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Active human herpesvirus infections in adults with systemic lupus erythematosus and correlation with the SLEDAI score

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Abstract

Background: Human herpesviruses (HHVs) are responsible for a significant number of clinical manifestations in systemic lupus erythematous (SLE) patients. The aim of this study was to determine the frequency of active HHV infections in SLE patients and correlating them with disease activity.

Methods: Serum samples were collected from 71 SLE patients and their DNAs were extracted and analyzed to detect HHV-DNA viruses using the nucleic acid amplification technique.

Results: Fifteen out of the 71 (21.1%) patients tested positive for the HHV-DNA virus. Of them, 11/15 HHV-DNA-positive patients (73.3%) had SLE activity index (SLEDAI – Systemic Lupus Erythematosus Disease Activity Index) ≥8 ($p = 0.0001$). Active HCMV infection was the mostly frequently observed infection, occurring in 6/15 patients (40%). The frequencies of other active viral infections were 22% for HSV-1, 16.7% for HHV-7, and 5.5% for HSV-2. Viral coinfection (two or more viruses detected in the same sample) occurred in three patients (16.7%). Active HHV infections in SLE patients are more frequent in those with active SLE (≥8), who is at high risk of HHV reactivation and HCMV disease.

Conclusion: Viral surveillance is important to identify active HHV infections that can cause clinical symptoms and other complication in SLE patients.

Keywords: *Herpesviridae*, Systemic lupus erythematosus, Polymerase chain reaction

Introduction

Herpesvirus (HHV) infections in patients with systemic lupus erythematosus (SLE) are an important cause of morbidity and mortality [1–6]. Primary HHV infections and reactivation can cause a large spectrum of diseases, some of which can be fatal for immunocompromised patients. The human herpesvirus simplex 1 (HSV-1), and 2 (HSV-2) can cause orolabial and genital infections as well as keratitis, encephalitis and neonatal infections [7]; the varicella-zoster virus (VZV) is the causative agent of varicella and herpes zoster [8]; the Epstein-Barr virus (EBV) is associated with infectious mononucleosis, nasopharyngeal carcinoma, Burkitt's lymphoma, non-Hodgkin B-cell lymphomas and post-transplant lymphoproliferative diseases [9]; and the human cytomegalovirus (HCMV) is responsible for mononucleosis-like syndromes as well as systemic and organ-specific diseases (e.g., pneumonitis, gastrointestinal lesions, hepatitis, retinitis, pancreatitis, myocarditis, encephalitis and peripheral neuropathy) in immunocompromised patients

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[10], having also been described as a trigger for the development of SLE [11]. Infections with human herpesvirus 6 (HHV-6 A/B), and more rarely human herpesvirus 7 (HHV-7), result in *exanthem subitum* in infants, whereas primary infections with HHV-6A are generally asymptomatic [12]. HHV-6B and HHV-7 are also associated with severe diseases (e.g., encephalitis and pneumonitis) in immunocompromised patients. Finally, human herpesvirus 8 (HHV-8) is mainly associated with Kaposi's sarcoma, one of the neoplasms that is most frequently encountered in HIV-infected patients [13]. Few studies have evaluated the impact of HHV infections on patients with SLE, therefore infection remains as the main cause of death, mostly due to their immunosuppressive therapy (i.e., steroids, such as prednisone) and abnormal immune response [14, 15]. This transversal study was undertaken to determine the frequency of HHV infections in patients with SLE using the Nested PCR (NPCR) technique, and to evaluate the laboratorial findings with disease activity.

Study sample and methods

Study sample

Seventy-one patients aged from 18 to 62 years old, with SLE, who were treated in the Rheumatology Service of the University of Campinas' Clinical Hospital between September 2007 and April 2009, in any stage of treatment, were included in this study. The median age of the patients was 40 years old (Table 1). Two different groups of patients were analyzed based on their Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (Table 1), group 1 patients corresponding to those with active SLE (SLEDAI ≥8), and group 2 patients to those without active SLE (SLEDAI< 8) [16–18]. Patients with SLEDAI ≥8 were arbitrarily considered as showing disease activity [19]. All procedures performed were in accordance with the ethical standards for research involving human beings of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments.

Inclusion criteria

1. Patients with SLE diagnosis, with active SLE or not, according to the SLEDAI criterion; 2. Consent of the patient or guardian authorizing the collection of the serum sample for the study; 3. Laboratory analysis of the serum samples collected from the SLE patients for detection of the presence of HHVs-DNA.

