms of AtD in children averages up to 30% [6, 8, 9].

The high frequency of herpes simplex virus (HSV) I and II infection is considered by researchers in the development of AtD and the subsequent atopic march (AM) from diametrically opposed positions.

In recent years, various diagnostic and prognostic markers for AtD have been actively sought. For example, the attention of researchers has been drawn to the study of the role of signaling proteins produced by vascular endothelial cells / vasoendothelial factor (VEGF) / and epidermal cells / epidermal growth factor (EGF), which regulate angiogenesis processes, growth and division of epidermal cells as important pathogenetic mechanisms of inflammation [1, 2, 4, 7, 10].

Similar studies have not been conducted in children with AtD.

At the same time, determining the levels of vasoendothelial and epidermal growth factors in pediatric patients with AtD may be promising

both for clarifying the pathogenetic mechanisms of inflammation in this disease, including infection with HSV types I and II, and for predicting the further course of the disease and a substantiated approach to personalized therapy in children with AtD.

THE AIM OF THE STUDY

To develop an algorithm for an individual prognosis of the development of associated atopic pathology in children with atopic dermatitis against the background of infection with the herpes simplex virus based on a comprehensive clinical and laboratory examination of patients.

MATERIALS AND METHODS

The study is analytical cross-sectional and is presented by a comprehensive examination of 140 children with AtD aged 2 to 12 years, divided into 2 groups: 70 children with an established diagnosis of AtD; 70 children with a diagnosis of atopic dermatitis infected with the herpes simplex virus (AtD + HSV). The control group consisted of 70 somatically healthy children.

The study was conducted with the permission of the Local Ethics Committee of the Federal State Budgetary Educational Institution of Astrakhan State Medical University. There were no amendments to the original protocol. The diagnostic criteria and the therapy administered complied with the clinical guidelines "Atopic dermatitis — 2021, 2022, 2023", approved by the Ministry of Health of the Russian Federation on 08/26/2021.

In addition to collecting complaints and anamnesis, the examination of patients included a physical examination of the patient's organs and systems; traditional laboratory examination (clinical blood test, biochemical blood test); instrumental examination (electrocardiography, ultrasound); Special laboratory examination included determination of: specific antibodies of classes IgM and/or IgG to antigens of the HSV virus types 1–2 by the enzyme-linked immunosorbent assay (ELISA) using reagent kits from Vector-Best, Novosibirsk, Russia; determination of deoxyribonucleic acid (DNA) of the studied herpes viruses in blood samples — by the polymerase chain reaction (PCR) using test systems manufactured by the Central Research Institute of Epidemiology of Rospotrebnadzor, Moscow; determination of vasoendothelial growth factor A (VEGFA) and EGF in the blood plasma of patients was carried out by the ELISA method using highly sensitive HEA143Hu reagent kits from Cloud-Clone Corp. Reference values in the range of 1.0–98.6 pg/ml.

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

In each group, the median (Me), the values of the 1^{st} and 3^{rd} quartiles (Q1; Q3), and the 5^{th} and 95^{th} 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 differences, the Mann–Whitney test (U) 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. To test the normality of the data distribution, the Kolmogorov–Smirnov test with Lilliefors correction (for n >50 in the group) and the Shapiro–Wilk test (for n <50 in the group) were used. To test the hypotheses about the homogeneity of general variances, the Levene test was used.

The study of the relationships between the features was carried out by calculating the Spearman rank correlation coefficient (r). Correlation relationships were considered statistically significant at p <0.05. The strength of the correlation was assessed qualitatively: at r 0.0–0.3 — as its absence or indicators of a weak relationship; at r from 0.4–0.7 — as moderate; at r more than 0.70 — as strong.

RESULTS AND DISCUSSION

Using correlation analysis, among the studied indicators and factors, those associated with the development of the atopic march in children with AtD + HSV were identified (Table 1). The coefficients characterizing the relationship between the development of AM and the level of VEGF, ng/ml (r=0.873; p <0.001), the presence of parasitic invasion (r=0.795757; p <0.001) had the greatest strength.

In connection with the data of the correlation analysis, the above factors were included in the algorithm developed using the binary logistic regression method for predicting the probability of

Table 1

Data of the correlation analysis in the group of children with atopic dermatitis infected with the herpes simplex virus

Indicator	Spearman	P-level
VEGF, ng/ml	0.87335	0.000012
Presence of parasitic invasion	0.795757	0.000018
EGF, nq/ml	0.65331	0.000134
Scoring of Atopic Dermatitis index, points	0.495223	0.005343
Intensity of clinical signs: 1-weak, 2-moderate, 3-strong	0.548274	0.003059
Severity of AtD: moderate, severe	0.466342	0.005726
Ig E, ME/ml	0.471126	0.007639
Gastritis, gastroduodenitis	0.345502	0.060721
Reactive pancreatitis	0.229232	0.198856
Reactive hepatomegaly	0.113535	0.582144
Hepatosplenomegaly	0.091266	0.621825
Number of red blood cells in complete blood count, 10^{12}/l	–0.216574	0.122027
Hemoglobin level in CBC, g/l	–0.158725	0.357092
Number of white blood cells in CBC, 10^9/l	0.173176	0.364639
Level of total blood protein, g/l	0.286763	0.138453
Level of blood albumin, g/l	0.238552	0.212337
Level of blood globulins, g/l	0.289002	0.093353
Activity of blood alanine aminotransferase, U/l	0.093752	0.610972
Activity of blood aspartate aminotransferase, U/l	0.092664	0.661136
Level of blood glucose, g/l	0.071385	0.830924

developing AM in children with AtD against the background of HSV (Formula 1).

