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HERPESVIRUS INFECTION IN CHILDREN IN THE ETIOLOGY OF HEMORRHAGIC VASCULITIS

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Abstract

Relevance. There is no predominant agent in the etiological structure of hemorrhagic vasculitis; instead, several factors play a role, including the activation of herpesvirus infections in the disease development. The objective of the study is determined by contradictory data and a lack of coordinated agreement regarding the etiology of hemorrhagic vasculitis.

Objective: To identify the role of herpesvirus infection in the etiology of hemorrhagic vasculitis in children.

Materials and methods. A cross-sectional study was conducted for 25 children aged from 2 months to 18 years with hemorrhagic vasculitis, who were on inpatient treatment at Medical Center "Children's Hospital" in Aktobe. All children underwent an enzyme-linked immunosorbent assay (ELISA) for herpesviruses: herpes simplex virus types I, II, (HSV-I, II), Epstein - Barr virus (EBV), cytomegalovirus (CMV), human herpesvirus type 6 (HHV – 6). The received data is processed by descriptive statistics, STATISTICS 10.0.

Results The herpesvirus infection was confirmed in 100% of the examined children, with herpes simplex virus I and II types being discovered in 25.9% of cases, Epstein-Barr virus in 28.46% of cases, cytomegalovirus (CMV) in 29.6% of cases, and human herpesvirus 6 (HHV-6) in 16% of cases. Moreover, they did not occur as mono-infections but rather in conjunction with the cytomegalovirus: CMV+ HSV-I, II (16 %); CMV+ EBV (8%); CMV+ HHV-6 (4%); CMV+ EBV+ HHV-6 (32%); CMV+ HSV-I, II + EBV+ HHV-6 (40%). A low concentration of herpesvirus antibodies in the blood of patients with hemorrhagic vasculitis was detected by ELISA anti-CMV IgG (11.62 U / ml), anti-HHV-6 IgG (6.82 U/ml), which indicates unstable immunity, the risk of activation of viral infection and recurrent hemorrhagic vasculitis.

Conclusion. According to the study, herpesvirus infections can lead to hemorrhagic vasculitis in children. If vasculitis recurs, it is advised to check for the presence of antibodies to herpesvirus antigens; if so, an infectious neurologist's consultation and etiotropic antiviral therapy are advised.

Key words: *children, hemorrhagic vasculitis (HV), herpes simplex virus types I, II (HSV-I, II), Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpes virus type 6 (HHV-6).*

Резюме

ГЕРПЕСВИРУСНАЯ ИНФЕКЦИЯ У ДЕТЕЙ В ЭТИОЛОГИИ ГЕМОРРАГИЧЕСКОГО ВАСКУЛИТА

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Актуальность. В этиологической структуре геморрагического васкулита нет преобладания какого-либо одного агента, а играет роль совокупность нескольких факторов, в том числе активация герпесвирусных инфекций в развитии болезни. Противоречивые данные, отсутствие единого мнения об этиологии геморрагического васкулита определяет цель исследования.

Цель. Определить роль герпесвирусной инфекции в этиологии геморрагического васкулита у детей.

Материалы и методы. Одномоментное поперечное исследование проведено 25 детям с диагнозом геморрагический васкулит в возрасте от 2 мес. до 18 лет, которые находились на стационарном лечении в Актюбинском Медицинском Центре «Детском стационаре» г. Актобе. Всем детям проводился иммуноферментный анализ (ИФА) на герпесвирусы: вирус простого герпеса I, II-го типов, (HSV- I, II), вирус Эпштейна – Барр (EBV), цитомегаловирус (CMV), вирус герпеса человека 6-го типа (HHV-6). Полученные данные обработаны описательной статистикой, СТАТИСТИКА 10.0.

