J Infect Chemother xxx (2016) 1–5

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original Article

Cross-sectional and longitudinal investigation of human herpesvirus 8 seroprevalence in HIV-1-infected individuals in Osaka, Japan

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ARTICLE INFO

Article history:
Received 29 September 2016
Received in revised form
1 December 2016
Accepted 13 December 2016
Available online xxx

Keywords:
HHV-8
HIV-1
Seroprevalence
Seroconversion

ABSTRACT

Introduction: High human herpesvirus 8 (HHV-8) seroprevalence has been reported in men who have sex with men (MSM) and are infected with HIV-1. However, it is unclear when they become infected with HHV-8. Thus, we conducted cross-sectional and longitudinal investigations of HHV-8 seroprevalence in HIV-1-infected individuals in Osaka, Japan.

Patients and methods: Plasma was collected from 121 individuals infected with HIV-1 and the anti-HHV-8 antibody titer was measured using an enzyme-linked immunosorbent assay with whole virus lysate. Subjects were classified into those with and without a past medical history of HHV-8-associated disease; the latter group was then classified into 3 subgroups based on the assumed route of HIV-1 infection: blood products, homosexual contact, and other routes. HHV-8 seroprevalence was compared among the groups and measured again approximately 3 years after the baseline measurement. The relationship between HHV-8 seropositivity and possible associated factors was also investigated.

Results: All 15 subjects with HHV-8-associated disease were seropositive, and all 11 subjects in the blood product group were seronegative. In the MSM group, 25 (30%) of 79 subjects were HHV-8 seropositive and, in the non-MSM group, 1 (6%) of 16 subjects was ($p < 0.0001$). In the longitudinal investigation, seroconversion was observed in 10 (19%) of 52 subjects in the MSM group who were seronegative at baseline. A correlation was observed between seroconversion and symptomatic syphilis ($p = 0.0432$).

Conclusions: HHV-8 seropositivity and seroconversion rates were high in HIV-1-infected MSM, suggesting that, currently, HHV-8 is an epidemic pathogen in this population.

1. Introduction

Human herpesvirus 8 (HHV-8), also known as Kaposi's sarcoma (KS)-associated herpesvirus, is a virus of the Herpesviridae family. In addition to KS [1,2], HHV-8 is involved in the development of primary effusion lymphoma and multicentric Castleman's disease (MCD) [3,4]. The anti-HHV-8 antibody is detected in the blood of almost all KS patients. In Western countries, HHV-8 seroprevalence is low in the general population, but is higher in individuals infected with human immunodeficiency virus 1 (HIV-1), particularly those infected with HIV-1 through homosexual contact [5–7]. Likewise, high HHV-8 seroprevalence in HIV-1-infected men who have sex with men (MSM) has been reported in Japan [8,9]. In a Japanese study reported in 2000 by Katano et al. [8], HHV-8 seroprevalence was 1.4% in the general population, 63.6% in HIV-infected subjects infected through sexual intercourse without a past medical history of KS, and 100% in acquired immune deficiency syndrome patients who developed KS. However, HHV-8 seroprevalence was 0% in subjects infected with HIV-1 through blood products [9,10].

Many studies of HHV-8 seroprevalence are cross-sectional only. In addition, the routes and opportunity of HHV-8 infection have not

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http://dx.doi.org/10.1016/j.jiac.2016.12.007
1341-321X/

yet been clearly determined. Therefore, it is unclear when HIV-1-infected individuals were infected with HHV-8. To elucidate these, we carried out cross-sectional and longitudinal investigations of HHV-8 seroprevalence in HIV-1-infected individuals in Osaka, Japan, and compared HHV-8 seroprevalence among our study groups.