Table 1 Patient's characteristics

Characteristics	n
Gender – Female	71 (100%)
Median age	40 years old (18–78 years old range)
Active SLE (SLEDAI ≥8)	20/71 (28%)
Inactive SLE (SLEDAI < 8)	51/71 (72%)

Legend: *SLE* Systemic Lupus Erythematosus, *SLEDAI* Systemic Lupus Erythematosus Disease Activity Index

Exclusion criteria

1. Patients who did not meet the criteria described above.

Criteria used to characterize lupus activity

Active SLE was considered when the patient's SLEDAI was greater than or equal to 8, as recommended by the American College of Rheumatology and internal protocols [16–18]. The active and non-active SLE data described in the study were collected from the patients' medical records.

Methods

This was a descriptive transversal single-center study. All data were collected from clinical reports stored in the medical clinical reports service of the Clinical Hospital of the State University of Campinas to evaluate their correlation with positive HHV-DNA, e.g., SLEDAI, hospitalization and symptoms, allowing the inference of a diagnostic status.

Biological samples were collected and serum samples were obtained after centrifugation. The samples were stored at − 80 °C until the time of analysis.

All procedures performed in this study were in accordance with the ethical standards for research involving human beings of the institutional ethical committee of State University of Campinas and Brazilian national research committee, and with the 1964 Helsinki declaration and its later amendments. The Research Ethics Committee (Comitê de Ética em Pesquisa - CEP) of the Faculty of Medical Science (Faculdade de Ciências Médicas – FCM) of State University of Campinas (Unicamp) approved this study under the 789/2006 project number.

All patients that the samples were included in this study have signed the written informed consent form at the beginning of the study allowing the usage of this material.

Nested PCR for detection of HHV-DNA

The DNA was extracted from 200 μL of serum sample, according to the manufacturer's instructions (QIAamp DNA Blood Mini Kit, Cologne, Germany). The resulting DNA was eluted in 20 μL of TE-buffer. Two primer sets were used for each conserved region of HSV-1, HSV-2, VZV, EBV, HCMV, HHV-6 (types A and B), HHV-7, and HHV-8 DNA. HHV-DNA was detected in the serum samples using the NPCR technique. The primers used were chosen according to the respective authors [20–25]. The sizes of the NPCR amplification products

were 138, 101, 266, 209, 167, 195 (HHV-6 type A), 423 (HHV-6 type B), 264, and 213 base pairs, respectively. The same protocol was used to amplify the human β2-microglobulin gene sequence to ensure quality.

Degree of immunosuppression

The degrees of immunosuppression were estimated according to the protocol of the University of Campinas' Rheumatology Service: 0 – *No immunosuppression* = prednisone concentrations lower than 5 mg kg/day; 1 – *Low Immunosuppression* = prednisone concentrations greater than or equal to 5 mg kg/day and less than 30 mg kg/day; 2 – *Moderate Immunosuppression* = prednisone concentrations greater than or equal to 30 mg kg/day and less than or equal to 59 mg kg/day; 3 – *High Immunosuppression* = prednisone dosage greater than or equal to 60 mg kg/day and/or dosage of the following drugs: azathioprine, cyclophosphamide, methotrexate and methylprednisolone (pulse therapy) [26].

Criteria for confirming HHV infection or likely HCMV disease

In the studied patients' samples, the criterion for defining the presence of active HHV infection was the presence of one positive HHV-DNA result in the DNA extracted from the serum samples. HHV coinfection was considered in case of two or more positive HHV-DNA results in the same serum sample. The following isolated and/or combined symptoms were used to characterize active HHV infection, and/or likely HCMV disease: fever, headache, abdominal pain, seizure, changes in behavior, low levels of consciousness, mental confusion, motor dysfunction, neuropathy, paresthesia, drowsiness, vomiting, weakness, weight loss, myoclonus, memory loss, visual and psychomotor impairment, genital and orofacial herpesvirus, ocular infection, dermatitis, varicella, mononucleosis syndrome, Burkitt's lymphoma, nasopharyngeal carcinoma, Hodgkin's disease, HCMV colitis, retinitis, hepatitis, pneumonitis, *roseola infantum* or *exanthem subitum*, Kaposi's sarcoma, primary effusion lymphoma and Cattleman's disease [27–32].

