https://doi.org/10.47183/mes.2024-26-3-92-97

A MODERN APPROACH TO THE DIFFERENTIAL DIAGNOSIS OF HUMAN BETAHERPESVIRUS INFECTION 6A/V IN CHILDREN

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Introduction. Herpesvirus infections — in particular, those caused by human betaherpesvirus 6A/B (HHV-6A/C), are a serious problem at the present time due to their ubiquity, polymorphism of manifestations, lifelong persistence in the body with the possibility of reactivation, and need for comprehensive diagnostics to the form of infection. Herpesvirus infections are especially serious when occurring in children with recurrent respiratory diseases.

Objective. To propose a modern method of differential diagnosis (DD) of active and latent forms of HHV-6A/B infection in children to optimize patient management tactics.

Materials and methods. To build a discriminant model, 152 patients aged 1 month to 17 years inclusive were included in the study, 112 of them making up a training sample, while 40 comprised a test sample. A dichotomous variable was taken as a response variable: 1 — latent form of HHV-6A/B infection (n = 89), 2 — active (n = 23). 27 potential predictors were considered. The test sample consisted of 40 children. Statistical processing was performed using Microsoft Excel and StatSoft Statistica 7.0

Results. The developed prognostic model of DD of active and latent forms of HHV-6A/B infection in children, which takes into account the severity of fever, the presence of cough, the absolute neutrophil count and the value of threshold cycles of HHV-6A/B DNA, is characterized by its high sensitivity (91.3%) and specificity (94.4%). The presented example reflects the step-by-step use of the model.

Conclusions. The prognostic model can be used in practice for identifying DD forms of HHV-6A/B infection in the presence of lymphoproliferative and respiratory syndromes in children, for the detection of HHV-6A/B DNA in the blood, and to substantiate indications for immunotropic therapy.

Keywords: human betaherpesvirus infection 6A/B; active form; latent form; recurrent respiratory diseases; diagnosis; children

For citation: Tyan N.S., Babachenko I.V., Goleva O.V., Zheleznova L.I., Baziyan E.V., Glotov O.S. A modern approach to the differential diagnosis of human betaherpesvirus infection 6A/V in children. *Extreme Medicine*. 2024;26(3):92–97. https://doi.org/10.47183/mes.2024-26-3-92-97

Funding: the study was performed without external funding.

Acknowledgements: the authors would like to express their gratitude to Academician of the RAS, Dr. Sci. (Med.), prof. Yuri V. Lobzin, Honored Scientist, corresponding member of the RAS, Dr. Sci. (Med.), prof. Konstantin V. Zhdanov, Honored Scientist, Dr. Sci. (Med.), and prof. Natalia V. Skripchenko for their comprehensive support and the opportunity to perform research. We also thank Dr. Sci. (Med.) prof. Stepan G. Grigoriev, Senior Research Officer and patent specialist Nelly A. Dobroskok for their assistance in obtaining a patent for an invention.

Compliance with the principles of ethics: the study was conducted in accordance with the principles of the Helsinki Declaration and approved by the Local Ethics Committee of the Federal State Budgetary Institution "Children's Scientific and Clinical Center for Infectious Diseases of the Federal Medical and Biological Agency" (Protocol No. 160 dated 09/27/2022). Clinical and laboratory examination of patients was carried out after familiarization of their legal representatives with the stages of the study set out in the brochure and signing of informed consent, consent to the use of personal data.

Potential conflict of interest: the authors declare no conflict of interest.

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Received: 10 Sep. 2024 **Revised:** 18 Oct. 2024 **Accepted:** 21 Oct. 2024

СОВРЕМЕННЫЙ ПОДХОД К ДИФФЕРЕНЦИАЛЬНОЙ ДИАГНОСТИКЕ БЕТА-ГЕРПЕСВИРУСНОЙ ИНФЕКЦИИ ЧЕЛОВЕКА 6А/В У ДЕТЕЙ

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Введение. Герпесвирусные инфекции, вызванные, в частности, бетагерпесвирусом человека 6А/В (ВГЧ-6А/В), являются важной проблемой современности ввиду повсеместной распространенности, полиморфизма проявлений, пожизненной персистенции в организме с возможностью реактивации, необходимости комплексной диагностики для установления формы инфекции, особенно у детей с рекуррентными респираторными заболеваниями.

Цель. Предложить современный способ дифференциальной диагностики (ДД) активной и латентной форм ВГЧ-6А/В инфекции у детей для оптимизации тактики ведения пациентов.