2. Patients and methods

2.1. Subjects and measurement of anti-HHV-8 antibody titer

This study was performed after approval by the Institutional Review Board of the National Hospital Organization Osaka National Hospital (approval number: 11061). Written informed consent was obtained from all subjects. The subjects were 121 HIV-1-infected individuals who visited the National Hospital Organization Osaka National Hospital from April to September 2009; they were selected without use of random sampling techniques because proportionally more individuals than occurred randomly in the hospital population were needed to obtain serum for the positive control group. Plasma was collected and the anti-HHV-8 antibody titer was measured using an enzyme-linked immunosorbent assay (ELISA) kit with whole virus lysate (Advanced Biotechnologies Inc., Columbia, MD) [11]. The signal-to-cut-off absorbance ratio (S/CO) was calculated with the cut-off value at an absorbance 3 times higher than that of the negative control. An S/CO ratio of 0.75 or lower, higher than 0.75 and lower than 1.0, and 1.0 or higher were judged as negative, borderline positive, and positive for anti-HHV-8 antibodies, respectively.

2.2. Cross-sectional and longitudinal investigation

The subjects were classified into the following 4 groups: the KS/MCD group comprised 15 subjects (12%) with a past medical history of HHV-8-associated disease (KS, primary effusion lymphoma, and MCD) and served as a putative anti-HHV-8 antibody-positive population. The remaining 106 subjects (88%), with no past medical history of HHV-8-associated disease, were classified into 3 subgroups based on the assumed route of HIV-1 infection: subjects, such as hemophilia patients, in whom the route of infection was blood products, were designated as the blood product group (11 subjects, 9%); men in whom the assumed route of HIV-1 infection was homosexual contact were designated as the MSM group (79 subjects, 65%); and the remaining subjects were designated as the non-MSM group (16 subjects, 13%). HHV-8 seroprevalence was compared among the groups. Multivariate logistic regression analysis was performed to investigate factors related to HHV-8 seropositivity. Analysis was performed using the forced entry method on the following variables: sex, age (40 years old or older), nationality (Japanese), assumed route of HIV-1-infection (homosexual contact), CD4 count (greater than 350 cells/μL), and the presence or absence of anti-HIV therapy and HHV-8-associated disease.

The anti-HHV-8 antibody titer was measured at 2 time points (April–September 2009 and June–August 2012), and seroconversion and seroreversion rates were determined. Data on sexually transmitted infectious diseases (STDs) newly developed between these time points were collected from medical records, and their association with the anti-HHV-8 antibody was investigated. Data were collected on the following symptomatic STDs: syphilis, amebiasis, gonococcal infection, genital chlamydial infection, and acute hepatitis B and C.

2.3. Statistical analysis

Logistic regression analysis was performed as described above. The χ^2 test was used for 4 × n cross tabulation analyses, and Fisher's exact test for 2 × 2 cross tabulation analyses. For intergroup comparisons of continuous variables, the Wilcoxon rank-sum test was used. The significance level was set at 5%. These analyses were performed using JMP 11.2.1 software (SAS Institute, Cary, NC). The seroconversion rate of anti-HHV-8 antibody was calculated using the person-years method on the assumption that seroconversion occurred at the midpoint between baseline and follow-up HHV-8 seropositivity assays. The 95% confidence interval for seroconversion was calculated using R software, version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

The baseline characteristics of the study subjects are shown in Table 1. Plasma was assayed for anti-HHV-8 antibody. Of the 121 subjects, 15 (12%) had a past medical history of HHV-8-associated disease: 1 subject had a past medical history of MCD and the other 14 subjects had a past medical history of KS. They were served as a putative anti-HHV-8 antibody-positive population. Eleven subjects infected with HIV-1 through blood products served as a putative anti-HHV-8 antibody-negative population. The assumed route of HIV-1 infection was homosexual contact in the majority of cases (92 subjects, 76%). The plasma HIV-1-RNA level was suppressed below 40 copies/mL in 90 (74%) of the 99 subjects (82%) who had received antiretroviral therapy.

