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Research Report

Analysis of the relationship between human cytomegalovirus DNA and gB-1 genotype in the saliva of HIV/AIDS patients with xerostomia and salivary flow rate

Irna Sufiawati,[1] S. Suniti,[1] Revi Nelonda,[1] Rudi Wisaksana,[2] Agnes Rengga Indrati,[3] Riezki Amalia[4] and **Isabellina Dwades Tampubolon[5]**
[1]Department of Oral Medicine, Faculty of Dentistry, Universitas Padjadjaran
[2]Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran
[3]Department of Clinical Pathology, Faculty of Medicine, Universitas Padjadjaran
[4]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran
[5]Molecular Biology Laboratory, Rajawali Hospital
Bandung – Indonesia

ABSTRACT

Background: *Human immunodeficiency virus (HIV) infection increases vulnerability to opportunistic viral infection, including Human cytomegalovirus (HCMV) infection, that has been detected in saliva. The HCMV envelope glycoprotein B (gB) is highly immunogenic and has been associated with HCMV-related diseases.* ***Purpose:*** *The purpose of this study is to assess the prevalence of HCMV and gB-1 genotype in the saliva of HIV/AIDS patients and to analyse their relationship with xerostomia and salivary flow rate (SFR).* ***Methods:*** *This cross-sectional study involved 34 HIV/AIDS patients. Saliva was tested for the presence of HCMV DNA using PCR microarrays, and nested PCR for gB-1 genotype detection. Xerostomia was measured using a Fox's questionnaire. Unstimulated whole saliva flow rate was measured by means of the spitting method.* ***Results:*** *The composition of the research population consisting of 73.5% males and 26.5% females with HIV/AIDS. HCMV was found in 64.7% of HIV/AIDS patients, while gB-1 genotype was detected in 59.1%. Xerostomia was closely associated with the presence of HCMV in saliva ($p<0.05$), but not with gB-1. There was no significant relationship between xerostomia and SFR rates in the research subjects with HCMV positive saliva ($p> 0.05$).* ***Conclusion:*** *The presence of xerostomia-associated HCMV in saliva was elevated among HIV/AIDS patients. Further investigation is required to identify other gB genotypes that may be responsible for xerostomia and SFR changes in HIV/AIDS patients.*

Keywords: *glycoproteins B-1; human cytomegalovirus; human immunodeficiency virus; xerostomia*

Correspondence: Irna Sufiawati, Department of Oral Medicine, Faculty of Dentistry, Universitas Padjadjaran. Jl. Sekeloa Selatan no. 1, Bandung 40132, Indonesia. E-mail: irna.sufiawati@fkg.unpad.ac.id

INTRODUCTION

Human cytomegalovirus (HCMV) or human herpesvirus 5 is a beta-herpesvirus classified as an opportunistic virus pathogen in patients infected with human immunodeficiency virus (HIV). HCMV may also play a role in HIV disease progression.[1] Epidemiological studies have confirmed a high seroprevalence of HCMV infection worldwide estimated at between 50% and more than 90% in HIV-infected individuals.[2–4] Previous studies conducted in West Java, Indonesia also indicated a high seroprevalence of HCMV in excess of 90%.[5] In addition to sera, several studies have investigated HCMV DNA in saliva by means of PCR microarrays as a useful method for the diagnosis of CMV infection.[6,7] The prevalence of HCMV in the saliva of HIV/AIDS patents has been reported as ranging from 5% to 50%.[8–11]

Of the various herpes virus (HHVs) families, HCMV is the largest HHVs member virus 100-nm in diameter, an icosahedral nucleocapsid containing a linear 230 kb double-stranded DNA surrounded by a protein layer called tegument. All particles are wrapped in a lipid bilayer envelope containing 6 gp, namely; gp UL55 (gB), gp UL73 (gN), gp UL74 (gH), gp UL100 (gM), and gp UL115 (gL).

