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Cytomegalovirus Retinitis: Current State in People with HIV-AIDS in Peru

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

Purpose: To describe the incidence and progression of cytomegalovirus retinitis (CMVR) in public hospital patients from Peru.
Study Design: Prospective study conducted in HIV-AIDS diagnosed patients.
Place and Duration of Study: Department of Ophthalmology and Department of Tropical Medicine, Hospital Nacional Dos de Mayo, from 2004 to 2013.
Methodology: Descriptive statistics were obtained for age, gender, associated disease, CMVR location and ganciclovir treatment. Data were analyzed by the Pearson Chi. Square test, Mann-Whitney test, and the two-tailed exact Fischer's Exact test. SPSS version 20.0 for Windows software program was used
Results: 2627 patients were evaluated, 75 had CMVR diagnosis. Active CMVR was found in 68 eyes (90.7%). Median age at diagnosis of CMVR was 37 years (IQR 30-41 years). Median CD4 level of 25 cells/μL (IQR 12.2-57.7 cells/μL), viral load > 1000,000 in 39 (52%) patients. Median mortality rate was 7.1 deaths per 1000 PY and mean survival time from HIV diagnosis to death was 29,5 months (95% 8,7-43,0 months) and from CMVR diagnosis, 6,2 months (95% IC 2,0-8,0 months). Duration since HIV diagnosis to CMVR onset was 12 months (IQR 3-48 months). Tuberculosis (TB) was present in 23 (30.7%) patients. Incidence rate of HIV patients with CMVR was 28.2 cases per 1000 PY. 51 patients received ganciclovir: endovenous 34 (91.17%), intravitreal 6 (26.5%) and orally 4 (11.8%).

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Conclusion: CMVR has a high prevalence in young people with an elevated value of HIV-TB co-infection (30.7%). CMVR diagnosis was a predictor for early mortality, including highly active antiretroviral therapy (ART).

Keywords: Cytomegalovirus retinitis; HIV; AIDS; blindness.

1. INTRODUCTION

There are 65,000 persons living in Peru with Human Immune Virus (HIV) – Acquired Immunodeficiency Syndrome (AIDS) infection. It is a concentrated epidemic, with a 0.23% of prevalence in general population and 12.4% in men with have sex with men [1].

In 2004 highly active antiretroviral therapy (ART) is initiated by Health Minister in hospitals and health centers. During 2011, 92.7% of the people that needed to receive ART and had access to the health system were receiving it. Between 2005 and 2011 the number of AIDS-related deaths, had been reduced by 55% [1,2].

HIV- AIDS patients with a CD4 count below of 50 cells / mL are more likely to have opportunistic infections that will cause death or disabilities that affect their quality of life in ART era [3].

Cytomegalovirus retinitis (CMVR) is a common opportunistic disease among HIV - AIDS patients, this infection contributes to mortality [4]. Before ART era, it was responsible of 90% HIV-related blindness in developed countries. Immune recovery produced by ART has resulted in an approximate 80% reduction in the incidence of CMV retinitis [5,6].

In developing countries, CMVR in AIDS patients is a neglected disease with no strategy for management and its complications. Their lower prevalence compared to the developed countries is explained by the fact that generally most lower-income patients living in Africa, Asia and Latin America die before the diagnosis [7]. Between 5% and 25% of all HIV-infected patients in the developing world can be expected to develop blindness at some time during their illness [8].

To define a strategy for CMVR diagnosis and treatment in our countries, is important know the epidemiological data. This study describes the incidence and progression of CMVR in public hospital patients from Peru.

2. METHODOLOGY

This prospective study was conducted in HIV-AIDS diagnosed patients treated at Hospital Nacional Dos de Mayo, a tertiary care hospital in Lima, Peru between April 2004 and December 2013. Institutional Ethics Committee approval was obtained before for this prospective study and consent forms were not required.

Patients were referred from Tropical Medicine Department for ophthalmological evaluation before starting ART (supported by the Global Fund). Demographic, HIV infection history, CD4 T cell counts, and plasma HIV viral load, associated diseases, characteristics and treatment of the CMVR data were obtained.