3.1. Comparison of HHV-8 seroprevalence among the groups

The subjects were classified into 4 groups based on the presence or absence of a past medical history of HHV-8-associated disease and the probable route of HIV-1 infection, as described in the Patients and Methods section. The S/CO ratios of anti-HHV-8 antibody in these groups are shown in Fig. 1. All subjects in the KS/MCD group were HHV-8 seropositive, and the S/CO ratios were far higher than the reference value for a positive test result (1.0). In contrast, in the non-MSM and blood product groups, only 1 subject (from the non-MSM group) was seropositive. The S/CO ratios (range: 0.28–0.38) in seronegative subjects in these 2 groups were far lower than the reference value for a negative test result (0.75). In the MSM group, the S/CO ratio was continuously distributed from a

Table 1
Characteristics of participants at baseline.

Age (year), median [range]	41	[23–77]
Males (n, %)	116	(96%)
History of HHV-8 related diseases (n, %)		
Kaposi's sarcoma	14	(12%)
Multicentric Castleman's disease	1	(1%)
None	106	(87%)
Assumed route of HIV-1 infection (n, %)		
Homosexual	92	(76%)
Heterosexual	16	(13%)
Blood products	11	(9%)
Others	2	(2%)
Nationality		
Japanese	118	(98%)
Non-Japanese	3	(2%)
Current ART use (n, %)	99	(82%)
CD4 cell count (cells/μL), median [IQR]	371	[252–483]
HIV-1-RNA level (copies/mL), median [IQR]	<40	[<40–45]
Participants with HIV-1-RNA level < 40 copies/mL (n, %)	90	(74%)

Abbreviations: HHV-8 = human herpes virus 8; HIV-1 = human immunodeficiency virus 1; ART = antiretroviral therapy; IQR = interquartile range.

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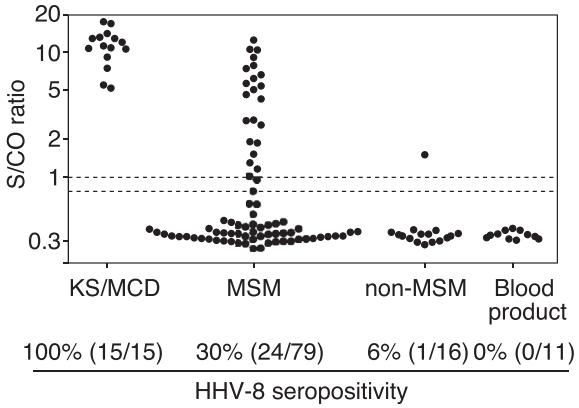

Fig. 1. Distribution of the S/CO ratio for HHV-8 seropositivity and HHV-8 seropositive rates in groups of HIV-1-infected individuals. Dots represent the signal to cut-off absorbance (S/CO) ratio of anti-HHV-8 antibody titer measured by ELISA for each subject by group. Two dotted lines represent the reference value distinguishing HHV-8 seropositive from borderline results, and borderline from seronegative results, respectively. The seropositive rate is shown by group. The 2 subjects judged as borderline positive were classified as seropositive. Statistical analysis was performed using the χ^2 test ($p < 0.0001$). Abbreviations: S/CO = signal-to-cut-off absorbance; HHV-8 = human herpesvirus 8; HIV-1 = human immunodeficiency virus 1; KS/MCD = Kaposi's sarcoma/multicentric Castleman's disease; MSM = men who have sex with men; ELISA = enzyme-linked immunosorbent assay.

high to low value without interruption. The S/CO ratio was within the borderline positive range (0.76–0.99) for 2 subjects. As the S/CO ratio was far lower than 0.76 in the blood product group, assumed to be an anti-HHV-8 antibody-negative population, a borderline positive result was regarded as positive. Seroprevalence in the MSM group was 30%.

3.2. Factors associated with HHV-8 seropositivity

Factors associated with HHV-8 seropositivity were investigated using logistic regression analysis (Table 2). On univariate analysis, being male, homosexual contact as the assumed route of HIV-1 infection, and a past medical history of HHV-8-associated disease were significantly associated with HHV-8 seropositivity. No association was observed between age (≥40 or not) and HHV-8 seropositivity. For a detailed analysis of the association between age and HIV-8 seropositivity, all subjects were divided into 4 categories according to median and interquartile age ranges, and then univariate logistic regression analysis was performed. No significant association was found ($p = 0.1103$). On multivariate analysis, homosexual contact as the assumed route of infection, and a past medical history of HHV-8-associated disease were independent associated factors (Table 2).