Материалы и методы. Для построения дискриминантной модели в исследование включили 152 пациента в возрасте от 1 месяца до 17 лет включительно, из них 112 — это тренировочная выборка, а 40 — тестовая. В качестве переменной отклика взята дихотомическая переменная: 1 — латентная форма ВГЧ-6А/В инфекции (n = 89), 2 — активная (n = 23). Рассмотрено 27 потенциальных предикторов. Тестовую выборку составили 40 детей. Статистическая обработка выполнена с использованием Microsoft Excel, StatSoft Statistica 7.0

Результаты. Разработанная прогностическая модель ДД активной и латентной форм ВГЧ-6А/В инфекции у детей учитывает выраженность лихорадки, наличие кашля, абсолютное число нейтрофилов и значение пороговых циклов ДНК ВГЧ-6А/В и характеризуется высокими показателями чувствительности (91,3%) и специфичности (94,4%). Представлен пример, отражающий пошаговое использование модели.

Выводы. Прогностическая модель может использоваться в практике для ДД форм ВГЧ-6А/В инфекции при наличии у детей лимфопролиферативного, респираторного синдромов и выявлении ДНК ВГЧ-6А/В в крови и для обоснования показаний к проведению иммунотропной терапии.

Ключевые слова: бета-герпесвирусная инфекция человека 6А/В; активная форма; латентная форма; рекуррентные респираторные заболевания; диагностика; дети

Для цитирования: Тян Н.С., Бабаченко И.В., Голева О.В., Железова Л.И., Базиян Е.В., Глотов О.С. Современный подход к дифференциальной диагностике бета-герпесвирусной инфекции человека 6A/B у детей. *Медицина экстремальных ситуаций*. 2024;26(3):92–97. https://doi.org/10.47183/mes.2024-26-3-92-97

Финансирование: работа выполнена без спонсорской поддержки.

Благодарности: академику РАН, д-ру мед. наук, профессору Лобзину Юрию Владимировичу, президенту ФГБУ «Детский научно-клинический центр инфекционных болезней» Федерального медико-биологического агентства, заслуженному деятелю науки Российской Федерации, член-корреспонденту Академии РАН, д-ру мед. наук, профессору Жданову Константину Валерьевичу, исполняющему обязанности директора ФГБУ «Детский научно-клинический центр инфекционных болезней» Федерального медико-биологического агентства, заслуженному деятелю науки Российской Федерации, д-ру мед. наук, профессору Скрипченко Наталье Викторовне, заместителю директора по научной работе ФГБУ «Детский научно-клинический центр инфекционных болезней» Федерального медико-биологического агентства, за всестороннюю поддержку и предоставленную возможность выполнить исследование в стенах Центра; д-ру мед. наук, профессору Григорьеву Степану Григорьевичу, старшему научному сотруднику отдела организации медицинской помощи ФГБУ «Детский научно-клинический центр инфекционных болезней» Федерального медико-биологического агентства Доброскок Нелли Александровне, патентоведу ФГБУ «Детский научно-клинический центр инфекционных болезней» Федерального медико-биологического агентства, за помощь в оформлении патента на изобретение.

Соответствие принципам этики: Исследование проведено в соответствии с принципами Хельсинкской декларации и одобрено Локальным этическим комитетом ФГБУ «Детский научно-клинический центр инфекционных болезней» Федерального медико-биологического агентства (протокол № 160 от 27.09.2022). Клинико-лабораторное обследование пациентов осуществлялось после ознакомления их законных представителей с этапами исследования, изложенными в брошюре, и подписания информированного согласия, согласия на использование персональных данных.

Потенциальный конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

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Статья поступила: 10.09.2024 **После доработки:** 18.10.2024 **Принята к публикации:** 21.10.2024

INTRODUCTION

Herpesvirus infections are a serious problem at the present time due to their ubiquity, high infection rate of the population, and the possibility of their reactivation in the development of immunodeficiency conditions having a high risk of adverse outcomes [1–3]. In recent years, increasing attention has been paid to herpesviruses due to the increasing case numbers of active herpesvirus infections, including human betaherpesviruses 6A/B, in people with infectious diseases caused by the SARS-CoV-2 virus (COVID-19) [4–6], as well as in children with recurrent respiratory diseases (RRD). Although human betaherpesvirus 6A/B (HHV-6A/B) was first detected in 1985 in immunocompromised patients [7], it is currently known as one of the most common herpesviruses with the level of seropositive individuals to HHV-6A, HHV-6B or both types in the adult population reaching 95% [8]. Like other representatives of the family, HHV-6A/B is characterized by polymorphism of clinical manifestations and acts as a trigger of autoimmune and lymphoproliferative diseases [9–13].

