Epidemiol. Infect. (2000), **125**, 415–420. Printed in the United Kingdom

Is cytomegalovirus infection a co-factor in HIV-1 disease progression?

M. ROBAIN[1]*, F. BOUFASSA[1], J. B. HUBERT[1], E. DUSSAIX[2], K. SADEG[1] AND L. MEYER[1]

[1] *Department of Epidemiology, INSERM U292, Hôpital du Kremlin-Bicêtre, AP-HP, Le Kremlin-Bicêtre, France*
[2] *Department of Virology, Hôpital Paul Brousse, Villejuif, France*

(*Accepted 10 April 2000*)

SUMMARY

The influence of cytomegalovirus (CMV) infection as a co-factor in HIV-1 disease progression has mainly been studied in haemophiliacs and remains controversial. Based on the files of 1683 HIV-1-infected patients in the Seropositive Cohort (SEROCO) and Haemophiliacs Cohort (HEMOCO) cohorts, we studied the role of CMV infection in progression to $CD4^+$ cell counts of less than 200 μl, AIDS onset and death, in various HIV exposure groups. Adjusted relative risk (aRR) of progression to AIDS and to death was respectively 1·30 ($P = 0{\cdot}05$) and 1·58 ($P = 0{\cdot}007$). In the sexual exposure group the influence of CMV infection on the risk of progression to AIDS was of borderline significance (aRR = 1·50; $P = 0{\cdot}07$) and was more marked on the risk of death (aRR = 2·00; $P = 0{\cdot}03$). No such influence of CMV infection was observed in the transfusion and intravenous drug use exposure groups. When we studied the influence of CMV infection according to the stage of HIV disease, the main effect was on progression from AIDS to death, probably because CMV disease is a late event. Sexual CMV transmission and frequent re-exposure to CMV may explain why CMV infection emerged as an important co-factor for HIV progression only in the sexual exposure group.

INTRODUCTION

Human immunodeficiency virus (HIV) and cytomegalovirus (CMV) both target $CD4^+$ cells, and are both associated with immunodeficiency in humans [1]. The role of CMV as a co-factor in progression to AIDS is controversial. Hypothetical biological mechanisms whereby CMV may influence HIV disease progression abound, but epidemiological studies have given conflicting results [2–5].

After 13 years of follow-up, a British cohort of 111 haemophiliac patients continues to suggest that CMV seropositivity is associated with progression to AIDS, even after adjustment for age and the $CD4^+$ cell count [6–8]. Recently, Sinicco and colleagues found that CMV seropositivity was related to shorter survival in 291 subjects, more than half of whom were intravenous drug users (IVDU) [9]. Spector and colleagues found in homosexual men that CMV DNA load was an independent risk factor for mortality [9–10]. However, Rabkin and colleagues, studying 393 haemophiliac subjects, found that CMV seropositivity was no longer associated with AIDS onset when age was taken into account (RR = 1·0) [11]. In 1996, Shepp and colleagues, studying 196 subjects belonging to various risk groups, found that CMV serological status had no effect on the risk of death or AIDS-related illnesses other than CMV disease [12].

These studies mainly involved haemophiliac subjects, and very few included patients infected during sexual intercourse. However, multiple sexual exposure

* Author for correspondence: Hôpital du Kremlin-Bicêtre, INSERM 292, 82 rue du Général Leclerc, 94276 Le Kremlin-Bicêtre Cedex, France.

to CMV has been linked to faster progression to AIDS [13, 14]. As CMV infection is more likely to occur in sexually active subjects, it is important to take the exposure group into account in epidemiological analyses.

Based on the heterogeneous populations of the French SEROCO and HEMOCO cohorts comprising 1683 HIV-1 infected subjects, we assessed the influence of CMV infection as a cofactor in HIV-1 disease progression before the advent of highly active antiretroviral therapy (HAART).