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The gp UL55 or gB is a highly immunogenic virus envelope and plays an important role in the process of inserting the virus into the host cell, the spread from cell to cell, cell fusion, and ripening of the virion. HCMV gB genotype is classified into four main variants of genotypic gB (gB 1-4) based on the sequence of gB.[12–15] The gB genotype distribution among HIV/AIDS patients has been extensively studied with varying results.[16–18]

The responsibility of HCMV for a variety of diseases, including salivary gland dysfunction, with the most common symptom being xerostomia in HIV/AIDS patients, has been widely investigated.[19–22] Xerostomia is the subjective sensation of a dry mouth usually associated with low salivary flow rate (hyposalivation). However, xerostomia can occur with or without a decrease in saliva production and, thus, may not always be associated with salivary gland dsyfunction.[23] A previous study reported a strong relationship between the presence of HCMV DNA in saliva with xerostomia and salivary flow rate which suggests that HCMV may be a cause of salivary gland dysfunction in AIDS patients with low CD4 counts.[24] A compromised immune system in HIV-infected patients causes reactivation of HCMV.[25] The HCMV gB genotypes have also been studied to determine their role in the pathogenesis of HCMV-associated diseases.[26] The role of HCMV and its gB-1 gene as the risk factors causing xerostomia and salivary flow rate in HIV/AIDS patients remains unclear and has not been widely investigated. The present study was conducted to investigate the prevalence of HCMV and gB-1 genotype in the saliva of HIV/AIDS patients and to analyze its relationship with xerostomia and salivary flow rate (SFR).

MATERIALS AND METHODS

This cross-sectional study enrolled 34 HIV/AIDS patients, selected by consecutive sampling, who were not undergoing anti-retroviral therapy (ART) at Dr. Hasan Sadikin General Hospital, Bandung, West Java, Indonesia. The study included HIV/AIDS patients aged 18 or over, excluding those who were taking xerogenic drugs (except ART). Xerostomia was assessed by means of a Fox's questionnaire whose validity and reliability when written in Indonesian had previously been assessed.[27] The questionnaire consisted of the following four questions: "(1) Does the amount of saliva in your mouth seem to be a). too little, b). too much, or c). noticeable" (2) Do you have difficulties swallowing any particular foods? (3) "Does your mouth feel dry when eating a meal? (4) Do you sip liquids to help you swallow dry foods?". Positive responses to any of the preceding questions was considered to be evidence of xerostomia.[27] Unstimulated whole saliva flow rate was collected using the spitting method under standardized conditions with the rate being measured as previously reported.[28] Subjects expectorated the saliva into a test tube once a minute for a period of five minutes and the flow rate was recorded in ml/min. The research subjects were allocated to one of three groups (very low ≤ 0. 1/min, low 0.1-0.2 mL/min, and normal > 0.2 mL/min).[29] Ethical approval was granted by the Ethics Committee of the Faculty of Medicine, Universitas Padjadjaran no. 1433/UN6. KEP/EC/2018.

PCR microarrays were used to investigate positive HCVM DNA in saliva. The PCR used a primary sequence of 5'-TCATCTACGGGGACACGGAC-3' (forward primer) and 5'CGCACCAGATCCACG CCCTT-3' (reverse primer) and a positive control probe sequence of 5'-ACGAAAGCGGACAAACACG-3'.

To detect gB-1 HCMV positive saliva, a nested PCR was carried out at the Biomolecular Laboratory of Rajawali Hospital, Bandung. Nested PCR of primary PCR used primary primer with a sequence of 5'GGC ATC AAG CAA AAA TCT-3' (foward primer) and 5'CAG TTG ACG GTA CTG CAC-3' (reverse primer) HCMV to obtain an amplicon of gB-1 HCMV.6. The primers in the second stage of the inner PCR were 5'TGG AAC TGG AAC GG 3 GTT' (foward primer) and 5 '-GAA ACG CGC GGC AAT CGG-3' (reverse primer). The PCR-nested reaction was conducted with a final volume of 25 ul for each stage. For stage 1 PCR, 12.5 ul GoTaq Green Master Mix 2X (Promega) was added to each 2.5 ul outer primer (Macrogen) FHCMV1 and RHCMV2, 6.5 ul dH2O free RNAse (Promega) and 1 ul sample DNA.