The high level of infection with HHV-6A/B leads to the frequent detection of markers of betaherpesvirus HHV-6A/B infection, difficulties in differential diagnosis (DD) of active and latent forms, especially in children with lymphoproliferative and catarrhal syndromes, as well as RRD, overdiagnosis of active forms of infection and subsequent administration of immunotropic therapy with antiviral purpose [8, 14–16].

The aim of our study is to propose a modern DD method for active and latent forms of HHV–6A/B infection in children as a means of optimizing patient management tactics.

MATERIALS AND METHODS

The study, carried out in the Children's Scientific and Clinical Center for Infectious Diseases of the Federal Medical and Biological Agency of Russia from 2021 to 2023, included 152 patients aged 1 month to 17 years 11 months and 29 days, 112 of whom made up a training sample for training the classifier, while 40 comprised a test sample for validating the classifier. Inclusion criterion for the training sample: detection of HHV-6A/B DNA in whole blood by qualitative polymerase chain reaction (PCR) with subsequent assessment of the levels of threshold amplification cycles (cycle threshold, Ct). Exclusion criteria: disagreement of legal guardians of patients to participate in the study; severe somatic diseases in the decompensation stage; detection of SARS-CoV-2 RNA in the upper respiratory tract by PCR.

Depending on the severity of the condition, The patients were admitted to a 24-hour or day hospital. Upon admission, anamnestic data was collected, including the data of medical documentation of the outpatient stage (history of the child's development — form No. 112/U or an extract from it). During the examination, special attention was paid to assessing the presence and severity of lymphoproliferative syndromes typical of herpesvirus infection, namely: adenoiditis, tonsillitis, lymphadenopathy, hepatosplenomegaly.

On the first day of hospitalization, clinical and biochemical blood tests were performed to assess the level of C-reactive protein (CRP). To interpret the results of the laboratory examination, reference values of manufacturers of test systems were used, taking into account age characteristics. All patients underwent a whole blood examination using high-quality real-time PCR to detect HHV-6A/B DNA with an assessment of Ct level (kits "AmpliSens EBV/CMV/HHV6-screen-FL" (Central Research Institute of Epidemiology, Russia). The Ct level is the value at which the threshold line intersects the S-shaped signal accumulation curves in the test samples and control samples. Thus, this indicator indicates the number of amplification cycles required to start

detecting the virus DNA in the sample. A low Ct value indicates a significant amount of isolated viral DNA in the sample, which indicates a high viral load, while a high Ct value indicates a low viral load [17].

Statistical processing was carried out using Microsoft Excel modules, the StatSoft Statistica 7.0 software package. Using a training sample, a model was built for the dependence of the patient's belonging to one of two groups according to the value of factors in various combinations, where 1 is the latent form of HHV-6A/B infection (n = 89), 2 is the active form of HHV-6A/B infection (n = 23). The group of active infection included children with sudden exanthema caused by laboratory-confirmed HHV-6A/V [18–20]. 27 anamnestic, clinical and paraclinical signs were considered as potential predictors in the initial training model. The discriminant model was constructed using the step-by-step inclusion of predictors using the Fisher F-criterion (the value of the F–criterion is 4.0, the lower limit of tolerance is 0.01). The significance level $p < 0.05$ was used for all types of statistical analysis.

RESULTS OF THE STUDY

In order to improve the accuracy and timeliness of diagnosis based on a comprehensive clinical and laboratory examination, including a PCR study, a predictive model using discriminant analysis was developed. Of the 27 studied features, 4 parameters were identified as demonstrating the greatest statistically significant differences between the groups — $p < 0.001$ (Table 1).

The obtained model of DD of latent and active forms of HHV-6A/B infection in children demonstrated high statistical significance ($p < 0.001$) and classificatory ability at the level of 93.75%. The model, which takes into account such parameters as severity of fever, the presence of a cough, the absolute number of neutrophils and the Ct DNA level of HHV-6A/B, has high sensitivity (91.3%) and specificity (94.4%).