METHODS

SEROCO and HEMOCO cohorts

Started respectively in 1988 and 1989, SEROCO and HEMOCO are two French prospective multicentre HIV antibody positive patient cohorts. The SEROCO cohort, which involves 17 hospitals and a network of private practitioners, enrolled HIV-1-infected adult volunteers, no more than 1 year after HIV diagnosis (unless their date of infection was known) [15]. Apart from haemophiliacs, all HIV exposure groups are represented. The HEMOCO cohort involves four hospitals and enrolled only haemophiliac patients infected by HIV-1 through blood product exposure between 1978 and 1985 [16]. As of November 1998, 1536 subjects had been enrolled in SEROCO and 197 in HEMOCO. HIV antibody positivity is routinely diagnosed by means of ELISA and confirmed by Western blot.

Data collected

Sociodemographic characteristics and the exposure group were recorded at enrolment, as reported by the subjects themselves. Clinical and biological data are recorded during follow-up (every 3 or 6 months according to clinical status). Serological testing for CMV infection is performed at enrolment and then every 6 months in CMV-antibody negative subjects.

CMV diagnosis

CMV antibodies (IgG and IgM) were detected by using immunoenzymatic methods (ELISA) or immunocapture kits from Abbott, Becton-Dickinson, Behring, Murex and Wellcome. The tests were considered positive if specific IgG or IgM values were above the cut-off value of the relevant kit.

Study population

Among the 1733 subjects, 1 with unknown CMV antibody status at enrolment and 21 with AIDS at enrolment were excluded. All the subjects were censored on 1 January 1996, before widespread use of HAART. Twenty-eight subjects included after 1 January 1996 were therefore excluded from the analysis. This analysis thus focused on 1683 subjects. The 'blood exposure' group included haemophiliacs and subjects infected through transfusions. The IVDU exposure group comprised subjects who reported intravenous drug used before the diagnosis of HIV infection. The sexual exposure group comprised homosexual and heterosexual men and women who did not belong to the blood or IVDU exposure group.

Statistical analysis

We studied CMV infection as a co-factor for progression to $CD4^+$ cell counts below 200 μl on at least two occasions less than 12 months apart ($n = 780$), clinical AIDS (European classification 1993 [17]) ($n = 482$), and death ($n = 342$). As Kaposi's sarcoma (KS), an early AIDS-defining disease, occurs more frequently in homosexual men (who are also more frequently infected by CMV), we excluded KS from the definition of AIDS [18, 19].

Crude relative risks (cRR) and adjusted relative risks (aRR) were calculated using a Cox model. No deviation from the proportional hazards assumption was observed by introducing a time interaction factor [20]. Relative risks of progression to $CD4^+$ cell counts below 200 μl, AIDS and death were adjusted for age and the $CD4^+$ cell count at baseline (treated as continuous variables). Statistical analysis was done using SAS software (SAS Institute Inc., Cary, NC).

RESULTS

Baseline characteristics

The mean age of the 1683 study patients (1248 men) was 30·9 years (29·5, 32·1 and 27·6 years, respectively, in the blood, sexual and IVDU exposure groups). Two-thirds of the patients had been infected by HIV

https://doi.org/10.1017/S0950268899004549 Published online by Cambridge University Press

Table 1. *CMV antibody prevalence at enrolment according to age, exposure group, CD4⁺ at baseline, and CCR5 deletion*

	Total	CMV antibody prevalence (%)	*P*
Age (years)			
> 35	442	91·6	< 0·001
25–35	779	86·4	
< 25	462	67·7	
Exposure group			
Blood	324	58·6	< 0·001
IVDU	248	78·2	
Sexual	1111	90·2	
CCR5			
wt/wt	1356	82·9	0·50
wt/Δ 32	231	80·1	
Unknown	96	80·2	
CD4⁺ cells/μl			
> 500	743	83·2	0·42
200–500	758	82·5	
< 200	181	79·0	

through the sexual route (homosexuals 60·7%, heterosexuals 39·3%), 19·3% through the haematogenous route (58% haemophiliacs and 42% transfusion recipients) and 14·7% after IVDU; 90% of subjects had CD4⁺ cell counts above 200 μl at baseline. Except for the blood exposure group, in which most patients were included 3–9 years after primary HIV infection, CD4⁺ cell counts at baseline were unrelated to the exposure group.

