CMV Disease in AIDS Patients: Incidence of CMV Disease and Relation to Survival in a Population-based Study from Oslo

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CMV disease is an important cause of morbidity and mortality in patients with AIDS. The purpose of this study was to investigate the incidence of CMV disease in a well-defined population of AIDS patients with a high rate of autopsy. No such study has previously been published from Scandinavia. A total of 248 patients who developed clinical AIDS in Oslo during the period 1 January, 1983 to 31 December, 1995 were included. Autopsy was performed in 152 of 213 deaths (71.3%). CMV disease was diagnosed in 95 patients. In the autopsy group, 73 patients (48%) had CMV disease, and in 52 of these patients CMV disease was first detected at autopsy. Retinitis was the most frequent manifestation, followed by adenitis, pneumonitis, encephalitis and gastrointestinal disease. No intravenous drug users (IVDUs) were diagnosed alive with CMV disease. All patients diagnosed with CMV disease before death had evidence of CMV disease at autopsy despite anti-CMV treatment. CMV disease was associated with increased risk of death. We conclude that CMV disease was frequent in patients with AIDS during the study period, was associated with increased mortality and was often diagnosed too late for the administration of appropriate therapy.

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INTRODUCTION

The prevalence of CMV seropositivity is high in HIV-infected individuals, and almost all homosexuals are infected (1). CMV disease is the most common serious opportunistic viral infection in patients with AIDS (2–7), usually occurring in patients with CD4 cell counts < 0.05 × 10^9/l (2, 8, 9). Until the introduction of effective antiretroviral therapy, the incidence of CMV disease was reported to be increasing among patients with HIV infection, probably due to improved survival of patients with severe immunodepression (10, 11).

In autopsy studies, evidence of CMV disease has been reported in 38–76% of AIDS patients (3–7, 12–15). The diagnosis of CMV disease is often difficult, and there is a high rate of discordance between clinical diagnosis and post-mortem findings (4–6, 13–15). However, most of these studies suffer from possible selection bias.

In addition to causing significant morbidity and mortality due to end-organ disease, there has also been concern that CMV may induce more rapid progression of HIV infection (16–22). In vitro there is evidence that CMV can interact with, and cause, increased HIV replication, and several reports have suggested that this is also plausible in vivo (23). However, other studies of the effect of CMV seropositivity and CMV disease on the progression of HIV infection and AIDS have not found an association with the progression of HIV disease (1, 24, 25). In addition, previous studies have suggested that the development of CMV disease is a predictor of increased risk of death (14, 26, 27). The aim of this study was to investigate the incidence of CMV disease in the pre-HAART (highly active antiretroviral therapy) era in a well-defined population of AIDS patients in Scandinavia with a high rate of autopsy, and also to examine the impact of CMV seropositivity and end-organ disease on the survival of AIDS patients. No such study has previously been published from Scandinavia.

MATERIALS AND METHODS

Study population

The study population comprised patients treated at the Department of Infectious Diseases, Ulleval University Hospital, representing > 90% of adult AIDS patients in Oslo. All patients fulfilling the clinical criteria for AIDS (28) during the period 1 January 1983 to 31 December 1995 were included in this retrospective population-based study. No haemophiliac patients were included. Computerized data and patient files were used to collect information regarding demographic, HIV exposure category, laboratory results (T-cell subsets, CMV serology, biopsy and autopsy results) and the presence of CMV disease.

Laboratory methods

In the case of CMV retinitis, ante-mortem diagnosis was based on typical ophthalmoscopic findings. The characteristic histopathological features of cytomegalocytes with inclusions were required for diagnosis of all other CMV disease manifestations. Demonstration of CMV by culture of biopsies, blood or urine without histopathological verification was not accepted for diagnosis. In the autopsy group, a full autopsy including neuropathological examination was performed in each case. Paraffin-embedded sections were routinely stained with haematoxylin–eosin but immunohistochemistry for CMV was performed in a few cases of doubt to confirm CMV infection.

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Statistical analysis

To compare groups we used 2-sample $t$-tests for continuous variables, $\chi^2$ tests for categorical variables and Kaplan–Meier plots for survival (event history) type data. Cox proportional hazard regression was used to evaluate the impact of CMV disease on survival. CMV disease was then represented as a time-dependent indicator variable changing from 0 to 1 when CMV disease was diagnosed (ante-mortem). Based on repeated CD4 measurements, the times at which cell counts dropped below $0.1 \times 10^9/l$ and $0.05 \times 10^9/l$ were estimated for each patient. This information was used to define additional time-dependent covariates in the Cox analysis.