The homogeneous mixture was then placed in an Analytik Jena Biometra thermal cycler and followed a stage 1 PCR program, which consists of an initial cycle at 95° C for two minutes, followed by 30 cycles of denaturation at 95° C for one minute, primary attachment at 60°C for 30 seconds, installation of nucleotide base (extension) at 72°C for one minute, and one final cycle extension at 72°C for five minutes. During stage 1, a negative control was included, where the DNA sample was replaced with dH2O free RNAse. For PCR stage 2, 12.5 ul GoTaq Green Master Mix 2X (Promega) was added to each 2.5 ul of primary inner (inner primer) (Macrogen): FHCMV3 and RHCMV4, 5.5 ul dH2O free RNAse (Promega) and 2 ul DNA from the results of stage 1 PCR.

The homogeneous mixture was then placed into an Analytik Jena Biometra thermal cycler and followed a first stage PCR program consisting of one cycle at 95°C for two minutes, followed by 35 denaturation cycles at 95°C for one minute, primary attachment at 68°C for 30 seconds, installation of nucleotide (extension) at 72° C for 1.5 minutes, and a final cycle extension at 72°C for seven minutes. In stage 2, the negative control DNA template was taken from the results of the first PCR negative control. The results of PCR electrophoresis were carried out using agarose gel (Promega) with 2% concentrated gel to which 2 ul of Etidium Bromide (Sigma) dye were added. The agarose gel was placed into the electrophoresis tank and TAE 1Xbuffer was added until it was flooded. 5 ul negative control, 5 ul of 100 bp DNA marker (Thermo Fischer) and 5 ul of PCR sample were subsequently added to the gel wells. Electrophoresis was carried out at a voltage of 75V

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for 25 minutes. Electrophoretic gel was placed on top of the UV laminator to visualize the DNA bands obtained which were recorded with digital cameras.

The data was analyzed using frequency variables with the results being presented in percentages. The relationship between the presence of HCMV in saliva and xerostomia and salivary flow rate were analyzed using Chi-Square and Mann Whitney Tests.

RESULTS

The present study was conducted on 34 HIV/AIDS patients consisting of 25 males (73.5%) and 9 females (26.5%). The highest percentage (61.8%) occurred in the 30-39 years age group and the lowest (2.9%) in the š50 years age group. The CD4 counts varied from 17 to 790 cells/mm^3, with up to 38.3% with CD4 counts <200 cells/mm^3, while up to 50% had received ART. The characteristics of the research subjects can be seen in Table 1.

In order to detect HCMV in the saliva of HIV/AIDS patients in this study, a microarray PCR technique was performed. The results showed that 22 (64.7%) of all subjects had HCMV DNA in their saliva (Figure 1). Furthermore, nested PCR was examined to detect the presence of gB-1 HCMV. The results of the analysis under an illumination beam in 2% algarose gel were detected in 13 positive patients (59.1%) and 9 negative patients (40.9%) (Figure 2). The positive results of nested PCR gB-1 HCMV amplification can be seen from the presence of a band which is indicated in the DNA marker location of 100 bp (M) with a location at 500bp (Figure 3).

The Fox's questionnaire results indicated that of the 22 HCMV positive subjects, 15 (68.2%) had complained of xerostomia and 12 (54.5%) had low SFR (Figure 4). A chi-square test was performed and confirmed a significant relationship between xerostomia and the presence of HCMV in saliva ($p<0.05$). The median salivary flow rate in HCMV positive subjects was 0.2 ml per minute lower than that of HCMV negative subjects of 0.4 ml/min, but no significant difference between the two groups on a statistical test ($p>0.05$) was detected. Low SFR (0.1–0.2 ml/min) in

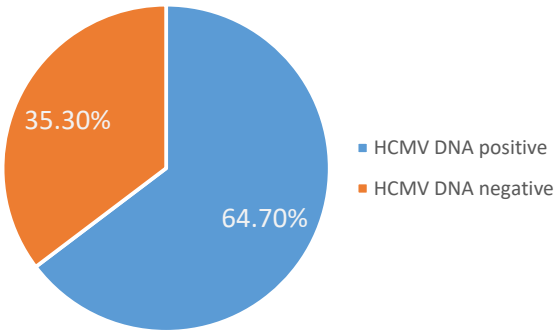

Figure 1. Prevalence of HCMV DNA in the saliva of HIV/AIDS patients.