Formula 1:

$$p = 1/1 + e - z,$$

where $z = 2.696 \cdot X + 0.175 \cdot У - 8.462$, where X — presence (2) or absence (1) of parasitosis; У — level of endothelial growth factor (ng/ml).

The significance of the coefficients was tested using Wald statistics. The level of statistical significance of the model coefficients was 0.019, which is less than 0.05 and indicates the statistical significance of the prediction results using this model (Table 2).

The significance of the developed algorithm was also assessed using the Omnibus Test (Table 3). The results indicate the statistical significance of the algorithm (χ^2=56.194; df=2; p <0.0001).

Below is a classification table in which the observed indicators of belonging to the group (1 — no AM (atopic march), 2 — there is AM) are contrasted with those predicted on the basis of the calculated algorithm.

From Table 4, it can be concluded that out of the total number of patients included in the work (70 people), "strictly positive" results were obtained in 29 patients (41%), false negative (recognized by the test as healthy, although they are sick) — in 3 patients (4%). "Strictly negative" results were obtained in 31 patients (44%), false positive (recognized as sick, although they are healthy) results — in 7 patients (10%). In total, 60 cases were correctly recognized, which is 86%.

The significance of the coefficients was checked using the Wald criterion (Table 5). The level of statistical significance of the coefficients is less than 0.05, which allows using these indicators in the prognostic algorithm.

Based on the values of the regression coefficients, the VEGF factors and parasitosis have a direct relationship with the likelihood of developing AM. The presence of parasitic invasion increases the chances of the AM by 14.8 times (95% CI 2.873–76.474), an increase in the VEGF level by 1 ng/ml increases the chances of the AM by 1.195 times (95% CI 1.045–1.359).

The diagnostic sensitivity of the developed prognostic model is 82%. The diagnostic specificity of the test is 90%. The diagnostic efficiency

Table 2

Variables in the equation of the prognostic algorithm

	B (regression coefficient	S.E. (standard error)	Wald (wald statistical test value)	df	Sig. (significance)	Exp (B)
Step 0 Constant	–0.961	0.328	5.511	1	0.019	0.372

Table 3

Testing the significance of the algorithm (Omnibus Tests)

	Chi-square	df	Sig.
Step 1 Step	56.194	2	p <0.0001
Block	56.194	2	p <0.0001
Model	56.194	2	p <0.0001

Table 4

Classification table

Observed indicator		Predicted indicator		
		AM		Percentage of correct predictions
		1 — no	2 — yes	
No AM Yes AM	1	31	7	81.7
	2	3	29	90.7
Total percentage indicator				85,8

Table 5

Significance check of the algorithm coefficients

		B	Wald	df	Sig.	Exp (B)	95% C.l. for Exp (B)	
							Lower	Upper
Step 1[a]	VEGF	0.175	6.87	1	0.009	1.192	1.045	1.359
	Parasitosis	2.696	10.372	1	0.001	14.823	2.873	76.474
	Constant	–8.866	16.101	1	0.000	0.000		

(Accuracy) is 86%. The prognostic value of a positive result is 82%. The prognostic value of a negative result is 90%. The prognostic criterion prognostic validity of the test was calculated. The validity coefficient is r=0.6. Also, the quality assessment of the developed model was carried out using ROC analysis, with the calculation of the area under the ROC curve (AUC).

For the developed algorithm, the AUC was 0.845±0.02 (95% CI 0.678; 0.991), indicating excellent quality of the developed algorithm.

The proposed algorithm allows predicting the development of the AM in children with AtD against the background of herpes-virus infections (HVI).

In order to establish the threshold value of VEGF for predicting the development of the AM

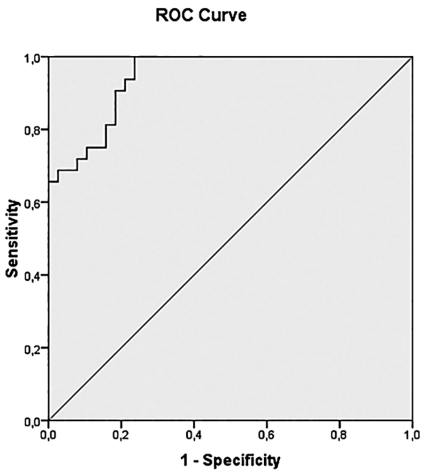

Fig. 1. Quality assessment of the developed model — area under the ROC curve (AUC)

in children with AtD + HVI, a “cut off” was established using ROC analysis.

The threshold value of VEGF for predicting the development of the AM in children with AtD + HVI was 19.15 ng/ml, while the area under the ROC curve was 0.922±0.03 [0.863–0.98] (p <0.001). The sensitivity for this threshold value was 84.4%, specificity 73.7%.

CONCLUSIONS

An algorithm for individual prediction of the development of the atopic march in children with atopic dermatitis infected with the herpes simplex virus has been developed, with an assessment of the quality of the model and calculation of the area under the ROC curve (AUC=0.845±0.02 (95% CI 0.678; 0.991).

The obtained data expand the understanding of the pathogenesis of the disease and can be used in pediatric practice to improve the quality of diagnosis, therapy and prevention of AtD.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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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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