RESULTS

Study population

A total of 248 patients were included. Characteristics of the study population are presented in Table I. Autopsy was performed in 152 patients (71.3%). Tissue was taken from all internal organs except for the gastrointestinal tract in 47 patients, adrenal glands in 35 patients and eyes in 21 patients. An average of 40–50 sections were taken per autopsy. The autopsy and non-autopsy groups were similar, except for longer survival from AIDS in the non-autopsy group.

CMV disease was the first AIDS-defining diagnosis in 13 patients (6.1%) who died during the study period (7 diagnosed at autopsy, 6 ante-mortem). In addition, 2 patients with CMV disease as their initial AIDS-defining diagnosis were alive at the end of the study period.

CMV serology

The results of CMV serological testing are shown in Table II. With 1 exception, all tested homosexuals were CMV IgG-positive. The difference between homosexuals and intravenous drug users (IVDUs) was highly significant ($p < 0.0001$).

Incidence of CMV disease

Ninety-five of 248 patients with AIDS developed CMV disease during the study period (Fig. 1). CMV disease was diagnosed in 73 of 152 autopsies (48%), but only 21 of these patients (14%) had a known diagnosis of CMV disease ante-mortem. In 61 non-autopsy deaths, CMV disease was diagnosed in 16 cases (26%). When taking the longer survival of patients in the non-autopsy group into account, there was no difference in the incidence of CMV disease before death between the 2 groups (Fig. 2).

All patients with an ante-mortem diagnosis of CMV disease also had evidence of CMV disease at autopsy. With the exception of 2 patients who died before ganciclovir or foscarnet were available, all patients with CMV disease diagnosed before death received anti-CMV therapy for variable lengths of time.

Among patients in the autopsy group, there was a rising incidence of CMV disease from 39% to 51% when comparing deaths during the period 1983–89 to those during the period 1990–95. Survival from onset of AIDS to death was 190 and 432 d during the early and later periods, respectively, and this difference may explain the rise in the incidence of CMV disease.

End-organ disease

Retinitis was the most frequent manifestation of CMV disease, closely followed by adrenalitis (Table III). Thirty-two patients were diagnosed with retinitis ante-mortem. All diagnoses of adrenalitis and encephalitis were made at autopsy, as histopathological confirmation was required for diagnosis, and biopsies of these organs were not performed. In this study only 14 of 20 patients with encephalitis had a previous or concomitant diagnosis of retinitis.

| Table I. Characteristics of the study population. Values shown are incidences, with percentages in parentheses |
|-----------------------------------------------|-----------------|-----------------|-----------------|
| Characteristic                               | Died during study period ($n = 213$) | Autopsy group ($n = 152$) | Non-autopsy group ($n = 61$) | Total number of patients ($n = 248$) |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Exposure category                            |                 |                 |                 |                 |
| Homosexual                                   | 169 (68)        | 107 (70.4)      | 41 (67.2)       | 169 (68)        |
| IVDU                                         | 41 (17)         | 27 (17.8)       | 7 (11.5)        | 41 (17)         |
| Other                                        | 38 (15)         | 18 (11.8)       | 13 (21.2)       | 38 (15)         |
| Age at AIDS diagnosis (y)                    | 38.5            | 36.6            | 38.5            | 38.5            |
| Male sex                                     | 219 (88.3)      | 139 (91.4)      | 51 (83.6)       | 219 (88.3)      |
| CMV seroprevalence a                         |                 |                 |                 |                 |
| IgG-positive                                 | 222 (92.9)      | 140 (94.0)      | 55 (93.2)       | 222 (92.9)      |
| IgG-negative                                 | 17 (7.1)        | 9 (6.0)         | 4 (6.8)         | 17 (7.1)        |
| No. of patients receiving antiretroviral treatment | 183 (73.8)    | 101 (66.4)      | 49 (80.3)       | 183 (73.8)      |
| Median survival from AIDS (d)                | 409             | 275             | 509             | 409             |

a Percentage of tested patients.
Table II. **CMV serological results according to HIV exposure category in 248 patients with AIDS. Values shown are incidences, with percentages in parentheses**

| Exposure category | Homosexual a | IVDU a | Other a | Total |
|-------------------|--------------|--------|---------|-------|
| CMV IgG           |              |        |         |       |
| Positive          | 166 (99.4%)  | 27 (71.1) | 29 (83.3) | 222 (92.9) |
| Negative          | 1 (0.6%)     | 11 (28.9) | 5 (16.7)  | 17 (7.1) |
| Not tested        | 2            | 3       | 4        | 9     |
| Total             | 169          | 41      | 38       | 248   |

a Percentage of tested patients.

