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Original Article

Risk for the occupational infection by cytomegalovirus among health-care workers☆

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ABSTRACT

Background: Cytomegalovirus (CMV) are ubiquitously distributed worldwide, causing a wide range of clinical manifestations from congenital infection to a life-threatening disease in immunocompromised individuals. CMV can be transmitted via human-to-human contact through body fluids; however, the risk of CMV infection among healthcare workers (HCWs) has not been fully evaluated.
Aim: This study aimed to assess the risk of CMV infection among HCWs through daily medical practices.
Methods: Serum samples from HCWs at Osaka University Hospital (Japan) were analysed. Initially, we compared CMV IgG seropositivity among HCWs (medical doctors, nurses, and others) in 2017, which was examined after 1 year to evaluate seroconversion rates among those with seronegative results. Then, we examined CMV seroconversion rates in HCWs who were exposed to blood and body fluids.
Findings: We analysed 1153 samples of HCWs (386 medical doctors, 468 nurses, and 299 others), of which CMV seropositivity rates were not significantly different (68.9%, 70.3%, and 70.9%, respectively). Of these, 63.9% (221/346) of CMV seronegative HCWs were followed after 1 year, with CMV seroconversion rates of 3.2% (7/221). Among 72 HCWs who tested negative for CMV IgG when exposed to blood and body fluids, the CMV seroconversion rate was 2.8% (2/72). The CMV seroconversion rates between the two situations were not significantly different.
Conclusion: Our study indicated that CMV infection through daily patient care seems quite rare. Further well-designed studies with a large sample size are warranted to verify our finding.

1. Introduction

Cytomegalovirus (CMV) is one of the most common human herpesvirus that prevails worldwide, with seroprevalence ranging from 45% to 100% in the general population [1]. Patients with CMV latent infection unknowingly shed the virus in their urine, saliva, blood, vaginal discharge, semen, stool, and breastmilk, and human-to-human transmission involves contact with CMV-infected blood or body fluids by healthy individuals. CMV causes asymptomatic infection but possibly creates a serious burden, such as congenital CMV infection [2,3].

Healthcare workers (HCWs) frequently encounter various infectious agents, such as hepatitis B and C viruses and human immunodeficiency virus, through blood and body fluid exposure (BBFE). However, there are no relevant data on the risk of CMV infection among HCWs. The prevalence of the anti-CMV antibody in the general population is reportedly high; 83% of the global general population [4], 76.6% of Japanese blood donors [5], and 56.7% of the German population [6] were CMV positive. These studies reported that CMV seroprevalence increases with ageing, which could be attributed to the improvement in public sanitation and hygiene practices. This situation, i.e. a growing number of CMV-susceptible young individuals, may possibly place HCWs at risk of CMV

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occupational infection. Thus, this study aimed to determine the risk of CMV infection among HCWs.

2. Materials and methods

This study was conducted at Osaka University Hospital, an academic, tertiary medical facility in Japan. This study was approved by the Institutional Review Board of Osaka University Hospital (No. 10105–2 and 11183–2). Informed consent was waived because the samples were retrospectively measured after de-identifying the information of the study participants.

The study constitutes two different parts to compare CMV seroconversion rates between HCWs with BBFE and those without BBFE. First, we conducted a comparison of CMV seropositivity among three different job categories of HCWs (medical doctors, nurses, and others [pharmacists, medical clerks, and nutrition experts]) with a 1-year follow-up (Study 1). Second, we investigated the CMV IgG seroconversion rates following BBFE (Study 2). In the first part, we analysed serum samples of HCWs that were submitted and preserved at our clinical laboratory for the purpose of annual medical checkups. Serum samples obtained in June 2017 and June 2018 were used to assess seroconversion rates in a year through a natural course. HCWs, who reported BBFEs during the study period were excluded. In the second part, we used serum samples of HCWs after BBFE and those of exposure sources. Between January 2013 and March 2018, there were 401 reported cases of BBFE at our facility. Of these, we regarded cases as eligible when the exposed HCWs were negative for the CMV antibody, and the exposure sources were positive for CMV. The flow of the two studies is presented in Fig. 1. In this study, we tested for CMV positivity by examining the anti-CMV antibody, for both the exposed HCWs and the exposure sources, using Alinity CMV-G (Abbott Diagnostic Division, Tokyo, Japan) with a cutoff level of 6.0 AU/mL according to the manufacturer's instructions. The samples had been stored at −60 °C before measurement.

Continuous variables were reported as medians and interquartile ranges (IQRs) and assessed using the Mann–Whitney *U* test or Kruskal–Wallis test with Bonferroni adjustment. Categorical variables were reported as numbers and percentages and assessed using Fisher's exact test. Statistical analysis was performed using the EZR software, a graphical user interface for the R 3.5.2 software (The R Foundation for Statistical Computing, Vienna, Austria) [7]. All reported *P*-values < 0.05 were considered statistically significant.

