Egyptian Journal of Chest Diseases and Tuberculosis (2014) 63, 239–245

The Egyptian Society of Chest Diseases and Tuberculosis

Egyptian Journal of Chest Diseases and Tuberculosis

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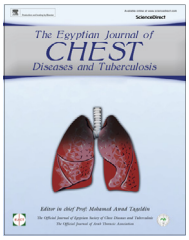

ORIGINAL ARTICLE

The impact of cytomegalovirus infection on mechanically ventilated patients in the respiratory and geriatric intensive care units

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Received 22 September 2013; accepted 25 September 2013
Available online 16 October 2013

KEYWORDS

Cytomegalovirus;
Intensive care;
Critical care;
Ventilator;
Sepsis;
Critically ill

Abstract *Background:* Reactivation of cytomegalovirus (CMV) has been reported in critically ill patients (especially elderly) lying in the intensive care units. So identifying such patients to treat is important.

The aim of this study: To detect the frequency of CMV infection in mechanically ventilated patients, and its correlation with patients' risk factors, and outcomes.

Subjects and methods: The present study was carried out on 51 mechanically ventilated patients admitted to the Respiratory (20) and Geriatric ICU (31) of the Ain Shams University hospitals over a 3 month period. Serum CMV load was measured by real-time PCR.

Results: The overall rate of active CMV infection by RT-PCR among the studied populations was (68.6%), (77.4%) in patients of geriatric ICU versus (55%) in respiratory ICU patients. Comparison between CMV positive and negative cases showed a significant difference in the duration of mechanical ventilation and mortality rate. A statistically higher CMV load was recorded in respiratory ICU patients admitted due to exacerbation of chronic respiratory disease or stroke and developing ventilator associated pneumonia (VAP) or septic shock. Also there was a significant direct correlation between CMV load and age of the patient, duration of mechanical ventilation and duration of ICU stay.

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Peer review under responsibility of The Egyptian Society of Chest Diseases and Tuberculosis.

ELSEVIER Production and hosting by Elsevier

 http://dx.doi.org/10.1016/j.ejcdt.2013.09.022

Conclusion: CMV infection is frequent in mechanically ventilated critically ill patients especially the elderly. It is associated with poor outcomes, leads to increased mortality and morbidity in terms of increased ICU stay, longer duration of mechanical ventilation, and higher rates of nosocomial infections.

Introduction

Cytomegalovirus (CMV) is a major β herpes virus, latently persisting in the majority of the adult human population worldwide. Infection is common with seroprevalence rates increasing steadily from 65% among 40–49 year olds to 91% in those aged 80 years or over [1]. It has been suggested that chronic CMV infection is a driving force in age related T cell immunosenescence [2]. It has increasingly come to be recognized that critically ill patients who are traditionally considered immunocompetent may also be at risk for CMV infection. Reactivation from the latency rather than primary infection is believed to be the cause of CMV infection [3]. CMV serology is not useful for the diagnosis of active infections and its culture is impractical for clinical purposes. Real-time PCR is a sensitive, specific and reliable marker to monitor the clearance of viremia [4].

The presence of CMV infection in critically ill patients was associated with a significant increase in morbidity and mortality, although this infection might be self-limited with spontaneous resolution within 2–3 weeks after reactivation [5]. Several studies showed that a CMV infection in this population was associated with prolonged ventilator support, high rates of nosocomial infections and prolonged hospital and/or ICU stay. However, the impact of CMV infection on the outcome of those patients is still debated [4].

The aim of the current study was to detect the frequency of CMV infection in mechanical ventilated patients, and its correlation with patients' risk factors, and outcomes, aiming to evaluate the need for screening for CMV infection.

Subjects and methods: This prospective study was performed in the Respiratory and Geriatric ICU of the Ain Shams University hospitals. Over a 3 month period, 20 patients were admitted to the Respiratory ICU and 31 patients were admitted to Geriatric ICU. All consecutive patients (18 years or older) were included in this study if they were mechanically ventilated.

Exclusion criteria: Patients were not included if they were pregnant, HIV positive, had solid organ or bone marrow transplantation, had received immunosuppressive agents or, long-term treatment with corticosteroids (□ 3 months), had solid cancer or hematologic malignancy with previous anticancer radiotherapy or chemotherapy.