In the autopsy group, homosexuals had a significantly ($p < 0.05$) higher incidence of CMV disease (55/107) compared to IVDUs (7/27). However, this difference was not significant when restricting the analysis to CMV IgG-positive individuals (55/105 and 7/19 in homosexuals and IVDUs, respectively). No patients with intravenous drug use as the only risk factor for HIV infection were diagnosed alive with CMV disease. Only 1/7 IVDUs with CMV disease at autopsy had retinitis. There was a strong trend ($p = 0.07$) towards lower incidence of CMV retinitis among IVDUs (1/19) compared to homosexuals (27/105) among CMV IgG-positive individuals.

**T lymphocytes**

Patients with CMV disease at autopsy had significantly ($p < 0.001$) lower final mean CD4 cell counts ($0.031 \times 10^9/\ell$) compared to patients without CMV disease ($0.101 \times 10^9/\ell$). There was no significant difference in the time from last CD4 cell count to death between these groups. Final CD4 cell counts were significantly ($p < 0.05$) higher during the period 1983–89 ($0.149 \times 10^9/\ell$) than during the period 1990–95 ($0.044 \times 10^9/\ell$). Again, there was no significant difference in the time from last CD4 cell count to death between these periods. Similarly, patients with CMV disease at autopsy had lower final CD8 cell counts ($0.368 \times 10^9/\ell$) than patients who died without CMV disease ($0.602 \times 10^9/\ell$), but this difference was not statistically significant.

**Survival from AIDS according to CMV serology and CMV disease**

For the total population there was no significant difference in survival from AIDS between patients who were seropositive or seronegative for CMV.

In a time-dependent Cox regression analysis, where CMV disease diagnosed before death was handled as a time-dependent covariate, CMV disease was found to be a significant risk factor, with a relative risk for death of 1.50 (Table IV).

**DISCUSSION**

This is the first population-based report of the incidence of CMV disease in Scandinavian AIDS patients. Haemophiliacs were excluded, but in other respects the study population is representative of adult patients with AIDS in Oslo. An autopsy rate of 71.3% is the highest reported to our knowledge, with the exception of highly selected populations.

The autopsy and non-autopsy groups were similar, with the exception of longer survival from AIDS in the latter group. Two factors contribute to this difference. Firstly, there was a lower autopsy rate in the last part of the study period when survival was longer. Secondly, long-term survivors and their next of kin had an increased tendency to refuse autopsy. Longer survival from AIDS is a known risk factor for CMV disease, explaining the higher incidence of

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Table III. **Incidence of CMV end-organ disease**

| CMV manifestation     | Autopsy group ($n = 152$) | Total deaths ($n = 213$) |
|-----------------------|----------------------------|--------------------------|
|                       | Diagnosed alive            | Diagnosed alive and/or post-mortem | Diagnosed alive | Diagnosed alive and/or post-mortem |
| Retinitis             | 17                         | 34                       | 32             | 49                        |
| Adrenalitis           | 0                          | 43                       | 0              | 43                        |
| Pneumonitis           | 2                          | 34                       | 3              | 35                        |
| Encephalitis          | 0                          | 24                       | 0              | 24                        |
| Gastrointestinal      | 5                          | 16                       | 9              | 20                        |
| Miscellaneous         | 1                          | 9                        | 3              | 11                        |
| Any manifestation     | 21                         | 73                       | 37             | 89                        |
CMV disease diagnosed in alive patients in the non-autopsy group. The incidence of CMV disease in the autopsy group may therefore underestimate the “true” incidence that would have been expected if autopsy had been carried out on all deceased patients. However, as the autopsy group included > 70% of the population, this difference is most likely moderate.

In the autopsy group, we found evidence of CMV disease in almost half of the patients. In accordance with previous studies (4–6, 12–15), CMV disease was often first diagnosed at autopsy. This underscores the danger of grossly underestimating the incidence of CMV disease in studies with low autopsy rates, as well as the need for better diagnostic methods. Certain advances have already been made since the end of the study period, such as the use of PCR to detect CMV in cerebrospinal fluid and blood (29–32).