Statistical methods

The data were analyzed using descriptive statistics (median and range for continuous variables and percentages for categorical variables). The significance level adopted for this study was 5%. Statistics were calculated using the SPSS 16.0 software.

Results

Table 1 shows the characteristics of the 71 patients included in the study.

It was observed that in patients with active SLE (SLEDAI equal to or greater than 8), HHVs-DNA detection in the DNA extracted from the serum samples occurred more frequently, and this difference was statistically significant between the serum samples extracted from the DNA of patients without active SLE (SLEDAI < 8), $p < 0.0001$ (Table 2).

Of these positive HHV results, 26.6% had HSV-1-DNA; 1/15 (6.6%) had HSV-2-DNA; 6/15 (40%) had HCMV-DNA; and 20% had HHV-7-DNA. Coinfection with HCMV+HHV-7 occurred in 2/15 (13.3%) of the DNA extracted from the serum samples; 1/15 (6.6%) patient tested positive for both HSV-1 and HHV-7-DNA.

Of the four patients with SLEDAI ≥8, three had HHV-1-DNA and one had HHV-7 + HCMV coinfection. These patients did not show viral symptoms.

Of the four patients with SLEDAI ≥8, two with HHV-7-DNA, one with HSV-1-DNA and one with HSV-2-DNA, none showed any HHVs symptoms (SLEDAI 8, 10, 12 and 9, respectively).

Table 3 presents the patients' HHV test results and correspondent SLEDAI score and clinical symptoms in case of positive HHV-DNA. More details can be seen supplementary materials.

Discussion

One of the most common viral infections in immunocompromised patients is that caused by HHV, due to the immunosuppressive therapy used to treat the disease itself in the cases of autoimmune diseases, favoring the activity and reactivation of these opportunistic agents, leading to severe diseases if the virus replicates [15].

Our main objective was to determine the presence of the genome of herpesviruses in DNA extracted from serum samples of patients with SLE attested in institutional protocols and receiving immunosuppressive treatment. High SLEDAI score and increased risk of development of HHV diseases, especially those caused by HCMV, could be observed ($p < 0.0001$).

NAAT (nucleic acid amplification test) was chosen for detection of the herpesvirus in the DNA samples (active infection). Nested PCR (NPCR) techniques were used for this purpose, due to their capacity of detection of viral HHV copies, low cost and fast diagnosis. These NAAT applications allowed the detection of viral DNA, which is a relevant indicator for patients with increased risk of developing viral diseases. Also, the use of serum samples avoids the detection of latent herpesvirus. HHV-DNA can only be found with NAAT in the serum

Table 2 Patients with Active HHV infection and the SLEDAI score

	Positive HHV	Negative HHV	*p**
Patients with SLEDAI ≥8	11	9	*0.0001
Patients with SLEDAI< 8	4	47	

Legend: *HHV* Human Herpesvirus, *HSV* Herpesvirus Simplex Virus, *SLEDAI* Systemic Lupus Erythematosus Disease Activity Index; *p* = *Fisher's Exact test

Table 3 Active HHV infection detected via Nested-PCR in the DNA extracted from the serum samples