Dilated indirect fundoscopy was performed by an experimented ophthalmologist at the beginning and at 2-3 weekly intervals until CMVR was inactive. The diagnosis and site of CMVR was based on clinical features previously described [9]. Patients were treated with ganciclovir (endovenous, oral and/or intravitreal). Endovenous ganciclovir was given for two weeks at 7.5 to 15 mg/kg/day followed by maintenance therapy of 5 mg/kg/day. Intravitreal ganciclovir induction dose was 1000 µgr/0.1 ml twice weekly for the first week and maintenance dose one weekly to see inactivity of the disease. Oral ganciclovir was given for maintenance therapy at 1 g three times a day. An informed consent was obtained from all patients for each eye treated.

Descriptive statistics were obtained for age, gender, associated disease, CMVR location and ganciclovir treatment. Comparisons were done for survivors and deceased patients. Potential shorter survival time at CMVR diagnosis predictors were identified by extended Cox regression models. Data were analyzed by the Pearson Chi. Square test, Mann-Whitney test and when one of the numbers was less than 5, by the two-tailed exact Fischer's exact test. SPSS version 20.0 for Windows software program was used.

3. RESULTS

At the time the study was performed 2659 patients were diagnosed with HIV-AIDS. 2627 had ophthalmological examination and cytomegalovirus retinitis was found in 75 cases. In 26 patients damage was bilateral. CMVR was active in 68 eyes (90.7%). In Table 1 is shown that the median age at diagnosis of CMVR was 37 years (IQR 30-41 years). Males were 61 (81.3%). Median CD4 level of 25 cells/μL (IQR 12.2-57.7 cells/μL), viral load >1000,000 in 39 (52%) patients. Incidence rate of HIV patients with CMVR was 28.2 cases per 1000 PY. The duration since HIV diagnosis to CMVR onset was 12 months (IQR 3-48 months).

As indicated in Table 2, Tuberculosis (TB) was present in 23 (30.7%) patients. The most affected area in the retina was zone 1 in (55.4%) eyes. 51 patients received ganciclovir: endovenous 34 (91.17%), intravitreal 6 (26.5%) and orally 4 (11.8%). Inactivity of CMVR was observed at four weeks in 17 eyes with endovenous ganciclovir, three of them also received the drug via intravitreal. 46 patients had a minimum follow up of three months, with the longest observed follow-up of 9 years. CMVR was reactivated in 22 eyes (14.6%) of 16 patients. Nine cases of this group had CD4 counts <50 cells. Seven eyes (4.6%) showed immune reaction syndrome (vitreitis and macular edema).

Comparing deceased and survivors patients, there was no difference in demographic and clinical characteristics as is observed in Table 3.

Median mortality rate was 7.1 deaths per 1000 PY and mean survival time from HIV diagnosis to death was 29,5 months (95% 8,7-43,0 months) and from CMVR diagnosis, 6,2 months (95% IC 2,0-8,0 months). In the multivariate analysis was found that age at diagnosis of CMVR is not related to the patient's death as is shown in Table 4. The cumulative curve for survival of patients with CMVR is shown in Fig. 1.

4. DISCUSSION

Since 1983 to January 2014, a total of 52490 HIV and 31157 AIDS cases in Peru had been reported [1]. ART began in 2004 in public medical centers provided by Global Fund to Fight AIDS, Tuberculosis and Malaria. During 2011, 92.7% of the people that needed to receive ART and had access to the health system were receiving it. 62.3% of HIV cases and 72.2% of AIDS cases reported in 1983-2012, originate in Lima and Callao, urban regions inhabiting a third of the population of the whole country [1,2].

The prevalence of CMVR in HIV-AIDS patients in developing countries is generally lower than in industrialized countries explained this on the short survival time of this patients. Our results showed an overall incidence rate of CMVR of 28.2 cases per 1000 P Y, similar values are observed in Togo a country in sub-Saharan Africa (21.4%) [10]. It is remarkable that the highest value 62.4 cases per 1000 P Y was obtained in 2004 before starting ART.

The studied patients comprised young adults with a median age at diagnosis of CMVR of 37 years (IQR 30-41 years). Lowest levels of CD4 in most of the cases explain the highest incidence of CMVR compared with other reports [11,12]. The patients had severe immunosupression because a high percentage of them, requested medical care at an advanced stage of their disease. Factors preventing the prompt care of these patients were low socioeconomic and educational levels, plus stigma and discrimination in health centers similar to observed in other developing countries [1,8,11,13]. The beginning of CMVR was at a median of 12 months after HIV diagnosis (IQR 3-48 months) shorter than described in the literature (18 and 26 months) [11,14].