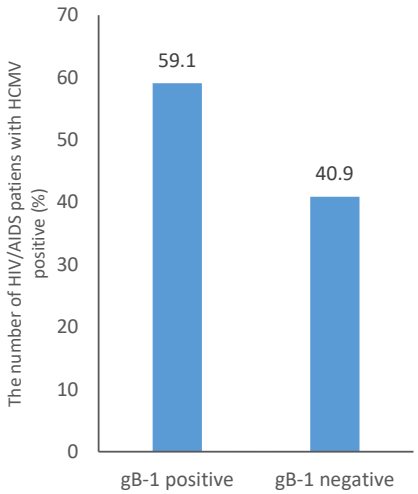

Figure 2. Prevalence of gB-1 genotype in saliva among HCMV-positive HIV/AIDS patients.

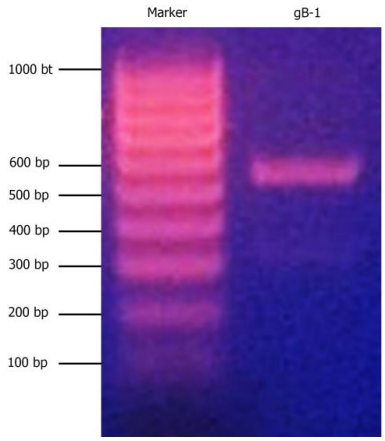

Figure 3. The band of gB-1 gene detected in the saliva of HCMV-positive HIV patients at 500bp with 100bp marker (M) DNA using nested PCR.

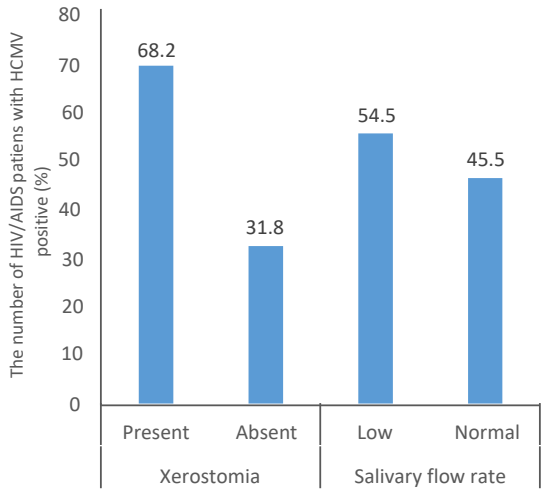

Figure 4. The prevalence of xerostomia and salivary flow rate among HCMV positive HIV/AIDS patients.

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HCMV positive subjects was 54.5%, whereas only 25.0% in HCMV negative subjects, but no statistically significant different was found between the two groups (p>0.05) (Table 2). When identifying the relationship between xerostomia and salivary flow rates in HCMV positive saliva, statistical analysis revealed that there was no significant relationship between the two conditions (p> 0.05) (Table 3).

Furthermore, eight (66.7%) of subjects with gB-1 genotype positive were found to have experienced xerostomia. However, as seen from the contents of Table 4, there was no statistically significant relationship between xerostomia and gB-1 genotype (p<0.05).