A total of 297 of the 1683 subjects were not infected by CMV at baseline (Table 1). CMV seroprevalence increased with age ($P < 0·001$), was highest in patients in the sexual exposure group ($P < 0·001$), and, as previously described, was particularly low in the blood exposure group [21]. Neither the CCR5 Δ32 deletion nor the CD4⁺ cell count at baseline was associated with CMV infection ($P = 0·50$ and $P = 0·42$, respectively).

CMV infection and HIV disease progression

Older subjects and those with low CD4⁺ counts at baseline progressed significantly more rapidly to CD4⁺ counts below 200 μl, AIDS and death. The CCR5 Δ32 deletion was related to slower progression to AIDS, as previously reported [22].

Compared to CMV antibody negative subjects, CMV-infected subjects did not progress more rapidly to CD4⁺ counts below 200 μl (RR = 1·11 [0·92–1·34]), even after adjustment for age and the CD4⁺ cell count at baseline (Table 2). The association between CMV infection and progression to AIDS was of borderline significance ($P = 0·05$), but the deleterious effect was small (adjusted relative risk (aRR) = 1·30 [1·00–1·69]). In contrast, the relative risk of death associated with CMV infection was significantly increased (aRR 1·58, 95% CI 1·13–2·20; $P = 0·007$).

To take into account a potential bias due to the inclusion of patients with an unknown date of HIV infection [23], we also conducted a subgroup analysis focusing on HIV seroconverters, most of whom were infected through the sexual route ($n = 457$, 86·4% CMV-infected). Similar relative risks were observed, but they did not differ significantly from 1·0 because of the smaller sample size. For example, the aRR of progression to death associated with CMV infection was 1·63 ($P = 0·20$).

We then carried out a stratified analysis according to the HIV exposure group. In the blood and IVDU exposure groups, the relative risks of progression to CD4⁺ < 200 μl, AIDS and death were around 1·0, and no significant association was found (Table 3). Conversely, in subjects infected through the sexual route, the risk of progression to death was multiplied by 2 in case of CMV infection ($P = 0·03$).

No primary CMV prophylaxis was prescribed before AIDS onset during the study period. CMV disease was the first AIDS-defining event in 42 (8·7%) patients. Among the patients with AIDS, the proportion of those who developed CMV disease ranged from 3·8% ($n = 4$) in the blood exposure group to 11·0% ($n = 35$) in the sexual exposure group. The analysis was repeated after excluding CMV disease from the definition of AIDS: the risk of progression to AIDS was still increased in CMV-infected subjects infected through the sexual route, but remained non significant [aRR = 1·43; $P = 0·11$].

Apart from CMV disease, we found no links between CMV infection and particular AIDS-defining illnesses. For example, the first AIDS-defining event was a parasitic or fungal infection in 52·0% of CMV-infected subjects and a bacterial infection in 14·7%, compared to 50·5% and 15·7% in CMV-uninfected subjects. The degree of immunodeficiency at AIDS onset was very similar in CMV-infected and uninfected subjects (median CD4⁺ cell counts: 47·5 and 45·0 μl, respectively, $P = 0·28$).