Mean onset of ART was two years after HIV diagnosis. This therapy significantly decreased CMVR incidence in this group of patients. While ART is free, other diagnostic tests must be paid by the patient to access to this program and receive therapy. Perhaps, this is one of the main reasons for delay in receiving treatment.

Median mortality rate was 7.1 deaths per 1000 PY and mean survival time from CMVR diagnosis was 6.2 months (95%, 2,0-8,0 months). The fact that the mortality rate in our study was lower than that found by Balo in Togo [10] and Tun in Myanmar [13], it can be explained that approximately one third of patients did not have follow-up. Survival time from CMVR was 6 months, early similar mortality, as described in previous studies in developing countries mentioned above. Sadly, it is observed that the, HIV epidemic continues to have a greater impact in terms of mortality in young population of our country, occupying the eighth leading cause of death in young (18-29 years old) [1].

Table 1. Demographic characteristics of HIV patients with cytomegalovirus retinitis in Lima –Peru, 2004 to 2013

	Years										
Characteristic	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**Total**
CMV Retinitis, n (%)											
Male	16 (26.2)	9(14.8)	6(9.8)	3(4.9)	5(8.2)	4(6.6)	5(8.2)	2(3.3)	7 (11.5)	4 (6.6)	61 (81.3)
Female	7 (50.0)	0	0	2 (14.3)	1 (7.1)	0	0	2 (14.3)	2 (14.3)	0	14 (18.7)
Total	23 (30.7)	9 (12.0)	6(8.0)	5 (6.7)	6(8.0)	4(5.3)	5 (6.7)	4 (5.3)	9 (12.0)	4 (5.3)	75 (100.0)
Cumulative HIV cases, n	369	295	298	264	262	239	235	263	221	213	2659
Incidence (per 1000 PY)	62.3	30.5	20.1	18.9	22.9	16.7	21.2	15.2	40.7	18.7	28.2
Age (years), median [IQR]											
At HIV diagnosis	34.0 [27.0 – 40.0]	33.0 [30.5 – 44.0]	31.5 [25.0 – 35.5]	29.0 [23.0 – 34.0]	44.0 [31.2 – 60.0]	32.0 [28.2 – 45.5]	34.0 [25.5 – 40.0]	30.5 [29.0– 33.5]	34.0 [25.0 – 43.0]	38.0 [32.5 – 45.0]	34.0 [28.0 – 39.0]
At CMVR diagnosis	38.0 [30.0 – 42.0]	37.0 [32.5 – 48.0]	33.0 [26.7 – 37.0]	29.0 [29.0 – 34.5]	44.5 [31.5 – 60.0]	36.5 [29.7 – 47.0]	40.0 [26.5 – 41.5]	33.0 [31.2 – 37.7]	36.0 [25.0 – 43.5]	44.0 [39.5 – 50.0]	37.0 [30.0 – 41.0]
At HAART initiation	38.5 [30.0 – 44.2]	35.0 [35.0 – 44.0]	34.0 [27.0 – 36.5]	29.0 [29.0 – 34.0]	44.5 [31.5 – 60.0]	36.0 [29.0 – 36.0]	40.0 [28.5 – 42.5]	33.0 [31.2– 37.7]	35.0 [26.0 – 48.0]	38.0 [38.0 – 45.0]	36.0 [30.0 – 41.0]
CD4 count (cells/μL) Median [IQR]											
At CMVR diagnosis	20.0 [2.0 – 50.0]	25.0 [10.0 – 45.0]	43.5 [11.7 – 236.5]	26.0 [5.0 – 26.0]	25.0 [17.5 – 93.5]	286.5 [6.0 – 286.5]	23.0 [9.5 – 30.5]	8.0 [4.7 – 123.0]	57.0 [25.0 – 79.0]	333.0 [35.0 – 333.0]	25.0 [12.2 – 57.7]
Duration (months), median [IQR]											
HIV diagnosis to CMVR	24.0 [12.0 – 60.0]	48.0 [15.0 – 48.0]	15.0 [1.0 – 46.5]	8.5 [4.2 – 111.0]	4.5 [1.0 – 8.2]	25.5 [1.5 – 68.2]	24.0 [4.5 – 54.0]	12.5 [1.0 – 96.0]	1.0 [1.0 – 6.5]	25.5 [2.2 – 188.2]	12.0 [3.0 – 48.0]