Результаты. Герпесвирусная инфекция у обследуемых детей подтверждена в 100% случаев, из них вирус простого герпеса I, II-го типов выявлен в 25,9%, вирус Эпштейна – Барр – 28,46%, цитомегаловирус (CMV) – 29,6%, вирус герпеса человека 6-го типа (HHV-6) – 16% случаев. И они не встречались как моноинфекции, а в виде ассоциации с цитомегаловирусом: CMV+ HSV-I, II (16 %); CMV+ EBV (8%); CMV+ HHV-6 (4%); CMV+ EBV+ HHV-6 (32%); CMV+ HSV-I, II + EBV+ HHV-6 (40 %). Выявлено малая концентрация антител герпесвирусов в крови больных с геморрагическим васкулитом методом ИФА анти-CMV IgG (11,62 ЕД/мл), анти-HHV-6 IgG (6,82 ЕД/мл), что свидетельствует о неустойчивом иммунитете, риске активации вирусной инфекции и рецидивирующим течением геморрагического васкулита.

Заключение. Исследование показало роль герпесвирусной инфекций в развитии геморрагического васкулита у детей и при рецидивирующем васкулите рекомендуется обследование на наличие антител на антигены герпесвирусов и при их положительном результате рекомендуется консультация инфекциониста о решении этиотропной противовирусной терапии.

Ключевые слова: *дети, геморрагический васкулит (ГВ), вирус простого герпеса I, II типа (ВПГ-1,2), вирус Эпштейна-Барра (ВЭБ), цитомегаловирус (ЦМВ), вирус герпеса человека 6 типа (ВГЧ-6).*

Түйіндеме

ГЕМОРРАГИЯЛЫҚ ВАСКУЛИТ ЭТИОЛОГИЯСЫНДАҒЫ БАЛАЛАРДАҒЫ ГЕРПЕС ВИРУСТЫ ИНФЕКЦИЯСЫ

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Өзектілігі. Геморрагиялық васкулиттің этиологиялық құрылымында бір агент басым болмайды, бірақ бірнеше факторлардың жиынтығы, соның ішінде аурудың дамуындағы герпесвирустық инфекциялардың белсендірілуі маңызды рөл атарады. Қарама-қайшы дәлелдер, геморрагиялық васкулиттің этиологиясы туралы бірдей тұжырымның болмауы зерттеу мақсатын анықтайды.

Мақсаты. Балалардағы геморрагиялық васкулиттің этиологиясындағы герпесвирустық инфекцияның рөлін анықтау.

Материалдар мен әдістер. Ақтөбе қаласының Ақтөбе Медициналық орталығы Балалар стационарында" геморрагиялық васкулитпен стационарлық ем қабылдаған 2айдан 18 жасқа дейінгі 25 балаға бір мезгілде көлденең зерттеу жүргізілді. Барлық балаларға герпесвирустарға иммуноферменттік талдау (ИФА) жүргізілді: I, II типті қарапайым герпес вирусы, (HSV-I, II), Эпштейн - Барр вирусы (EBV), цитомегаловирус (CMV), 6 типті адамның герпес вирусы (HHV–6). Алынған мәліметтер сипаттамалық статистикамен өңделді, СТАТИСТИКА 10.0.

Нәтижелері. Зерттелеген балалардағы герпесвирустық инфекция 100% жағдайда расталды, оның ішінде I, II типті қарапайым герпес вирусы 25,9%, Эпштейн – Барр вирусы – 28,46%, цитомегаловирус (CMV) – 29,6%, 6 типті (HHV-6) адамның герпес вирусы -16% жағдайлар анықталды. Олар моноинфекция ретінде емес, цитомегаловируспен байланыс ретінде пайда болды: CMV+ HSV-I, II (16 %); CMV+ EBV (8%); CMV+ HHV-6 (4%); CMV+ EBV+ HHV-6 (32%); CMV+ HSV-I, II + EBV+ HHV-6 (40 %). Геморрагиялық васкулитпен ауыратын науқастардың қанында герпесвирус антиденелерінің төмен концентрациясы анти-CMV IgG (11,62 бірл/мл), анти-

HHV-6 IgG (6,82 бірл/мл) ИФА әдісімен анықталды, бұл тұрақсыз иммунитетті, вирустық инфекцияны белсендіру қаупін және геморрагиялық васкулиттің қайталанатын ағымын көрсетеді.