Table 1. Characteristics of the research subjects

Basic characteristics	Number
Gender	n = 34
Male	25 (73.5%)
Female	9 (26.5%)
Age	32 ± 0.88
18-29 years	12 (35.3%)
30-39 years	19 (55.9%)
40-49 years	2 (5.9%)
> 50 years	1 (2.9%)
CD4 (cells/mm^3)	
Median (min-max)	262 (17-790)
> 500	6 (17.6%)
350-499	7 (20.6%)
201-349	8 (23.5%)
<200	13 (38.3%)
Received anti-retroviral therapy	
Yes	17 (50%)
No	17 (50%)

DISCUSSION

In the present study, HCMV in saliva was detected in 64.7% of HIV/AIDS patients. This finding showed that the prevalence of HCMV in saliva was higher than in the published studies that had reported it as ranging from 5% to 50%.[8–11] It is well known that HCMV is transmitted through direct contact with the saliva or other bodily fluids of a HCMV-infected person. HCMV can be transmitted vertically (from mother to child in utero or through breastfeeding) and horizontally (person-to-person either through sexual contact and or contact with infected body fluids). In comparison with serologic studies that indicated the higher prevalence of HCMV positive in the sera of HIV patients (ranging from 50% to 90%)[2–4] than in saliva specimens, indicating that risk factors for horizontal HCMV transmission is more common than vertical.

In children, HCMV is most frequently found in their urine, but it is also often present in their saliva. Among adults, sera and genital secretions are both common fluids for HCMV shedding indicating that sexual transmission is considered a major route of HCMV transmission. However, HCMV can also be detected in saliva and, therefore, spread through kissing or oral sex between adults.[30,31] In HIV positive individuals, one suggested mechanism of viral opportunistic transmission (including HCMV) may be the sub-epithelial and intra-epithelial immune cells in the oral cavity becoming infected with HIV. HIV gp120 and Tat protein may induce tight junction disruption and lead the opportunistic virus to penetrate the oral mucosal epithelium.[32]

The distribution of HCMV gB genotypes in AIDS patients has also been widely investigated through analysis

Table 2. Relationship between xerostomia and the flow rate of saliva containing HCMV in HIV/AIDS patients

	Human cytomegalovirus DNA in saliva		p-value
	(+) n=22	(-) n=12	
Xerostomia, n (%)			
Present	15 (68.2)	4 (33.3)	0.051[a]
Absent	7 (31.8)	8 (66.7)	
Saliva flow rate (ml/min)			
Median (Min–Max)	0.2 (0.2 – 0.7)	0.4 (0.2 – 0.6)	0.230[b]
Saliva flow rate, n (%)			
0.1 – 0.2 (ml/min)	12 (54.5)	3 (25.0)	0.097[a]
> 0.2 (ml/min)	10 (45.5)	9 (75.0)	

[a]Analysis using chi-square test, [b]Mann Whitney test

Table 3. Relationship between xerostomia and the flow rate of saliva in HCMV-positive HIV/patients

	Saliva flow rate		p-value
	0.1 – 0.2ml/ min n=12	>0.2 ml/ min n=10	
Xerostomia, n (%)			
Present	10 (83.3)	5 (50)	0.172*
Absent	2 (16.7)	5 (50)	

*Analysis using the Fisher's exact test

Table 4. Relationship between xerostomia and gB-1 genotype in HIV/AIDS patients

Xerostomia	HCMV gB-1 Genotype		p-value
	Present n=12	Absent n=18	
Present	8 (66.7)	6 (33.3)	0.135*
Absent	4 (33.3)	12 (66.7)	

*Analysis using Fisher's exact test

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of blood, urine, semen, vitreous, and saliva specimens. The gB-1 HCMV present in saliva was detected in 57.1% of HIV/AIDS patients. This finding is consistent with those of previous studies showed that gB1 was found to be the predominant glycoprotein genotype (86.96%) among HCMV-infected AIDS patients.[16] Similar results have been reported that the most frequent HCMV genotype was gB1 followed by other genotypes among organ transplant patients in Turkey.[33] However, other studies confirmed that gB3 and gB2 were the most prevalent genotypes in the sera of AIDS patients and HCMV-infected neonates and a high incidence of mixed infection with the gB1 and gB3 genotypes.[34,35]

HCMV is known to be responsible for a variety of diseases, for example, in the oral cavity; persistent and atypical mucosal ulcers and xerostomia potentially accompanied by salivary gland dysfunction.[36] The prevalence of xerostomia among HIV-infected patients, has been estimated to range from 1.2 to 40%[22] and reduced salivary flow rate occurs in 2-30% of subjects.[37] The findings of the research reported here indicated that 68.2% of the subjects whose saliva contained HCMV positive had xerostomia, while 54.5% of the subjects experienced a low unstimulated salivary flow rate (0.1-0.2 ml/min). Statistical analysis confirmed a significant relationship between the presence of HCMV in saliva and xerostomia.