3. Results

3.1. Study 1: CMV seroconversion rate through natural courses (Table 1)

We analysed samples from 1153 HCWs, of which there were 447 men and 706 women. There were 386 doctors, 468 nurses, and 299 other HCWs. The median age (IQR) of nurses (31 [23, 43.25]) was significantly lower than those of medical doctors (38 [33, 46]) and others (41 [32, 47.5]) ($p < 0.001$). CMV positivity rates increased by 10-year age group: 61.1% in <30 years, 69.6% in 30 to <40 years, 73.3% in 40 to <50 years, 79.6% in 50 to <60 years, and 88.2% in 60 to <65 years (Supple Table 1). Of these, CMV positivity rates in all HCWs, medical doctors, nurses, and others were 70.0%, 68.9%, 70.3%, and 70.9%, respectively, in which there was no significant difference among the three occupational categories ($p = 0.84$).

Of 346 CMV seronegative HCWs in June 2017, 63.9% (221 in total; 72 medical doctors, 78 nurses, and 71 others) were followed after 1 year (June 2018) to examine the CMV seroconversion rates in their natural courses. Similar to those examined 1 year before, the median age (IQR) of nurses (33.5 [24, 44]) was significantly lower than those of medical doctors (40 [34, 45]) and others (39 [31.5, 44]) ($p < 0.001$). As a result, CMV seroconversion rates in medical doctors, nurses, and other HCWs were 2.8% (2/72), 2.6% (2/78), and 4.2% (3/71), respectively. Statistical analysis revealed no significant difference in the CMV seroconversion rates among these job categories ($p = 0.80$).

3.2. Study 2: CMV seroconversion rates after BBFE (Table 2)

For those who were exposed to blood and body fluids of patients, there were 119 CMV seronegative HCWs at the time of exposure (29.7%). Of these, 12 cases were excluded because the source of exposure tested negative for the CMV antibody. Finally, 107 cases (26.7%) were selected for follow-up as eligible cases, of

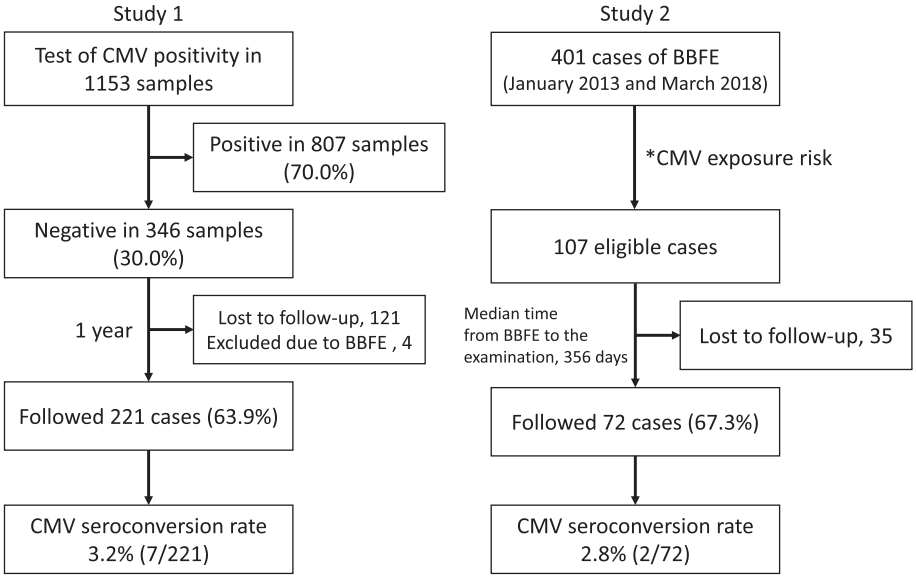

Fig. 1. Flow of the study. Study 1: CMV seroconversion rate through natural courses. Study 2: CMV seroconversion rates after BBFE. *In Study 2, the inclusion criteria were as follows: exposed HCWs being negative for CMV and exposure sources being positive for CMV. BBFE, blood and body fluid exposure; CMV, cytomegalovirus.

Table 1
Cytomegalovirus (CMV) antibody positivity of 1153 serum samples obtained from healthcare workers of Osaka University Hospital in 2017 and seroconversion rates after one year.

		Total	Medical doctors	Nurses	[a]Others
CMV positivity in 2017					
Number		1153	386	468	299
Men/women		447/706	308/78	50/418	89/210
Median age (interquartile range) (yr)		36 (28, 46)	38 (33, 46)	31 (23, 43.25)	41 (32, 47.5)
CMV-IgG	Negative	346	120	139	87
	Positive	807	266	329	212
	(% [95% CI])	(70.0 [67.3–72.6])	(68.9 [64.0–73.5])	(70.3 [65.9–74.4])	(70.9 [65.4–76.0])
CMV seroconversion rates after 1 year (2018) in the seronegative healthcare workers					
Number		221	72	78	71
Men/women		93/128	64/8	8/70	21/50
Median age (interquartile range) (yr)		38 (30, 45)	40 (34, 45)	33.5 (24, 44)	39 (31.5, 44)
CMV-IgG	Negative	214	70	76	68
	Positive	7	2	2	3
	Positivity	3.2%	2.8%	2.6%	4.2%

Of 346 CMV seronegative healthcare workers in June 2017, 221 (63.9%) were followed in June 2018. CMV seropositivities among medical doctors, nurses, and other healthcare workers were not significantly different (Fisher's exact test, $p = 0.84$).
[a] Other healthcare workers include pharmacists, medical clerks, and nutrition experts. SD, standard deviation; CI, confidence interval.