When the stage of HIV disease was taken into account, we found that CMV infection mostly played a major role after AIDS onset. After adjustment for

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Table 2. *Relative risks of progression from baseline to a CD4 count below 200 μl, AIDS and death in 1386 CMV antibody positive patients at baseline (compared with 297 CMV antibody negative patients) (SEROCO-HEMOCO cohorts)*

	Progression to		
Relative risk	$CD4^+$ cells $< 200/\mu l$	AIDS	Death
Crude RR [95% CI]	1·11 [0·92–1·34]	1·32 [1·03–1·69]	1·58 [1·15–2·17]
P value	$P = 0·28$	$P = 0·03$	$P = 0·005$
A* RR [95% CI]	1·11 [0·91–1·35]	1·30 [1·00–1·69]	1·58 [1·13–2·20]
P value	$P = 0·31$	$P = 0·05$	$P = 0·007$

* Adjusted for age and the $CD4^+$ cell count at baseline.

Table 3. *Relative risks of progression from baseline to a CD4 count below 200/μl, AIDS and death in CMV antibody positive patients at (baseline compared with CMV antibody negative patients) in 1683 patients from different exposure groups (SEROCO-HEMOCO cohorts)*

	Progression to		
Relative risk	$CD4^+$ cells $< 200/\mu l$	AIDS	Death
Blood exposure group ($n = 324$)			
a*RR [95% CI]	1·18 [0·84–1·66]	1·20 [0·76–1·90]	1·22 [0·71–2·09]
P value	$P = 0·34$	$P = 0·44$	$P = 0·47$
IVDU group ($n = 247$)			
a*RR [95% CI]	0·85 [0·52–1·40]	0·88 [0·48–1·65]	1·61 [0·72–3·60]
P value	$P = 0·53$	$P = 0·70$	$P = 0·25$
Sexual exposure group ($n = 1111$)			
a*RR [95%CI]	1·35 [0·96–1·88]	1·50 [0·96–2·34]	2·00 [1·06–3·78]
P value	$P = 0·08$	$P = 0·07$	$P = 0·03$

* RR were adjusted for age and the $CD4^+$ cell count at baseline.

age and the baseline $CD4^+$ cell count, the aRR for progression from a $CD4^+$ cell count below 200 μl to AIDS was not significant (aRR = 1·33; $P = 0·07$). Conversely, the risk of progression from AIDS to death was increased by CMV infection (aRR = 1·49; $P = 0·03$). In the sexual exposure group, in which the relative risk of progression from enrolment to death was the highest, the aRR for progression from AIDS to death was 1·62 ($P = 0·16$).

DISCUSSION

The large number of HIV-infected subjects included in this study ($n = 1683$) allowed us to consider the role of CMV infection in various exposure groups and at various stages of HIV-1 infection. We observed no major influence of CMV infection on HIV-1 disease progression, except in patients infected by the sexual route. In these, although CMV antibody positivity may be a marker related to lifestyle, there was a trend towards a role of CMV infection in progression to $CD4^+$ cell counts < 200 μl and to AIDS, and a significant increase in the risk of death (adjusted RR = 2·00). In the other exposure groups (transfusion and intravenous drug use), CMV infection did not appear to be an important co-factor for HIV-1 disease progression.

Most previous studies in this field have involved haemophiliac patients. We found no influence of CMV infection on HIV disease progression in this exposure group, confirming the results of Rabkin [11]. These subjects differ in several respects from patients infected through sexual contact. The CMV antibody prevalence was lower in the blood exposure group than in the other exposure groups. In adults, CMV is often acquired during sexual intercourse [24]. The prevalence of CMV infection at inclusion in our cohorts increased with age and was significantly higher in the sexual exposure group (90·2%) than in the IVDU exposure group (78·2%) and the blood

https://doi.org/10.1017/S0950268899004549 Published online by Cambridge University Press

exposure group (58·6%), in keeping with previous studies [21, 25, 26]. This lower CMV prevalence in patient infected through blood products is likely to be due to a lower level of sexual activity, which implies that the risk of multiple infection by CMV and/or other virus is also probably lower in this group.

This could explain why we only found an increased risk of progression to death in CMV-infected subjects belonging to the sexual exposure group ($P = 0{\cdot}03$), in which multiple CMV reinfection has been shown to occur [13]. When we included KS in the definition of AIDS, the relative risk of progression to AIDS in the sexual exposure group was 1·68 ($P = 0{\cdot}02$). This could imply that co-infections such as CMV and HHV8 are associated.