This finding is consistent with that of a prior study demonstrating a link between HCMV in saliva and salivary gland dysfunction in HIV-infected patients.[24,38] Meanwhile, this investigation revealed no significant relationship between the presence of HCMV in saliva and the salivary flow rate. However, the median of salivary flow rate in HCMV positive saliva was lower at 0.2 ml/min than that of HCMV negative saliva at 0.4 ml/min. In contrast, a previous study observed that significant xerostomia, reduction in salivary flow rate and flavor alteration were all evident in HIV-positive patients receiving highly active antiretroviral therapy (HAART).[39] As seen in the present study, Xerostomia, a subjective complaint of dry mouth, is not always correlated to hyposalivation as objective reduction of salivary flow rates[40,41]. Xerostomia can also be experienced by patients with a normal salivary flow rate.

There are multiple causes of salivary gland dysfunction related to HCMV and HIV with various mechanisms. Several researchers have suggested that HCMV is often detected in the salivary gland during primary infection and reproduces in the oral epithelium. The local HCMV reactivation affecting the major salivary glands is responsible for xerostomia.[21,42] Salivary gland disfunction associated with HIV/AIDS has also been suggested as the result of diffuse infiltration of $CD8^+$ lymphocyte in salivary glands causing suppression of salivary gland functions.[43,44] A number of investigators have also reported that oral manifestation of HCMV correlates with the severity of immunosuppression in AIDS patients with CD4 counts below 100 cells/mm3 in the disseminated form of the disease.[37] This indicates that HCMV reactivation in HIV-infected patients may occur under advanced immunosuppressive conditions.

HIV infection induces the loss of and dysfunction in $CD4^+$ T cells, a failure to support $CD8^+$ T cells which leads to an increase in their expansion and causes greater HCMV replication. Signals from HCMV infection may also promote HIV persistence in $CD4^+$ T cells. $CD8^+$ T cell expansion, coupled with a loss of $CD4^+$ T cells, is linked to morbid outcomes of HCMV and HIV infections.[44] Furthermore, antiretroviral drugs (including nucleoside transcriptase inhibitors and protease inhibitors) may also cause xerostomia or hyposalivation.[37] However, the exact mechanism by which this ART can lead to salivary disfunction remains unclear. The suggested mechanism may be due to alteration of the structure and composition of saliva due to the chemical structure of antiretroviral drugs leading to a reduced salivary flow rate. In addition, antiretroviral drugs can alter adipose tissue deposition within the salivary gland itself.[44]

Differences in the gB HCMV genotype may play an important role in the pathogenesis of the disease.[26,34] It has been also reported that gB HCMV in immunocompromised individuals contributes to the molecular epidemiology and genetic variability of viruses in clinical manifestations and prognoses.[45] The research findings reported here indicated that there was no statistically significant relationship between the gB-1 genotype and the occurrence of xerostomia, although the majority of subjects (66.7%) with positive gB-1 genotype experienced xerostomia. Other gB genotypes or mixed infection with more than one gB in HIV/AIDS patients might be responsible for the occurrence of xerostomia and changes in salivary flow rate, as reported in previous studies. Therefore, further research is required to confirm the situation.

In conclusion, the high prevalence of HCMV and gB-1 gene in the saliva of HIV/AIDS patients supports the hypothesis that saliva constitutes an important reservoir for HCMV. There was a statistically significant relationship between xerostomia and the presence of HCMV in the saliva of HIV/AIDS patients. However, there was no statistically significant relationship between HCMV gB-1 and salivary flow rate. Studies featuring larger sample sizes are required to identify other gB genotypes as the specific risk factors associated with HCMV-related xerostomia and hyposalivation in HIV/AIDS patients.

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