On this basis, a diagnosis can be carried out as follows. When seeking medical help for a child with a suspected active form of HHV-6A/ B infection (fever, catarrhal and lymphoproliferative syndromes, clinical manifestations of infectious mononucleosis, the presence of RRD), a clinical blood test is performed on an automated hematology analyzer with an assessment of the absolute value of neutrophils, a whole blood study by PCR with Ct DNA determination of HHV-6A/V. The obtained data of predictor features are used for calculations using formulas (1, 2) of the linear discriminant function (LDF):

LDF1 (the latent form of HHV-6A/B infection): (1)

$$42.7 \times X1 - 49.2 \times X2 - 6.2 \times X3 + 5.2 \times X4 - 865,$$

LDF2 (the active form of HHV-6A/B infection): (2)

$$45.1 \times X1 - 53 \times X2 - 6.7 \times X3 + 4.7 \times X4 - 940,$$

where X1 — the maximum severity of fever, °C;
X2 — the presence of a cough: no — 0, yes — 1;
X3 — absolute neutrophil count, $\times 10^9$/L;
X4 — threshold cycle of HHV-6A/B DNA amplification.

The obtained values of LDF1 and LDF2 are compared as follows: if LDF1 is greater than LDF2, the latent form of HHV-6A /B infection is diagnosed; with LDF2 more than LDF1, the active form is diagnosed.

A classification of the test sample (n = 40) was performed. Discriminant analysis successfully identified 8 out of 10 cases of the active form of HHV-6A/B infection and 29 out of 30 cases of latent infection. The total percentage of correct diagnoses was 92.5%, which is comparable to the results in the training sample. The patent for invention No. 2817089 dated 09/04/2024 was obtained [21].

For a better understanding of the proposed model, we present our own clinical observation.

Clinical case No. 1

The girl Ksenia, 8 years and 2 months old, was admitted to the Children's Scientific and Clinical Center for Infectious Diseases of the Federal Medical and Biological Agency on a planned basis due to RRD accompanied by febrile fever, for examination and selection of therapy. The child has a history of Schinz disease, atopic dermatitis. The epidemiological history is not burdened. Upon admission, condition satisfactory, body temperature falling within the normal range (the value of the predictor X1 is "36.5"). Skin of normal color, moist, without an infectious rash. Rhinitis and cough absent (the value of the predictor X2 is "0"). Pharynx calm, tonsils not enlarged, no plaque. Peripheral lymph nodes not enlarged. Heart tones clear, rhythmic. Vesicular breathing carried out in all parts of the lungs; no wheezing heard. Abdomen soft, painless; liver and spleen not enlarged. Diuresis preserved. Following a clinical blood test, all parameters within the reference values (the value of the predictor X3 (absolute neutrophil count) is "3.35"). No

Table 1. List of predictors, coefficient values and their significance level

No.	Name and gradation of predictors	Code	LDF1 (latent form of HHV-6A/B infection)	LDF2 (active form of HHV-6A/B infection)	*p* value
1	The maximum severity of fever, °C	X1	42.7	45.1	<0.001
2	The presence of a cough: 0 — no; 1 — yes	X2	-49.2	-53	<0.001
3	Absolute neutrophil count, *10^9/L	X3	-6.2	-6.7	<0.001
4	Threshold cycle of HHV-6A/B DNA amplification	X4	5.2	4.7	<0.001
5	Constant	-	-865	-940	-

Table prepared by the authors using their own data

inflammatory changes detected in the general urine analysis. An increase in normobiota was observed in the crops of the discharge from the nasopharynx and oropharynx to the microflora. Taking into account the anamnestic data, in order to exclude reactivation of herpesviruses, high-quality whole blood PCR for HHV-6A/B DNA, Epstein-Barr virus and cytomegalovirus was performed by PCR: HHV-6A/B DNA was detected, Ct value (predictor X4) — 31. When examining blood by ELISA for specific antibodies of the IgM class, IgG to herpesviruses, the following results were obtained: IgG to cytomegalovirus (CMV) detected. IgM antibodies to CMV, IgG antibodies to the nuclear and capsid antigens of EBV, HHV-6A/B not detected. Given the positive result of PCR on HHV-6A/B DNA, final clinical diagnosis was interpreted as persistent HHV-6A/B infection in the activation stage. The child was prescribed immunotropic therapy with antiviral action consisting of meglumine acridonacetate according to the manufacturer's instructions in a course of 23 days.