Қорытынды. Зерттеу балалардағы геморрагиялық васкулиттің дамуындағы герпесвирустық инфекциялардың рөлін көрсетті және қайталанатын васкулит кезінде герпесвирус антигендеріне антиденелердің болуын тексеру ұсынылады және олардың оң нәтижесі болған кезде этиотропты вирусқа қарсы терапияны шешу үшін инфекционистпен кеңес жүргізу ұсынылады.

Түйінді сөздер: *балалар, геморрагиялық васкулит (ГВ), I, II типті қарапайым герпес вирусы (HSV-I, II), Эпштейн-Барр вирусы (EBV), цитомегаловирус (CMV), 6 типті адамның герпес вирусы (HHV-6).*

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Introduction

Hemorrhagic vasculitis is characterized by perivascular edema, neutrophil-infiltrating cells, and systemic inflammation of tiny capillaries, arterioles, and arteries [20]. The prevalence in childhood is 13 to 20 incidents per 100,000 individuals [20,24,27]. The causes and conditions contributing to the onset of the disease are still unclear. There are various clinical manifestations, however, the etiologically significant agent and pathogenesis remain not fully elucidated. There are provocative, “resolving” and mediated (stressful) factors. The provocative factors include cytomegalovirus, hepatitis B and C viruses, HIV, beta-hemolytic streptococcus group A, staphylococci, mycoplasma, klebsiella, yersinia, salmonella, and parasitic infestations. The “resolving” factors include preventive vaccinations, the introduction of immunoglobulins, and other drug loads. Mediated (stressful) factors include cooling, overheating, physical injuries, surgical interventions, insect bites, etc.

It is believed that within the etiological framework of hemorrhagic vasculitis, there is no predominance of any particular agent, but a combination of several factors plays a role, including the activation of herpesvirus infections in the development of the decease. Herpesvirus infects more than 90% of people, and in 20% of cases, it results in major health issues. There are currently more than 80 different serotypes of herpes viruses identified. The most prevalent diseases in children are caused by cytomegalovirus (CMV) or human herpes virus type 5, Epstein-Barr virus (EBV), herpes simplex virus (HSV I, II), and human herpesvirus type 6-HHV6. In 80-90% of children, undetected cytomegalovirus infection has no symptoms, and the infection may survive for a lifetime. Between 20 and 70% of children become carriers of the Epstein-Barr virus by the age of 3 [1,6,7,9,13,19]. The formation of circulating immune complexes (CIC) is crucial in the mechanism of hemorrhagic vasculitis development, and an abundance of them activates the complement system (C). The result is the formation of a sizable immunological complex (AG+AT+C), settling on the vascular endothelium and harming it. Platelet-activating factors and proteases are created when the tumor necrosis factor is damaged, this causes a rise in the adhesion and aggregation of platelets, platelet clot formation, and the development of local hypercoagulation. Vasculitis, an immune inflammatory condition, develops in the vascular wall of the microvasculature, increasing vascular permeability of the vessels by allowing plasma and erythrocytes to depart and enter the tissues [5,10,16-18, 24,26].

It's vital to note that viruses can cause cytopathic effects by demonstrating a tropism for blood vessels. Vascular damage in EBV is captured in 7-30% of cases, and in CMV – in 8% [2,5,8,10]. The role of herpesvirus infection in the etiology of hemorrhagic vasculitis is obvious, but there are also opposing opinions. Contradictory data and the lack of consensus on the etiology of hemorrhagic vasculitis require further investigation [11,14,15,22,23,25].

The objective of the study is to identify the role of herpesvirus infection in the etiology of hemorrhagic vasculitis in children.