3.3. Longitudinal investigation of changes in HHV-8 seropositivity, seroreversion and seroconversion rates, and factors associated with these.

A longitudinal investigation was performed. Anti-HHV-8 antibody levels were assayed in the 115 subjects at 2 time-points: baseline and follow-up. The duration of the period between baseline and follow-up ranged from 2.8 to 3.3 years, and the median was 2.9 years. Changes in HHV-8 seropositivity are shown in Table 3. No change in HHV-8 seropositivity was observed over the period from baseline to follow-up in any subject in the KS/MCD, non-MSM, or blood product group, whereas, in the MSM group (74 subjects), seroconversion and seroreversion of anti-HHV-8 antibody were noted in 10 and 2 subjects, respectively. The S/CO ratio rose six-fold or more in 8 of the 10 seroconverted subjects. In the 2 subjects in whom the increase in S/CO ratio was less than six-fold, the baseline S/CO ratios were 0.38 and 0.4, respectively, which were approximately equivalent to those of the blood product group. We followed 52 subjects in the MSM group who were HHV-8 seronegative at the baseline. The seroconversion rate over the approximate 2.9-year observation period was 19%. On the assumption that they were infected at the midpoint between baseline and follow-up, the total observation period was calculated to be 139 person-years and the incidence of HHV-8 infection was estimated to be 7.2 per 100 person-years (95% confidence interval: 3.4–13.2). Lastly, factors associated with anti-HHV-8 antibody seroconversion were investigated (Table 4). Seroconversion was not associated with immune status at baseline or follow-up, or the presence or absence of treatment with antiretroviral therapy, but it was associated with the development of symptomatic STDs including syphilis during the observation period.

4. Discussion

HHV-8 seroprevalence in HIV-1-infected subjects was higher (30%) in the MSM than in the non-MSM groups, and all subjects infected through blood products were negative for the anti-HHV-8 antibody. Our findings are consistent with those previously reported in Japan, although seroprevalence is different [8–10]. Katano et al. measured the anti-HHV-8 antibody titer using ELISA with mixed antigen, and observed that seropositivity was 63.6% in subjects without a past medical history of KS infected with HIV-1 through sexual intercourse. Fujii et al. measured anti-HHV-8 antibody levels using an immunofluorescence assay with a single antigen and observed that HHV-8 seroprevalence was 12% in HIV-1-infected subjects and that MSM was the most important risk factor. When comparing these results, it should be noted that there is no gold standard anti-HHV-8 antibody measurement method [13–15]. Measurement was performed with a single antigen in

Table 2
Association between variables and HHV-8 seropositivity at baseline.

	Univariate results			Multivariate results		
	OR	95% CI	p-value	OR	95% CI	p-value
Sex (male vs. female)	5.7×10^6	1.1–∞	0.0442*	2.8×10^{13}	0.230–∞	0.2305
Age ≥40 years	1.0	0.48–2.2	0.9465	0.93	0.34–2.5	0.8887
Nationality (Japanese vs. non-Japanese)	0.98	0.09–21.6	0.9918	3.6×10^{-8}	0–3.2	0.1478
Assumed route of HIV-1 infection (homosexual contact vs. non-homosexual contact)	5.8	1.9–26	0.0013*	9.2	1.7–171	0.0066*
CD4 cell count ≥350 cells/μL	1.0	0.48–2.2	0.9408	1.4	0.51–4.2	0.5181
ART use at baseline (yes vs. no)	1.9	0.67–6.0	0.2426	1.8	0.55–6.9	0.3542
History of HHV-8-related diseases	9.5×10^7	23–∞	<0.0001*	3.7×10^8	28–∞	<0.0001*

Abbreviations: HHV-8 = human herpesvirus 8; OR = odds ratio; CI = confidence interval; HIV-1 = human immunodeficiency virus 1; ART = antiretroviral therapy.
* Significant value.