Table 2
CMV seroconversion rates after blood and body fluid exposure.

		Total	Medical doctors	Nurses	Others
Number		72	38	31	3
Men/women		34/38	30/8	3/28	1/2
Median age (interquartile range)		30 (26, 34.25)	32 (30, 36.5)	26 (23, 29)	26 (25, 35.5)
CMV-IgG	Negative	70	37	30	3
	Positive	2	1	1	0
	Positivity	2.8%	2.6%	3.2%	0%

In 107 CMV seronegative healthcare workers exposed to blood and body fluids, 72 (67.3%) cases were analysed. CMV seroconversion rate was not significantly different from that observed in the natural course (3.2% vs 2.8%; Fisher's exact test, $p = 1.0$).

which 72 cases (67.3%) were followed. Sources of the BBFE included blood (n = 66), saliva (n = 4), ascites (n = 1); and skin (n = 1). Blood exposure occurred secondary to hollow needles (n = 40), non-hollow needles (n = 8), unknown needles (n = 8), prick injuries due to knives (n = 4), and splashes into the mucosa, such as the eyes (n = 6). All the HCWs were confirmed to be negative for CMV IgG at the time of BBFE, while the exposure sources were positive for CMV IgG. The time from BBFE to the examination ranged from 100 to 730 days (median, 356 days [222.75, 490]) after exposure. The median age (IQR) of nurses (26 [23, 29]) was significantly lower than those of medical doctors (32 [30, 36.5]) ($p < 0.001$). The proportion of CMV seropositive results in medical doctors, nurses, and others were 2.6% (1/38), 3.2% (1/31), and 0% (0/3), respectively. In these two seroconverted cases, the source of body fluid was blood from hollow needle-stick injuries. CMV seroconversion rates between the 1-year natural course (Study 1) and that after BBFE (Study 2) were not significantly different (3.2% vs 2.8%; $p = 1.0$) (Fig. 1).

4. Discussion

This study is remarkably new to the literature because it focuses on the potential risk of CMV infection in HCWs. We have revealed that CMV seroprevalence among HCWs was approximately 70%, which showed an increasing tendency with ageing. Among the seronegative individuals, the annual CMV seroconversion rates were approximately 3%, with no significant difference among job categories. Moreover, we demonstrated that the annual CMV seroconversion rates after BBFE were also approximately 3%, which was statistically not different from those with natural courses. The annual CMV seroconversion rates observed in this study were consistent with previous data obtained from pregnant women: 2.1% (24/1122) between first and third trimesters [8], 3.7% (23/621) between gestational week 17 and birth [9], and average of 2.3% in pregnancy period [10]. These results might suggest the rarity of CMV infection through the exposure events in healthcare settings.

Several studies report that current CMV seroprevalence in European countries is approximately 50%: 41.9% in France [11], 45.6% in the Netherlands [12], and 56.7% in Germany [6]. In contrast, other countries have higher positivity rates: 77% in Portugal [13] and Croatia [14] and 83% in Sweden [15]. In Japan, there have been several reports of CMV seroprevalence among pregnant women: 78% in 1999 [16], 68% in 2013 [17], 66% in 2003–2012 [18], and 69.1% in 2009–2014 [19]. While, there are limited data on the general population; 76.6% out of 2400 blood donor samples tested positive for CMV in 2013 [5]. Compared to these recent data, the overall CMV seroprevalence observed in our study (70.0%) seems to be reasonably comparable. A future study widely targeting the general Japanese population is warranted to clarify the current trends in CMV positivity.

This study has several limitations. First, this is a single-centre study with small sample size. Second, we did not examine the CMV serology immediately after BBFE (the median time from exposure to examination was 356 days). Thus, the possibility of a latent CMV infection through medical care was not directly evaluated. Third, CMV is not necessarily excreted in body fluids at any time, which could have influenced the results. Fourth, CMV positivity was determined based on CMV IgG alone, and not CMV DNA. Sequencing analyses would be an interesting means of identifying the clonality of CMV between the exposed HCWs and the exposure source. Due to technical and financial difficulties, we did not perform a molecular investigation. Lastly, the implementation rate of standard precautions among medical doctors and nurses was not evaluated, which could have influenced CMV transmission.

Our investigation did not suggest a possibility of CMV infection through daily patient care, although HCWs are at an increased risk of exposure to various infectious agents. However, due to several limitations, the present study does not deny the risk of CMV occupational infection in HCWs, and further studies are warranted to verify our results.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2020.02.011.

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