Patient	Age (years)	HHV-DNA	SLEDAI	Clinical symptoms in case of positive HHV-DNA	DI	Drug
MJBS	20	HCMV+HHV-7	12	CNS vasculitis, leukocyturia, headache, weakness, urinary tract infection.	3	Pred+Mtx
SRGS	45	HCMV	12	**Hospitalization**. Edema, fever, vomiting and diarrhea, **HCMV disease in GIT**; ganciclovir treatment.	3	Pred+CP + Aza
MPM	34	HSV-1	12	Abdominal pains and heart cramps when in the ventral decubitus position and bilateral paresthesia.	2	Pred
NDRS	43	HCMV	11	**Hospitalization** for UTI (antibiotic) and disseminated SLE.	2	Pred+CFF
LRM[a]	31	HCMV	10	**Hospitalization died of pulmonary HCMV**. Leucopenia, acute respiratory failure, sepsis and multiple organs failure, generalized edema, tachypnea, fever, anemia, high HSV, low C3 and C4, proteinuria, hematuria	3	Metpred, Pred, CP, Pred.100 mg
MMS	27	HHV-7	10	**Hospitalization. Died of sepsis and refractory shock**. *Pseudomonas aeruginosa,* skin with SLE, weakness, drowsiness, joint pain, and little urination with generalized edema, arthralgia in hands, shoulder, hips, knees and ankles	3	Aza
MFO	48	HHV-7	10	Arthralgia, headache	1	Pred
AMSA	33	HSV-2	9	Convulsion for more than 8 days. Severe headache and persistent joint pain in the lower limbs.	3	Pred
MPP	24	HCMV	8	Proteinuria, hypertension, obesity	3	Pred+Aza
LSR	41	HHV1 + HHV-7	8	Proteinuria, *Candida albicans* onychomycosis, multipolar dermatofibroma, psoriasis versicolor	3	Metilpred
SM	33	HHV-7	8	Headache, photosensitivity	3	Aza
FDO	34	HCMV+ HHV-7	4	Articular pains in the hands, lumbar spine with edema; pain in the sacral region when moving	3	Mtx
MASP	47	HSV-1	1	Joint pain mainly in the hands, limb femoral arthralgia, asthma and idiopathic thrombocytopenic purpura	3	Pred
MAB	46	HSV-1	0	Arthritis, photosensitivity, autoimmune hepatitis, neutrophilic cutaneous vasculitis, esophageal varices, aseptic leukocyturia	3	Pred/Aza
CMT	23	HSV-1	0	Intermittent joint and lumbar pain, cough with mucoid expectoration	3	Pred/Aza

Legend: *DI* Degree of Immunosuppression, *HCMV* human cytomegalovirus, *HHV* human herpesvirus, *HSV* herpesvirus simplex, *SLEDAI* Systemic Lupus Erythematosus Disease Activity Index, *GIT* gastrointestinal tract, *UTI* urinary tract infection, *Pred* prednisone, *Mtx* pethotrexate, *CFF* ciprofloxacin, *Aza* pzathioprine, *Metpred* Pulse dosing of methylprednisolone, *CP* cyclophosphamide; [a]death by HCMV pneumonitis

of viremic patients, making it a useful tool for identifying patients with active infection [33–36].

Our main finding in this study was that patients with SLE are at increased risk of development of active infection and disease caused by these agents. Also, all patients who were hospitalized and those who died during the study had both HHV and SLEDAI ≥8.

Despite the fact some symptoms and classifications could have an association with a higher SLEDAI score, the replication of viral genetic material and the detection of this nucleic acids by NAAT can only be performed in patients in whom the virus is present and in circulation. However, distinguishing SLE manifestations from infection symptoms remains a challenge. Some authors mention the importance of new scores, which could include the use of biomarkers and other factors to make a more accurate determination of the worsening of patients with SLE, and allow a better differentiation of infections [15].

One of these patients was a 31-year-old woman with severe HCMV disease, who showed a series of symptoms (Table 3), such as fever, oral ulcers and edema, but also tachypnea, which leads to respiratory insufficiency. The pulmonary manifestation of HCMV disease, SLEDAI 10, was responsible for the death of this patient, showing the importance of medical monitoring to avoid the aggravation of SLEDAI score.

It is important to note that HHVs are ubiquitous viruses, HCMV being present in almost 100% of adults in developing countries (based on seroprevalence). In SLE reports, these HHV rates can achieve high levels, close to 90%. If a higher SLEDAI score actually leads to a higher probability of complications due to HCMV infection, and considering the prevalence of these viruses in some populations, this relation could mean an undesirable prognosis. The monitorization of SLE patients avoiding deleterious manifestations of the disease by seeking for a balance of SLE manifestations and the immunological status of the patient associated to the immunosuppressors intake, may propitiate a reduction of the SLE manifestations and allows the immunological response reduce the HHV infection risks and, consequently, lower the risk of death and morbidities [37].

The most studied interaction is that between EBV-SLE and VZV-SLE [38]. However, in this study, neither of

these viruses were observed. The lack of EBV-DNA-positive patients was also demonstrated in the study by Kosminsky, 2006 [39]. Besides the absence of VZV, HHV-6 (A and B) and HHV-8, the detection could be performed in patients with the latent form of these viruses, and a follow-up study observing the viral kinetics in determined circumstances, especially more severe immunosuppression, could propitiate these detections.

The importance of HHV in SLE patients comes from a dysregulated immune response against these viruses. A likely molecular mimicry between EBV antigens and those targeted in SLE combined with increased seroconversion to EBV is also suggested, indicating higher viral reactivation in patients with SLE [38]. Several studies reposted a possible modulation of the immune system by EBV, which would cause an increase in the autoimmune activity [40–44].