Table 2. Clinical characteristics of HIV patients with cytomegalovirus retinitis in Lima –Peru, 2004 to 2013

	Years										
Characteristic	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**Total**
Associated disease, n (%)											
Tuberculosis	7 (30.4)	4 (44.4)	1 (16.7)	2(40.0)	0	2 (50.0)	0	1 (25.0)	3 (33.3)	3 (75.0)	23 (30.7)
Toxoplasmosis	0	0	0	0	0	0	0	1 (25.0)	1 (11.1)	0	2 (2.7)
Syphilis	0	0	0	0	2 (33.3)	2 (50.0)	0	0	0	0	4 (5.3)
Kaposis's Sarcoma	2 (8,7)	0	0	0	0	0	1 (20.0)	0	0	0	3 (4.0)
Non Hodgkin Lymphoma	0	0	0	0	0	0	0	0	2 (22.2)	0	2 (2.7)
CMVR location, n (%)											
Zone 1	15 (65.4)	3 (33.3)	3 (50.0)	3(60.0)	0	2 (50.0)	3(60.0)	1 (25.0)	3 (33.3)	2 (50.0)	35 (46.7)
Zone 2	2 (8.6)	0	1 (16.7)	0	3 (50.0)	1 (25.0)	2 (40.0)	3 (75.0)	5 (55.6)	2 (50.0)	19 (25.3)
Zone 3	6 (26.0)	6 (66.7)	2 (33.3)	2 (40.0)	3 (50.0)	1 (25.0)	0	0	1 (11.1)	0	21 (28-0)
Ganciclovir treatment, n (%)											
Endovenous	9 (39.1)	3 (33.3)	1 (16.7)	4 (80.0)	2 (33.3)	2 (50.0)	3 (60.0)	3 (75.0)	5 (55.6)	2 (50.0)	34 (45.4)
Intravitreal	3 (13.0)	0	2 (33.3)	0	0	1 (25.0)	0	0	0	0	6 (8.0)
Endovenous - intravitreal	1 (4.3)	0	3 (50.0)	0	2 (33.3)	1 (25.0)	2 (40.0)	1 (25.0)	4 (44.4)	1 (25.0)	15 (20.0)
Endovenous - oral	6 (26.1)	0	0	0	0	0	0	0	0	0	6 (8.0)
No report	4 (17.4)	6 (66.7)	0	1 (20.0)	2 (33.3)	0	0	0	0	1 (25.0)	14 (18.6)

Table 3. Characteristics of deceased and survivors patients with CMV retinitis, Peru 2004 to 2013

Characteristic	Deceased	Survivors	P value
CMVR, n (%)			
Male	13 (68.4)	48 (85.7)	0.09 ‡
Female	6 (31.6)	8 (14.3)	
Age, median [IQR]			
At HIV diagnosis	29 [27.0 8.0]	34.5 [29.0–40.7]	0.027†
At CMVR diagnosis	31 [29.0 8.0]	37.5 [30.2–46.2]	0.026†
At HAART initiation	38 [30.0 9.5]	35.5 [30.0–43.0]	0.65†
CD4 cells/μL, median [IQR]			
At CMVR diagnosis	17 [8.0–08.0]	26 [14.0–58.5]	0.63†
Duration (months), Median [IQR]			
HIV diagnosis to CMVR	10 [2.0–48.0]	12 [3.0–48.0]	0.78†
Associated disease, n (%)			
TB	6 (31.6)	17(30.4)	0.52*
Toxoplasmosis	1 (5.3)	1 (1.8)	
Syphilis	0	4 (7.1)	
Kaposi Syndrome	1 (5.3)	2 (3.6)	
Non Hodgkin Lymphoma	0	2 (3.6)	
No report	10 (52.6)	24 (42.9)	
ART, n (%)			
No	10 (52.6)	18 (32.1)	0.11‡
Yes	9 (47.4)	38 (67.9)	
Ganciclovir treatment, n (%)			
Endovenous	10 (52.6)	24 (42.9)	0.34*
Intravitreal	3 (15.8)	3 (5.4)	
Endovenous - intravitreal	2 (10.5)	13 (23.2)	
Endovenous - oral	2 (10.5)	4 (7.1)	
None	2 (10.5)	12 (21.4)	
CMVR location, n (%)			
Zone 1	15 (78.9)	46(82.1)	0.74*
Zone 2	0(0.0)	2 (3.6)	
Zone 3	4(21.1)	8 (14.3)	