Material and methods. Research design. The fragment of the work was carried out in accordance with the intra-university project “Characteristics of the clinical course and approaches of hemorrhagic vasculitis in children with herpesvirus infections” № 0113 RK 00438, 2019-2021. During the scientific project, the principles of scientific ethics were observed in accordance with the “Code on People’s Health and System of Healthcare of the Republic of Kazakhstan” of 07.07.2020. The children were examined with parental permission and issuing of an «Informed Consent Sheet», which reflects the validity of the research methods. The theme of the research was approved at the meeting of the Ethics Committee, Protocol № 12/4-1-17/133 of 30.01.2019. The management of the institution is informed of the research progress and has no objection to publishing the results of the study in the public press.

The children that we observed were in inpatient treatment at the Aktobe Medical Center “Children's Hospital” in Aktobe with a hemorrhagic vasculitis diagnosis in 2019-2021. The Clinical Protocol "Hemorrhagic vasculitis in children" served as the foundation for the diagnosis, approved by the Ministry of Health of the Republic of Kazakhstan № 21 dated 12.05.2017 (without including antiviral therapy) [12]. Exclusion criteria:

children with a group of hemorrhagic diatheses (autoimmune thrombocytopenia, thrombocytopathy, hemophilia), with connective tissue diseases (ankylosing spondylitis, Stephen-Jones syndrome, systemic lupus erythematosus). We have examined 25 children aged 2 months to 18 years diagnosed with hemorrhagic vasculitis receiving inpatient treatment at the Children's Hospital. The sample of children was based on 0.02% (hemorrhagic vasculitis morbidity among children of the Aktobe region) per 100 thousand children. In this work, no comparison groups were envisaged. All patients underwent physical, laboratory, and instrumental examinations. Girls accounted for 56 % (14), and boys - 44 % (11) of cases. The age composition of the examined children aged 2 months to 1 year – was 7 (28%), aged 1 year to 3 years - 3 (12%), and children over 3 years old – 15 (60%).

Methods. To determine the role of herpesvirus infection in the etiology of vasculitis, antibodies to herpesvirus antigens were determined by enzyme-linked immunosorbent assay (ELISA): herpes simplex virus types I, II (anti-HSV-IgM, anti-HSV-IgG I, II types), Epstein-Barr virus (to the capsid antigen anti-EBV-IgM, anti-EBV-IgG), cytomegalovirus (anti-CMV-IgM, anti-CMV-IgG), human herpesvirus type 6 (anti-HHV-IgM, anti-HHV- IgG) in the licensed laboratory "Invitro", using the equipment: BIO-RAD washer (USA), Hydroflex washer (Tecan, Austria), BIO-RAD photometer (USA), Elmi SkyLine shaker (Latvia), Sunrise reader (Tecan, Austria), TS-1/80STU dry-air thermostat (Russia), meanwhile using reagents produced by Vector Best, Russia.

Statistical analysis. Descriptive statistics were performed using STATISTICS 10.0, with the determination of the mean value of the median (Me), standard deviation (S), lower (Q1), upper quartile (Q2), minimum (Min), and maximum (Max) values.

Results. Clinical manifestations in patients were characterized by polymorphism. In 50% of the cases, the abdominal syndrome was registered in 13 (52%) patients. In 3 (12%) patients, skin syndrome manifested as a small petechial-urticaria rash on the extensor surfaces of the extremities, and 9 (36%) patients also had a lesion of the small and medium joints (skin-joint form). Attention was drawn to the recurrent course of vasculitis in observed children with positive results of antibodies to the antigens of the detected herpesviruses.

The analysis of the obtained data revealed that herpesvirus infection was confirmed in 100% of cases of examined children, with herpes simplex virus I and II types being discovered in 25.9% of cases, Epstein-Barr virus in 28.46% of cases, cytomegalovirus (CMV) in 29.6% of cases, and human herpesvirus 6 (HHV-6) in 16% of cases. As can be seen from the figure (Figure 1), the acute phase of viral infections caused by human herpesvirus I, II types, Epstein-Barr, and cytomegalovirus were observed with the same frequency of 2.46% of cases.