Retinitis was the most common CMV manifestation. This is in agreement with several other reports (14, 33, 34). Interestingly, over one-third of retinitis patients who died were first diagnosed at autopsy. Routine ophthalmoscopy of AIDS patients with low CD4 cell counts has been proposed. However, the effect of early detection and treatment of asymptomatic retinitis on survival and relapse has not been evaluated (35), and routine ophthalmoscopy is not common practice at our centre. Fourteen of 20 patients with CMV encephalitis had concomitant retinitis, and this association is weaker than that previously reported (36). This may be due to the higher total number of encephalitis cases in our study and possible under-reporting of retinitis.

Table IV. *Relative risk of death (estimated from Cox regression)*

| Variable                                      | Risk ratio (95% confidence interval) |
|-----------------------------------------------|--------------------------------------|
| Gender (male)                                 | 1.03 (0.65–1.62)                     |
| Age (10-y increments)                         | 1.15 (0.99–1.35)                     |
| Later period *                               | 0.78 (0.57–1.05)                     |
| CMV disease diagnosed alive                  | 1.50 (1.02–2.20)                     |
| CD4 cells < 0.10 × 10⁹/l                     | 1.25 (0.76–2.07)                     |
| CD4 cells < 0.05 × 10⁹/l                     | 1.97 (1.25–3.07)                     |

* Diagnosed with AIDS during 1983–89 vs. 1990–95.

Fig. 1. CMV disease in AIDS patients who died and patients who were still alive at the end of the study period 1983–95. CMV = CMV disease.

Fig. 2. Probability of CMV-free survival from time of AIDS diagnosis in the autopsy and non-autopsy groups.
as histopathological examination of the eyes of all patients was not performed.

In this study, all patients with CMV disease diagnosed ante-mortem had some manifestation of CMV disease at autopsy despite therapy with ganciclovir and/or foscarnet. This clearly indicates the inadequacy of conventional therapy. HAART has been shown to prevent reactivation of CMV in those responding to HIV therapy, but it remains to be demonstrated whether this will also influence histopathological evidence of CMV disease at autopsy. Certainly in patients not responding satisfactorily to antiretroviral treatment, more effective anti-CMV therapy is needed.

In agreement with previous reports (10, 11), we found an increasing incidence of CMV disease in AIDS patients in the period before effective combination therapy. This is probably due to the longer survival of patients with immunodeficiency in later years. However, during recent years, and in parallel with more effective HIV therapy, the incidence of CMV has stabilized and even decreased (33, 37–40). One recent autopsy-based study (7) also reported a decreasing incidence of CMV disease. Whether this is just a transient situation remains to be seen.

Homosexuals are known to have significantly higher rates of seropositivity for CMV compared to IVDUs, and this was confirmed in our study. This is probably because sexual exposure is a risk factor for infection with both HIV and CMV. Also, in accordance with previous studies (14, 26, 33), we found the incidence of total CMV disease to be higher in homosexuals than in IVDUs. However, this difference was not significant when considering only CMV IgG-positive individuals in whom autopsy was performed. Interestingly, no IVDUs were diagnosed with CMV disease ante-mortem.

CMV disease was the first AIDS-defining diagnosis in 13 cases (61%). This is similar to the incidence of 6.9% reported by the CDC for the period 1992–97 (33) but lower than the 9.5% reported by d’Arminio et al. (14).

It has previously been shown that a low CD4 cell count is a predictor for CMV disease (8, 14). Our study also shows that patients with CMV disease at autopsy had significantly lower CD4 cell counts than other patients. There was a non-significant trend towards the same effect when considering CD8 cell counts prior to death, as was previously shown in patients with CMV retinitis (9, 41, 42). As previously demonstrated (26), we found CMV disease to be a predictor of increased risk of death (14, 27) irrespective of treatment.

The majority of AIDS patients in Oslo, as in the rest of the world, are infected with CMV, a cause of significant morbidity and mortality in these patients. In this population-based study, CMV disease was frequently diagnosed too late for appropriate therapy to be given. Despite CMV treatment, evidence of CMV disease was nevertheless found at autopsy in all cases. HAART has proven effective in reducing the incidence of CMV disease in patients responding to treatment, but many are still at risk of developing CMV disease. There is a continuing need for improvements in diagnosis and therapy, and in an ongoing study we are looking into the predictive value of quantitative CMV PCR for diagnosing the development of CMV disease.

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