Baseline assessment and data collection

Informed consent was taken either from patients' relatives or their guardians before the start of this study. Each patient's hospital chart was prospectively implemented, and the following data were recorded during admission to the ICU: age, sex, presence of co-morbidities {diabetes mellitus (DM) and/or renal diseases}, Main cause of ICU admission; the time spent on a mechanical ventilator, and duration of ICU admission. Other relevant clinical characteristics and outcomes complicating the ICU stay as {adult respiratory distress syndrome (ARDS), ventilator-associated pneumonia (VAP), septic shock, and mortality} were also recorded throughout the ICU stay. Peripheral venous blood samples were collected; serum was separated and stored at −80 °C till use in PCR analysis.

Identification of CMV by real time PCR

The presence of CMV was tested with a quantitative real-time PCR. DNA was extracted from serum samples using a Qiagen kit (Qiagen, Valencia, CA, USA) and quantified using the standard laboratory protocol recommended by the manufacturer's instructions. Quantitative real for CMV was performed using a light Cycler H Instrument (Roche Diagnostics, Meylan, France) with the QuantiTect Probe PCR Kit (Qiagen). The presence of CMV was tested with forward primer (5′GCAGCCACGGGATCGTACT-3′) and the reverse primer (5′GGCTTTTACCTCACACGAGCATT-3′), and the specific TaqMan probe (6FAM-CGCGAGACCGTGGAACTGCG-TAMRA) according to Coisel et al. [6]. The reaction was carried out in 20 mL, in a final volume containing 10 mL of QuantiTect master mix, 0.2 mM of probe, 0.2 mM of each primer, and 4 mL of DNA. The PCR was initiated by an enzyme-activation incubation at 95 °C for 15 min to activate DNA Polymerase, followed by 40 cycles of denaturation at 95 °C for 10 s and an annealing-extension step at 60 °C for 1 min. Serial dilutions, ranging from 10^2 to 10^5 copies/ml of synthesized sequences that correspond to the targeted viral genes, were used as positive controls. These dilutions were also used to determine the viral load in positive samples. A CMV negative specimen was used as a negative control sample was considered positive by real-time PCR if it crossed the threshold.

Data management and statistical analysis

Quantitative data are presented as mean and SD for parametric data or median for non-parametric data and categorical data are presented as numbers of cases and percentages. Student *T* and Mann Whitney tests were used to assess the statistical significance of the difference between the two groups regarding Quantitative data. Chi square and Fisher's exact tests were used to examine the relationship between Categorical variables. Spearman's correlation coefficient was used to assess the correlation between quantitative variables. A significance level of $P < 0.05$ was used in all tests. All statistical procedures were carried out using SPSS version 15 for Windows (SPSS Inc, Chicago, IL, USA).

Results

Patients characteristics

This study was conducted on 51 mechanically ventilated patients, over a 3 month period, 20 patients were admitted to the Respiratory ICU and 31 patients were admitted to Geriatric ICU of the Ain Shams University hospitals. Their age was ranging from (33–81) years with mean (58.7 ± 12.7), 29 males (56.9%) and 22 females (43.1%).

As regards the different causes of ICU admission, patients with exacerbation of chronic respiratory disease were 33 (64.7%), patients with stroke were 11 (21.6%), patients with cardiac diseases were 8 (15.7%) and patients with other causes (hepatic failure, dehydration and electrolyte disturbance) were 3 (5.9%). Sixteen patients (31.4%) were diabetics while 17 (33.3%) had associated renal disease.

The overall duration of mechanical ventilation ranged from (1–12 days) with mean (3.94 ± 2.86) and median (3 days), while the duration of ICU stay ranged from (1–30 days) with mean (6.94 ± 6.11) and median (5 days).

As regards patient outcome, 6 patients (11.8%) developed septic shock, 15 (29.4%) developed bacterial VAP and 5 (9.8%) developed ARDS. Totally 20 patients (39.2%) were improved versus 31 (60.8%) dead. More specifically, mortality rate was higher in patients of geriatric ICU (80.6%) versus (30%) in respiratory ICU patients.

Virological results

The overall rate of active CMV infection by RT-PCR among the studied populations was (68.6%), (77.4%) in patients of geriatric ICU versus (55%) in respiratory ICU patients.

Comparison between CMV positive and negative cases showed that there were no significant differences in the demographic and clinical characteristics except for the duration of mechanical ventilation, developing VAP and mortality rate (Tables 1 and 2).

The present study showed a statistically higher CMV load in respiratory ICU, patients admitted due to exacerbation of chronic respiratory disease or stroke and developing VAP or septic shock (Tables 3 and 4). Also there was a significant direct correlation between CMV load and age of the patient, duration of mechanical ventilation and duration of ICU stay (Table 5, Figs. 1 and 2).