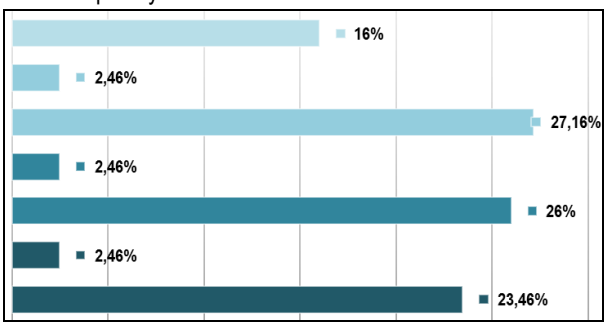

Figure 1. Detection of antibodies to herpesvirus antigens in children with hemorrhagic vasculitis.

The activation of viruses, meanwhile, was identified in the context of clinical manifestations of hemorrhagic vasculitis in children: hemorrhagic rash in the form of petechia located on the extensor surfaces of the lower extremities on both sides, in combination with the abdominal and articular syndromes. Herpesvirus infection in the examined children practically did not occur as a mono-infection but as an association of microorganisms with cytomegalovirus, which was observed in all patients with hemorrhagic vasculitis (Table 1).

Table 1.

The frequency of occurrence of herpesvirus association in children with hemorrhagic vasculitis.

№	Association of the viruses	% ratio
1	CMV+ HSV- I, II	4 (16%)
2	CMV+ EBV	2 (8%)
3	CMV+ HHV-6	1 (4%)
4	CMV+ EBV+ HHV-6	8 (32%)
5	CMV+ HSV- I, II +EBV+ HHV-6	10 (40%)

In this case, the clinical course of cytomegalovirus infection was considered in combination with infections HSV-I, II types, EBV, HHV-6: CMV + HSV-I, II; CMV + EBV; CMV + HHV-6; CMV + EBV + HHV-6; CMV + HSV-I, II + EBV + HHV-6. A complex combination of herpesvirus associations of 3-4 herpesviruses was registered in 72% of cases, while the 2-component combination was observed to a lesser extent.

The sample of patients with hemorrhagic vasculitis had an optical density ratio of 305.35 U/ml to the threshold average value of anti-EBV-IgG, with a norm of 20 U/ml. The 280.20 U/ml standard deviations were recorded with an anti-EBV-IgM average of 1.35 U/ml and an anti-EBV-IgM standard deviation of 0.04 U/ml. Anti-CMV-IgG had an average value of 11.62 U/ml and a standard deviation of 6.55 U/ml. Anti-HHV-6-IgG had an average value of 6.82 U/ml and a standard deviation of 4.77 U/ml, showing an insignificant concentration (Table 2).

Table 2.

The concentration of herpesvirus antibodies in the blood of patients with hemorrhagic vasculitis by ELISA (U/ml)

	N obs.	Average	Me	Min	Max	Q1	Q2	S
Anti-HSV IgG I, II types	19	19,29	20,67	2,01	37,56	15,88	22,43	8,55
Anti-HSV IgM I, II types	2	1,71	1,71	1,39	2,03	1,39	2,03	0,45
Anti-EBV IgG	21	305,35	201,00	17,80	750,00	100,00	603,00	280,21
Anti-EBV IgM	2	1,35	1,35	1,320	1,39	1,32	1,39	0,05
Anti-CMV IgG	22	11,62	9,05	2,80	25,56	7,09	16,03	6,55
Anti-CMV IgM	2	1,37	1,37	1,36	1,39	1,36	1,39	0,02
Anti-HHV-6 IgG	13	6,82	6,53	1,00	17,57	3,16	9,40	4,77

Discussion of the obtained data.