Recent studies have suggested that the association between HHV-7 and HCMV may raise the level of immunosuppression and increase the incidence of graft rejection, possibly due to it potentiating the effect of HCMV or modulating the recipient immune system [44–46]. This immunomodulation may predispose other opportunistic infections such as fungal invasion and other viral infections [47].

Immunomodulation is an important factor for the development of opportunistic infections, and therefore it is impossible to affirm which was the role of HHV-7 in a patient with blood culture positive for *Pseudomonas aeruginosa* who died of septic shock. HHV-7-DNA was detected but, the role of this viral detection is unclear.

HHV-7 seems to be more associated with solid organ transplants. HHV-7 and HCMV coinfection and immune modulation are important factors for this virus' pathogenic potential [48].

HHV-7 DNA was detected in the plasma of 6 patients, and in 5 of them, SLE was active. The other patient, whose SLE was not active (SLEDAI 4), had active infection with HHV-7, but also had active HCMV infection (identified as the 12th patient in Table 3). Symptoms associated with these infections were not observed in this patient.

Regarding HCMV, in this study, active HCMV infection was observed in 6 of 15 (40%) patients with active HHV infection, and of these, 5/6 (83%) had active lupus.

It was found that 28.6% of the children with SLE (6/21) tested positive for HCMV, also showing that the infection can occur prior to immunosuppressive therapy, but becomes more common after it [3].

This study detected the presence of HSV-1 and HHV-2-DNA in 5/71 patients (7%) in total, of whom 2/5 (40%) had active SLE disease. Infection caused by HSV-1, although uncommon, should be considered in patients with SLE showing atypical symptoms. SLE can be a serious condition and often requires prolonged intense immunosuppressive therapy, which may predispose to infections, particularly those with unusual organisms, such as patients affected by HSV-1. A delay and/or inadequate therapy can lead to life-threatening situations. The only patient with active HSV-2 infection also had active SLE disease, proving that HSV-1 and 2 must not be neglected when considering infections in SLE patients.

DNA virus detection in serum can be very useful for the clinical assessment of patients with SLE and for monitoring the disease's progression, which is important for clinical practice so as to avoid unnecessary immunosuppressive treatments and allow a better prognosis.

The main limitation of this study is the lack of multivariate analysis, especially by the fact that in SLE any occurrence of infection determines an increase in disease activity, which in turn requires a step-forward in the immunosuppressive treatment.

Finally, this study provides the basis for developing further studies on SLE and HHV. Tests for detection of HHV-DNA should be performed, especially in SLE patients with SLEDAI greater than or equal to 8 (lupus activity), with the clinical surveillance and laboratory detection of active HHV infection and a longitudinal follow-up.

Conclusion

This study suggests that patients with active SLE are at increased risk for the development of active HHV infections or reactivation, especially HCMV. Laboratorial screening to detect HHV-DNA using NAAT can be a tool for obtaining a more accurate diagnosis and a better prognosis, which may lead to a more suitable use of antiviral therapy.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s42358-020-00144-6.

Additional file 1. Information about the 15 patients with active viral infection and systemic lupus erythematosus (SLE).

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Authors' contributions

ADR, CM, MFP and SHAB designed the experimental procedure and conducted the data analysis, having also drafted and proofread the manuscript; LTLC, CLR, SCBC and LLL reviewed the design of this study and proofread the manuscript; SHAB coordinated all phases of the research in the Laboratory of Virology/FCM/UNICAMP, conceptualized and designed the

study, reviewed its design and proofread the manuscript. All authors approved the final manuscript prior to submission.

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Availability of data and materials
Not applicable.

Ethics approval and consent to participate
All procedures performed in this study were in accordance with the ethical standards for research involving human beings of the institutional ethical committee of State University of Campinas and Brazilian national research committee, and with the 1964 Helsinki declaration and its later amendments. The Research Ethics Committee (Comitê de Ética em Pesquisa - CEP) of the Faculty of Medical Science (Faculdade de Ciências Médicas – FCM) of State University of Campinas (Unicamp) approved this study under the 789/2006 project number.
All patients that the samples were included in this study have signed the written informed consent form at the beginning of the study allowing the usage of this material.

Consent for publication
Not applicable.

Competing interests
The authors declare no conflict of interest.

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