The calculation was performed retrospectively using the formulas:

$$LDF1 = 42.7\times36.5 - 49.2\times0 - 6.2\times3.35 + 5.2\times31 - 865 = 834.98$$

$$LDF2 = 45.1\times36.5 - 53\times0 - 6.7\times3.35+4.7\times31 - 940 = 829.41$$

Since LDF1 > LDF2, a 94.4% probability of a latent form of HHV-6A/B infection was pronounced.

This case demonstrates that, according to the proposed discriminant model, the probability of an active form of HHV-6A/B infection was extremely low (5.6%); on this basis, it was possible to avoid a long course of immunotropic therapy.

DISCUSSION

The existing problem of overdiagnosis of the active form of HHV-6A/B infection is related to the interpretation of the results of high-quality PCR of whole blood without taking into account the possible latency of the virus in mononuclear cells. Despite their unsuitability in most cases, the detection of HHV-6A/B DNA generally leads to the prescription of long-term repeated courses of immunotropic therapy. Thus, the developed prognostic model using discriminant analysis based on a comprehensive assessment of clinical and laboratory parameters solves the problem of DD of active and latent forms of HHV-6A/B infection in children with lymphoproliferative and respiratory syndromes.

Utkin et al. proposed a method for identifying infectious mononucleosis associated with human betaherpesvirus 6A/B. The invention takes into account such biomarkers as AVEN mRNA, CHUK transcript 2, CIRBP transcript 2, TRAF3 transcript 2 and IRAK4 transcript 10. Although the method is extremely interesting from the point of view of studying the molecular mechanisms of pathogenesis, its disadvantages include the assessment of infection activity in relation to only one nosological form (infectious mononucleosis), inaccessibility of implementation in practical healthcare with a large flow of patients, lack of technical equipment of laboratories and trained personnel necessary for the study of genes and transcripts, as well as high financial costs and difficulty in interpreting the obtained results [22].

As a solution of this problem, Melekhina et al. developed a method for identifying the indications for antiherpetic therapy of HHV-6A/B infection in children with acute respiratory diseases. The active form of infection, which requires the prescription of antiviral therapy, is established when more than 100 copies of the of HHV-6A/B DNA/10^5 cells are detected in the blood by quantitative PCR. The proposed method is characterized by its speed of execution and adequate approach to the obtained results taking into account different levels of viral load, as well as its convenience in the presence of quantitative PCR — which, however, is not an affordable diagnostic method at all levels of medical care [23].

It is possible to use reverse transcription PCR to differentiate the active and latent forms of HHV-6A/B infection. This method is characterized by its higher sensitivity and specificity than culture-based studies. The determination of the form of infection depends on the detected matrix RNA of viral proteins: the open reading frames U42, U22, U38, U100 indicate an active form of infection, while U94, conversely, indicates a latent infection [20]. Thus, the method is promising, but currently unavailable in practice.

Our described model offers additional advantages such as simplicity, accessibility, speed of execution, as well as the possibility of providing DD of active and latent forms of HHV-6A/B infection without involving additional financial costs for expensive laboratory tests. The uniqueness of the method is confirmed by the patent for the invention.

CONCLUSIONS

The developed prognostic model can be applied in clinical practice for the diagnosis of active and latent forms of HHV-6A/B infection in children with catarrhal, lymphoproliferative syndromes when HHV-6A/B DNA is detected in whole blood, as well as to justify the appointment of immunotropic therapy with antiviral action. When establishing the latent form of HHV-6A/B infection, it is necessary to conduct a further diagnostic search to exclude autoinflammatory diseases accompanied by an appropriate symptom complex or the active form of infectious mononucleosis of mono– and combined herpesvirus etiology along with lesions of organs and systems associated with viral infection.

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Authors' contributions. All the authors confirm that they meet the ICMJE criteria for authorship. The most significant contributions were as follows: Natalia S. Tian — formation of an idea, participation in scientific design, collection of clinical and anamnestic, paraclinical data, creation of a database, drafting of a manuscript, statistical data processing, approval of the final version; Irina V. Babachenko — formation of the idea, research objectives, development of methodology, approval of the final version; Olga V. Goleva — formation of the idea, research objectives, development of methodology, laboratory research, approval of the final version; Lyudmila I. Zhelezova — development of methodology, laboratory research, approval of the final version; Elena V. Baziyan — provision of biomaterials of patients, laboratory tests, approval of the final version; Oleg S. Glotov — formation of the idea, research objectives, development of methodology, approval of the final version.

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