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Table 3
Longitudinal investigation of HHV-8 seropositivity at baseline and follow-up.

HHV-8 status at baseline	At follow-up	KS/MCD group (n = 9)	MSM group (n = 74)	Non-MSM group (n = 15)	Blood product group (n = 11)
Positive	Positive	9 (100%)	20 (27%)†	1 (7%)	0 (0%)
Positive	Negative (seroreversion)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Negative	Positive (seroconversion)	0 (0%)	10 (14%)‡	0 (0%)	0 (0%)
Negative	Negative	0 (0%)	42 (57%)	14 (93%)	11 (100%)

Abbreviations: HHV-8 = human herpesvirus 8; KS/MCD = Kaposi's sarcoma/multicentric Castleman's disease; MSM = men who have sex with men.
Statistical analysis was performed using the χ^2 test ($p < 0.0001$); † including borderline results at both time-points (n = 1), borderline to positive (n = 1), and positive to borderline (n = 1); ‡ including negative to borderline results from baseline to follow-up time-points (n = 2).

Table 4
Comparison between seroconverters and non-seroconverters in the MSM group.

		Non-seroconverters (n = 42)	Seroconverters (n = 10)	p-value
At baseline	Age (year), median [range]	40 [24–77]	44 [26–68]	0.593
	CD4 cell count (cells/μL), median [IQR]	391 [232–534]	373 [147–599]	0.6591
	HIV-1-RNA level (copies/mL), median [IQR]	<40 [<40–3585]	<40 [<40–31,780]	0.626
	ART use (n, %)	30 (71%)	8 (80%)	0.7096
At follow-up	CD4 cell count (cells/μL), median [IQR]	395 (301–542)	479 (375–636)	0.2364
	HIV-1-RNA level (copies/mL), median [IQR]	<20 (<20–45)	<20 (<20–35.5)	0.4431
	ART use (n, %)	34 (81%)	10 (100%)	0.3278
Between baseline and follow-up	All symptomatic STDs	5 (12%)	5 (50%)	0.0151*
	Syphilis	2 (5%)	3 (30%)	0.0432*
	Acute hepatitis C	0 (0%)	1 (10%)	0.1923
	Amebiasis	3 (7%)	1 (10%)	1.0

Abbreviations: MSM = men who have sex with men; IQR = interquartile range; HIV-1 = human immunodeficiency virus 1; ART = Antiretroviral therapy; STD = sexually transmitted disease.
* Significant value.

some reports, whereas 2 or more antigens or whole virus lysate, as in our study, were used in others. The sensitivity is not 100% when only a single antigen is used, regardless of the antigen. In addition, only moderate correlation between different antigens is reported. When the anti-HHV-8 antibody is assayed using 2 tests, the sample can be judged to be seropositive when both tests are positive, or alternatively when only 1 of the 2 tests is positive. The former approach is adopted when greater importance is attached to the specificity, and the latter when sensitivity is necessary [14]. Therefore, it is impossible to compare seroprevalence directly using different methods, and one reason for the variation in the positive rate reported from Japan may be adoption of different methods. The incidence of HHV-8 infection (7.2 in 100 person-years) in our study may have been underestimated because the antigen for ELISA used in this study may lack latent proteins of HHV-8, such as ORF73 protein/LANA [8,16].

The ELISA kit in this study showed good sensitivity and good specificity for the KS/MCD and blood product groups, which served as antibody-positive and antibody-negative populations, respectively. However, the S/CO ratio of the KS/MCD group was far higher than the cut-off value, and that of the blood product group was far lower. The high S/CO ratio for the positive control may have resulted in antibody-positive individuals with low S/CO ratios being missed, indicating reduced sensitivity. We cannot exclude the possibility of false negative results from antibody-positive subjects in the MSM group, whose S/CO ratios ranged from approximately 0.5 to 0.74.