** Fisher's Exact test*
† Mann-Whitney test
‡ Pearson Chi-Square test

Table 4. Hazard ratios for time-to-death after HIV diagnosis in patients with CMV retinitis in Peru, 2004 to 2013

Age	n	Unadjusted HR (95% C.I)*	P value	Adjusted HR (95% C.I)*	P value
At HIV diagnosis	75	0.94 (0.89 – 0.99)	0.031	0.98 (0.85 – 1.13)	0.82
At CMVR diagnosis	75	0.94 (0.89 – 0.99)	0.026	0.95 (0.83 – 1.09)	0.51

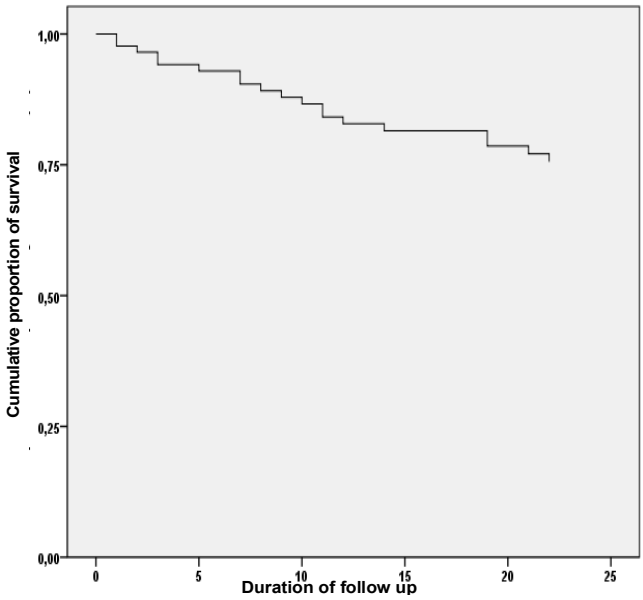

Fig. 1. Shows the Kaplan-Meier curve for survival

Peru is the second country with the most cases of patients with TB in Latin America, and has higher TB prevalence in HIV-AIDS patients. In this study, TB the most common associated disease was diagnosed in 23 patients (30.7%). HIV-TB co-infection is present in many countries of Latin America, and has an estimated prevalence of 25% [7]. National reports of 2013 showed that HIV-TB co-infection represents a serious public health problem in our country and only 42,4% of patients were treated [1,2].

In 55.4% of eyes, retinitis was localized in zone 1, an important retinal area which is associated with a high risk of vision loss. The management of CMVR consisted in intravenous initial therapy (induction therapy) and locally administered intravitreal ganciclovir as is reported previously [15,16]. Retinitis reactivation (10.6% of eyes) was observed generally after the first month. It is explained by many comorbidities in the patients, very low levels of CD4 and none or inadequate treatment with ganciclovir by the difficulty of accessing this medicine. At the beginning of the study, donated ganciclovir tablets were obtained and 6 patients received in the maintenance therapy of CMVR for few months. It should be noted as a limitation of the study have not recorded the side effects of systemic treatment with intravenous ganciclovir as neutropenia, thrombocytopenia, rash, nephrotoxicity, and gastrointestinal symptom whose incidence is reduced with oral treatment.

CMVR is a neglected disease, largely undiagnosed and untreated. Workable diagnostic and therapeutic strategies have not yet been defined, and CMV is absent from current and pending World Health Organization (WHO) guidelines for the management of HIV in resource-limited settings [17]. Clinical risk factors recognized as predictors for CMVR, may be useful to clinicians and health policy experts in developing guidelines for screening, examination frequency targeted prophylaxis for CMVR in patients with AIDS [18].

Future care by Health Ministries in developing countries and WHO worldwide, will prevent that

many HIV - AIDS young people be permanently blind by undiagnosed or poorly treated CMVR.

4. CONCLUSION

Results showed that cytomegalovirus retinitis has a high prevalence in young people with an elevated value of HIV-TB co-infection (30.7%). CMVR diagnosis was a predictor for early mortality, despite receiving ART.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Institutional Ethics Committee approval was obtained.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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