Discussion

CMV infection is common worldwide and affects 60–100% of the adult population with a reported increase in prevalence with age [7–9].

During recent years, CMV has been recognized as an emerging pathogen in critically ill patients who are not receiving immunosuppressive therapy [10–14]. Critically ill patients usually have severe immunologic impairment [15]. Active CMV infection is likely to occur in this context of ''ICU-acquired immunosuppression'' [16].

The present study showed that the overall rate of active CMV infection by RT-PCR among the studied populations was (68.6%), (77.4%) in patients of geriatric ICU versus (55%) in respiratory ICU patients.

However, the incidence of active CMV infection is debated [10,12,17]. Clinical trials examining the frequency of CMV infection in ICU patients have not shown uniform results. Serological positivity for CMV reported in critically ill patients ranged from 13% [18] to 100% [17]. Some studies [11,12,18,19]

Table 1 Comparison between CMV positive and negative cases as regards outcome.

		CMV				P^*	Sig
		Yes		No			
		N	%	*N*	%		
Outcome	Improved	9	25.7	11	68.8	.003*	HS
	Died	26	74.3	5	31.3		
Septic shock	Yes	6	17.1	0	.0	.159**	NS
	No	29	82.9	16	100.0		
ARDS	Yes	5	14.3	0	.0	.167**	NS
	No	30	85.7	16	100.0		
VAP	Yes	14	40.0	1	6.3	019**	S
	No	21	60.0	15	93.8		

* Chi-square tests.
** Fisher's exact test.

Table 2 Comparison between CMV positive and negative cases as regards duration of ventilation and ICU stay.

	CMV						*P*	Sig
	Yes			No				
	Mean	±SD	Median	Mean	±SD	Median		
Duration of ventilation	4.60	3.19	4.00	2.50	.97	2.00	.001	HS
Duration of ICU stay	8.14	6.99	6.00	4.31	1.70	4.00	.079	NS

Mann Whitney's test.

Table 3 Relation between risk factors and CMV load among all cases.

		CMV load			*P*	Sig
		Mean	±SD	Median		
Gender	Male	9627.63	6470.09	11100.00	.297*	NS
	Female	6690.63	5066.76	4700.00		
ICU	Geriatric	6385.42	5255.81	4325.00	.007*	HS
	Respiratory	12429.55	5501.15	12800.00		
Exacerbation of chronic respiratory disease	Yes	10420.24	5904.37	11625.00	.007*	HS
	No	5082.14	4615.43	3675.00		
Stroke	Yes	4056.25	3563.35	2750.00	.014*	S
	No	9537.96	6010.22	8400.00		
Cardiac diseases	Yes	6790.00	5614.31	5700.00	.741*	NS
	No	8534.17	6086.73	6775.00		
Others**	Yes	5775.00	6399.32	5775.00	.477*	NS
	No	8437.12	6018.73	6300.00		
DM	Yes	9120.83	6227.74	7025.00	.487*	NS
	No	7848.91	5931.93	5600.00		
Renal problem	Yes	8796.15	6303.06	5700.00	.609*	NS
	No	7982.95	5901.47	6775.00		

* Mann Whitney's test.
** Others: (hepatic failure, dehydration and electrolyte disturbance).

Table 4 Relation between CMV load and patients' outcome among all cases.

		CMV load			*P*	Sig
		Mean	±SD	Median		
Outcome	Improved	7991.67	6164.31	6300.00	.925*	NS
	Died	8386.54	6028.23	6250.00		
Septic shock	Yes	16291.67	2816.81	16400.00	.001*	HS
	No	6628.45	5034.27	4900.00		
ARDS	Yes	9770.00	4035.72	10300.00	.346*	NS
	No	8037.50	6257.43	5650.00		
VAP	Yes	12412.50	5437.70	13162.50	.001*	HS
	No	5533.33	4645.52	4150.00		

* Mann Whitney's test.

Table 5 Correlations between age, duration of ventilation, ICU stay and CMV load among all cases.

	CMV load
Age	
Rho	.470
P	.004
Sig	HS
Duration of ventilation	
Rho	.478
P	.004
Sig	HS
Duration of ICU stay	
Rho	.562
P	.0001
Sig	HS

report an incidence ranging from 25% to 35%, while others [17,20–22] indicate very low or no CMV infection.