CMV disease was the first AIDS-defining event in 8·7% of cases, a frequency close to that in the French AIDS case register (6·3%) [27]. In agreement with the literature, CMV disease was more likely to be the first AIDS-defining event in the sexual risk group (11·0%) than it was in the blood (3·8%) and IVDU exposure groups (5·3%) [28–29]. CMV disease generally occurs late in HIV disease, usually when the $CD4^+$ cell count falls below 50 μl. Jougla and colleagues reported that, in the year preceding death, 37% of HIV-infected subjects developed CMV disease [30]. The late occurrence of CMV disease could explain why CMV infection appears to play a role mainly in late disease progression, after AIDS onset.

CMV infection thus seems to act as a co-factor for HIV-1 disease progression only in subjects infected through the sexual route. One epidemiological study suggested that CMV infection after HIV infection considerably increased the risk of subsequent CMV disease relative to CMV infection before HIV infection [11]. The pathophysiological mechanisms underlying this phenomenon are unclear. It is known, however, that repeated infection by different CMV strains can occur in subjects with multiple partners [13]. Given the gravity of CMV disease in HIV-infected subjects, it will be interesting to confirm the effect of CMV seroconversion on the onset of these diseases, and to determine whether the presence of multiple CMV strains increases the risk of developing CMV disease.

APPENDIX

The members of SEROCO Study Group are: C. Rouzioux, M. Bary, M. Burgard, ACCTES (Paris); P. Dellamonica, J. Durant, Hôpital L' Archet (Nice); H. Gallais, A.M. Quinson, Hôpital de la Conception (Marseille); J.F. Delfraissy, P. Lebras, C. Goujard, Y. Quertainmont, M.T. Ranou, Hôpital du Kremlin-Bicêtre (Le Kremlin-Bicêtre); J.J. Lefrère, J. Lerable, J. Salpetrier, M.C. Meyohas, Hôpital Saint-Antoine, (Paris); J.P. Cassuto, M. Quaranta, Hôpital Cimiez (Nice); B. Dupont, V. Feuillie, M.P. Treilhou, Hôpital de l'Institut Pasteur (Paris); D. Vittecoq, L. Escaut, Hôpital Paul Brousse (Villejuif); S. Herson, A. Coutellier, M. Bonmarchand, Hôpital Pitié-Salpétriére (Paris); J.A. Gastaut, G. Fabre-Costeseque, M.P. Drogoul, Hôpital Ste-Marguerite (Marseille); P. Galanaud, F. Boué, A. Lévy, V. Chambrin, Hôpital Antoine Béclére (Clamart); D. Séréni, J. Krulick, Hôpital Saint-Louis (Paris); D. Sicard, Hôpital Cochin (Paris); J.L. Vildé, C. Leport, U. Colassante, W. Nouiouia, Hôpital Bichat (Paris); C. Katlama, M. Richard, C. Riviére, Hôpital Pitié-Salpétriére (Paris); A. Sobel, M. Lechevalier, Hôpital Henri Mondor (Créteil); M. Kazatchkine, M. Buisson, J. Vrtousnik, Hôpital Broussais (Paris); L. Guillevin, B. Jarousse, P. Cohen, P. Deny, Hôpital Avicenne (Bobigny).

The members of HEMOCO Study Group are: Y. Sultan, P. Molho, N. Stieltjes, Hôpital Cochin (Paris); C. Gazengel, C. Rothschild, M.F. Torchet, Hôpital Necker (Paris); T. Lambert, B. Doumenc, Hôpital de Bicêtre (Le Kremlin-Bicêtre); J. Peynet, C. Laux, Hôpital Mignot (Le Chesnay).

Financial support: Agence Nationale de Recherches sur le SIDA (ANRS).

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