According to research findings, hemorrhagic vasculitis affects children over three years old (60%), which corresponds to the literature data [11, 21]. A laboratory-confirmed herpesvirus infection, without the predominance of any of their representatives, was the predictor of observed children's hemorrhagic vasculitis development in 100% of cases. This is consistent with the opinions of researchers who emphasize the ability of herpesviruses to cause a cytopathic effect by showing a tropism for blood vessels. The authors note that the widespread herpesvirus infection in the human population, their immunotherapy, and their activation during a number of immunosuppressive conditions all indicate a connection between herpesvirus infections and the development of hemorrhagic vasculitis [3,4,9,13,14,19]. The formation, circulation, and deposition of immune complexes on the walls of vessels (CIC) are of great importance in the development of vasculitis, an excess amount of which activates the complement system (C). As a result, a major immune complex (AG+AT+C) is formed that settles on the endothelium and damages it [2, 5, 6, 7, 9, 11,13]. The activation of viruses, meanwhile, was identified in the context of clinical manifestations of hemorrhagic vasculitis in children: hemorrhagic rash in the form of petechia located on the extensor surfaces of the lower extremities on both sides, in combination with the abdominal and articular syndromes, as reflected in the work of other researchers [15,16,11,21].

According to the authors [9,13,14,21], primary infection and reactivation of the human herpesvirus type 6 in children causes infection of erythema with vasculitis symptoms, which is also observed in Epstein-Barr virus infection (EBV) and cytomegalovirus infection (CMV). We have found specific IgM immunoglobulins to herpesvirus antigens in patients with hemorrhagic vasculitis verifying the acute phase of Epstein-Barr virus, cytomegalovirus infection, as well as human herpesvirus infection type 6, once again substantiating the damage of the endothelial cells of blood vessels by these agents. In our study, herpesvirus infection did not occur as mono-infections but created complex viral associations found in scientific papers [13,14,25,26].

By using ELISA, it was discovered that patients with hemorrhagic vasculitis had a low concentration of herpesvirus antibodies in their blood. Anti-CMV IgG and Anti-HHV-6 IgG antibodies indicate unstable immunity, the risk of activation of viral infection, and recurrent hemorrhagic vasculitis. This is supported by the studies of foreign scientists [6,15,23], who highlight the significant role that herpesvirus infection plays in the development of hemorrhagic vasculitis and the course of the disease in children. The virus can reactivate under the right circumstances after entering the human body and staying there for life in a latent or persistent state. The following are the primary properties of herpesviruses: ubiquitousness, generic vulnerability, opportunism, pan-tropism, the capacity for using a variety of transmission methods, sophisticated parasitic strategy, immunosuppression, and oncogenicity.

Our main shortage is that the study would be complete without restrictions: an increase in the number of examined patients, expanded IFA testing for the presence of herpesvirus antigens in patients, and PCR-based virus genome detection in biological samples. Nevertheless, the detection of 100% herpesvirus infection in the examined children is significant and does not exclude the leading factor of herpes-resistant infection being the primary cause of hemorrhagic vasculitis. In this regard, the study of the etiology of hemorrhagic vasculitis will help to develop a new therapeutic level for this disease.

Conclusion. Thus, our study showed that herpesvirus infections play a significant role in children's hemorrhagic vasculitis development, and therefore it is necessary to examine children with hemorrhagic vasculitis for herpesvirus infection (CMV, EBV, HHV-6). In case of recurrent vasculitis, it is recommended to get tested for the presence of antibodies to herpesvirus antigens, and in case of a positive result, it is recommended to consult an infectious disease specialist on the decision of etiotropic antiviral therapy.

Conflict of interest. *The authors declare that they have no conflict of interest.*

Ethical approval: *All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.*

Possible limitations of the study. *The study would be complete without restrictions: an increase in the number of surveyed patients, an expanded patients' examination for the presence of antibodies to herpesvirus antigens by ELISA, and the determination of the virus genome in biological materials by PCR.*

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