Coisel et al. [6] investigated Cytomegalovirus effect on the prognosis of mechanically ventilated patients suspected to have ventilator-associated pneumonia using RT-PCR. They reported 22 patients (24%) were positive for CMV.

These discrepancies may be explained by study design differences, patient groups, and CMV infection diagnosis methods, including viral culture, antigenemia and PCR assays. Previous studies used culture-based assays (low sensitivity and time-consuming), whereas more recent studies have used antigenemia (more sensitive and quantitative results) or PCR assays [24].

The higher frequency (77.4%) in patients of geriatric ICU reported in this study is in agreement with Coisel et al. [6], whose results showed that patients with positive CMV results were older than patients with negative results.

The present work assessed the occurrence of CMV infection and evaluated potential risk factors in ICU patients. There was a significant direct correlation between CMV load and age of the patient. In the prospective study of Cook et al., [13] patients with active CMV infection were significantly older than those without CMV infection. Also in the study of Chiche et al., [23] age was a risk factor for CMV infection. This matched with Kanapeckien≟ et al., [25] who reported that the mechanisms associated with CMV infection have an impact on immunosenescence. CMV reactivation occurs in

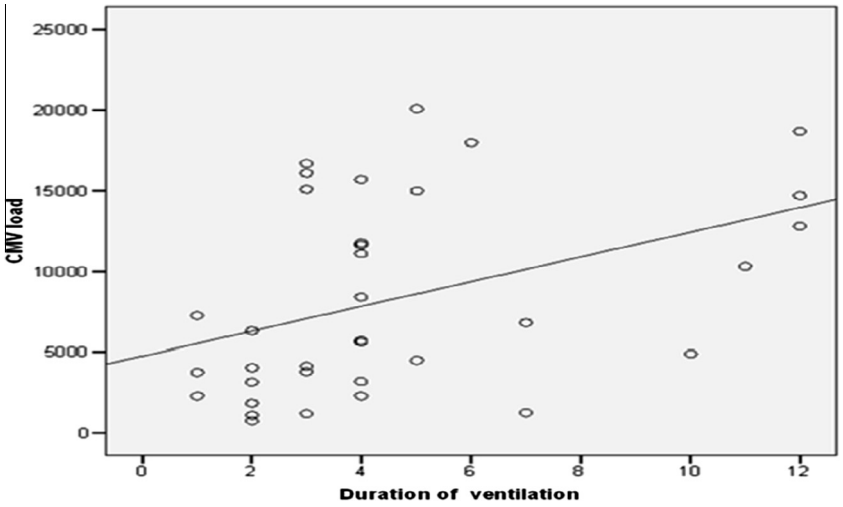

Figure 1 Correlations between duration of ventilation and CMV load among all cases.

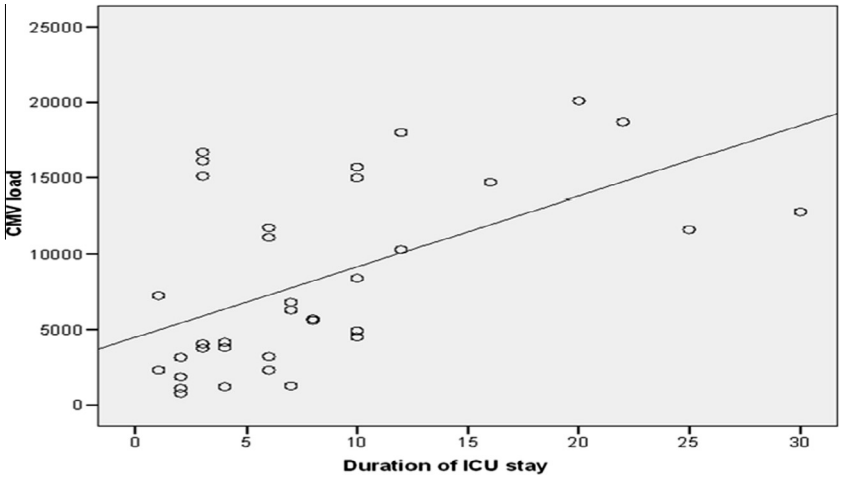

Figure 2 Correlations between duration of ICU stay and CMV load among all cases.

elderly because the immune system gets weaker with age. Age is a risk factor for CMV load in this study. One could argue that the elderly present an increased risk of developing CMV infection during critical illness because they are more likely to have been previously exposed to CMV, or because immunosenescence on the cellular immunity of elder patients may favor reactivation of the latent virus during ICU stay [26]. The results of the present study showed that there were no significant differences between males and females as regards active CMV infection. This is concordant with many studies [10,12–14,18,19,24], who found that the association between CMV infection and gender was inconsistent.