Data from longitudinal investigations of the anti-HHV-8 antibody in HIV-1-infected individuals is limited [17,18]. A seroconversion rate of 18% in a cohort after 1 year was reported from Brazil [17]. In that study, the participants were recently infected with HIV-1 and hence untreated with antiretroviral therapy at baseline. In our study, the seroconversion rate was 19% over approximately 3 years, which was also relatively high compared with the seroprevalence in the general population. The viral load was suppressed with antiretroviral therapy at baseline in 74% of our subjects, and seroconversion was not associated with the immune condition at baseline or follow-up, or the presence or absence of treatment with antiretroviral therapy. Recently, it was reported that the incidence of HHV-8 seroconversion in the HIV-1-infected US population was 4.07 in 100 person-years [18]. This study showed that the increasing CD4 cell count associated with antiretroviral therapy resulted in an approximate reduction in HHV-8 seroconversion of approximately 40%. Although antiretroviral therapy might play a protective role against HHV-8 infection, these observations indicated that even subjects in an improved immunological and virological state were frequently exposed to and infected with HHV-8. An association between the risk of STDs and HHV-8 seroprevalence has previously been observed [5,9], and our longitudinal investigation has clarified the direct association. In our study, STDs other than syphilis were not significantly associated with HHV-8 seroconversion. A possible reason for this is that syphilis was the most common STD in our cohort, and STDs other than syphilis lacked statistical power owing to the small number of cases.

In our study, seroreversion of anti-HHV-8 antibody was observed in 2 subjects. Possible reasons for seroreversion include the requirement of persistent antigen exposure to maintain HHV-8 seropositivity and technical error. However, technical error was unlikely because seroconversion and seroreversion were observed only in the MSM group, not in the other groups, suggesting good reproducibility. Although HHV-8 seroreversion has not been fully characterized, some studies report cases of HHV-8 seroreversion in HIV-1-infected individuals [15,19–22], indicating that HHV-8 seroreversion does not seem to be rare.

The number of subjects with HHV-8 seroconversion (n = 10) was greater than those who developed symptomatic syphilis (n = 5). Although asymptomatic syphilis was excluded from the analysis whereas HHV-8 infection is usually asymptomatic [23], HIV-1-infected MSM may be more frequently exposed to HHV-8 than to syphilis. In a study of HHV-8 seroprevalence among HIV-negative MSM in Nagoya, Japan, HHV-8 seropositivity (12%) was higher than seropositivity for syphilis (5%) and other STDs [12].

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Limitations of this study include that it was performed using a single measurement system at a single institution, and that not all STDs were detected because patients with asymptomatic STDs were excluded from analysis in the longitudinal study and seromarkers for STDs were not examined at baseline and follow-up. In addition, our results cannot reveal the route and opportunity of HHV-8 infection, although the timing of HHV-8 infection and its associated factors were clarified. Careful interpretation of our results is required because the route of HHV-8 infection may vary depending on the target population, as do the risk factors for contracting HHV-8. For example, reported risks for HHV-8 infection include an HHV-8 seropositive person at home and exposure to blood [24–26].

Despite the limitations of our study, HHV-8 seroprevalence was high in MSM infected with HIV-1. In addition, the HHV-8 seroconversion rate was high in these subjects, and an association between seroconversion and STDs was observed. These findings suggest that HHV-8 is still an epidemic pathogen among HIV-1-infected MSM.

Conflict of Interest

The authors do not have any commercial or other association that may pose a conflict of interest.

Acknowledgements

We are grateful to all the study participants. This work was partially supported by a Grant-in-Aid for AIDS research from the Ministry of Health, Labor, and Welfare of Japan to TU (H23-AIDS-Ippan-002), and by Research Program on HIV/AIDS from the Japan Agency for Medical Research and Development (AMED) to DW. We would like to thank Editage (www.editage.jp) for English language editing.

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