Comparison between CMV positive and negative cases showed that there were no significant differences in clinical characteristics of the patients except for the duration of mechanical ventilation, developing VAP and mortality rate. This is in accordance with Jain et al. [27], who reported that CMV reactivation in critically ill non-immunosuppressed patients leads to increased mortality and morbidity in terms of increased ICU stay, longer duration of mechanical ventilation, and higher rates of nosocomial infections.

The present study showed a statistically higher CMV load in respiratory ICU, patients admitted due to exacerbation of chronic respiratory disease and developing VAP.

Though CMV can virtually affect any organ system, lungs appear to be the most common organ of involvement. Lungs act as a reservoir in cases of latent CMV infection and thus act as the most consistent site for its reactivation [27]. Papazian et al. [11] reported CMV as a causative agent of pneumonia and all these patients had a more severe hypoxemia as compared to others [11].

The present study showed a statistically higher CMV load in patients admitted due to stroke. This might be explained by the relation between CMV infection and changes in clotting factors and the coagulation state. Also CNS manifestations are very common in immunocompromised patients but there have been reports of meningitis and other CNS manifestations as a result of CMV even in immunocompetent patients [28]. In critically ill patients, 10% (2/20) of those with CMV infection eventually developed severe CMV disease (pneumonitis, neurologic disease) in one study [12]. CMV pneumonia has also been diagnosed in 29 to 50% of patients with ARDS or

VAP [11,29,30], however, this does not necessarily mean that CMV is the cause of ARDS or VAP. Critical illness due to serious pulmonary disease may predispose these patients to CMV infection in the lungs [31].

The present study found significantly high rates of CMV infections in patients with severe sepsis/septic shock. Patients with severe sepsis and/or septic shock are more prone to have active CMV infections [19,28]. There are at least three biological explanations for CMV reactivation in these non-immunosuppressed patients that could act alone or in combination: (1) Patients with severe sepsis can develop a state called immunoparalysis, also called compensatory anti-inflammatory response syndrome. (2) Bacterial sepsis itself can reactivate latent CMV infection through endotoxin release by bacteria or tumor necrosis factor- α production and (3) exogenous catecholamine infusion can stimulate CMV activation [32,33]. Elevated tumor necrosis factor-α, level in blood during systemic inflammatory response syndrome might promote CMV reactivation by direct stimulation of the CMV immediate-early enhancer/promoter region [34], whereas acquired ICU immunosuppression, termed compensatory anti-inflammatory response syndrome, could permit an ''immunoevasion'' of the virus [35,36]

The present work showed that there was a significant direct correlation between CMV load and duration of mechanical ventilation and duration of ICU stay. This is in agreement with many studies which showed that the presence of CMV infection in critically ill ICU patients led to increased length of ICU stay and increased duration of mechanical ventilation as compared to patients negative for CMV infections even when both the groups had similar disease severity [10,13,14,24,37].

The present study showed that the CMV infected patients also had higher mortality. The results of this study are concordant with those of Heininger et al. [12], who found that the mortality rate tended to be higher in patients with active CMV infections, with a significant increase in ICU length of stay in survivors. Limaye et al. [24] also found an association between CMV reactivation and a composite end point (prolonged hospitalization or death). Other studies also reported that CMV infected patients had higher mortality as compared to CMV negative patients [10,37]. Kalil et al.[38], reported that the mortality rate associated with active CMV infection was 1.93 times as high as that for patients without infection.

CMV induces procoagulant and proinflammatory states by its changes in factor X and thrombin generation as well as in Von Willebrand factor and plasminogen inhibitor type 1 secretion [39,40]. These procoagulant and proinflammatory effects could further compromise the survival outcome of critically ill patients. Thus many different studies have highlighted the importance of CMV infection in ICU patients [12,14,28,37]. Limaye et al. [24] demonstrated an independent and quantitative association between CMV viral load and prolonged length of stay in a broad range of immunocompetent patients with critical illness. These findings, combined with data from prior investigations, provide a strong rationale for a randomized controlled trial of antiviral prophylaxis in this clinical setting.

Conclusions

CMV infection is frequent in mechanically ventilated critically ill patients especially the elderly. It is associated with poor outcomes, leads to increased mortality and morbidity in terms of increased ICU stay, longer duration of mechanical ventilation, and higher rates of nosocomial infections. So it is important to screen for active infection in those patients.

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