Journal of Cardiovascular Disease Research

ISSN:0975 -3583,0976-2833 VOL13, ISSUE 05, 2022

Original research article

CLINICAL CORRELATES OF CYTOMEGALOVIRUS AND HIV CO-INFECTION

[1]Dr. Bhatt Shrey Nandkishore, [2]Dr. Vilas Honnakatti, [3]Dr. Ulka Kamble, [4]Dr. Pratap Budhya

[1]Senior Resident, Department of General Medicine, ABVIMS and Ram Manohar Lohia Hospital, New Delhi, India

[2,4]Assistant Professor, Department of General Medicine, BIMS, Belagavi, Karnataka, India

[3]Associate Professor, Department of General Medicine, ABVIMS and Ram Manohar Lohia Hospital,
New Delhi, India

Corresponding Author:
Dr. Pratap Budhya

Abstract

CMV retinitis is the devastating consequence of advanced HIV infection which usually presents with painless, progressive loss of vision and complaints of blurred vision, floaters & scintillations. Patients with CD4 T-cell count less than 100/microliter should undergo ophthalmological examination every 3-6 months as majority of CMV retinitis occur in patients with CD4 T-cell count less than 50/microliter. CMV reactivation has dropped to close to 2% in the cART era which was seen in 25-30% patients with AIDS prior to the availability of cART. This study was an observational cross-sectional study, conducted at the Department of Medicine and ART centre in collaboration with the Department of Microbiology and Department of Ophthalmology. More than 18 years old HIV patients with CD4 T-cell count less than 100 cells/microliter were included in the study. Mean ± SD of CD4 T cell count(/µL) in patients with CMV manifestations was 26.8 ± 17.14 which was significantly lower as compared to patients with CMV Manifestations (55.55 ± 24.1). (p value=0.019). Mean ± SD of HIV viral load(/mL) in positive CMV DNA PCR was 79100 ± 35315.57 which was significantly higher as compared to negative CMV DNA PCR (49573.91 ± 30484.95). (p value=0.003)

Keywords: CMV retinitis, HIV, CMV DNA PCR

Introduction

CMV retinitis can manifest in the form of floaters, visual field defects or visual loss, with macula involvement or retinal detachment. Since the introduction of HAART, retinal detachment have reduced by 60-80% and decreased to 0.06/person years from 0.50/person years. CD4 T-cell count less than 50/microliter was the single most risk factor for CMV retinitis. Despite HAART, patients with CD4 T-cell count less than 50/microliter have a similar risk for developing CMV retinitis comparing with pre-

ISSN:0975 -3583,0976-2833 VOL13, ISSUE 05, 2022

HAART era [1].

In the pre-HAART era anti-CMV maintenance therapy was required for lifetime but now with the advent of HAART, selective discontinuation of anti-CMV therapy can be considered if the CD4 T-cell count remains more than 100/microliter for a minimum of 3 months or a 2-log unit or more reduction in the HIV viral load. Reduction in viral load seems to be a better predictor of CMV retinitis remission than the CD Chorioretinitis most commonly occurs with CD4 T-cell count <50 cells/microliter. CMV can be found in lungs usually in combination with pneumocystis carinii pneumonia. CMV can affect the gastrointestinal system and peripheral nerves. Encephalopathy and cauda equina syndrome have also been linked to CMV. In developing countries like India where the HIV/AIDS pandemic is rapidly unfolding, the magnitude of CMV retinitis is as yet not known as it is largely undiagnosed and untreated. It has been estimated that 5-25% of HIV infected patients in the developing world can be expected to develop blinding disorder. The emergence of AIDS in India has necessitated the establishment of reliable tests for diagnosis of cytomegalovirus infection as a damaged immune system permits cytomegalovirus infection [2, 3].

CMV retinitis is the devastating consequence of advanced HIV infection which usually presents with painless, progressive loss of vision and complaints of blurred vision, floaters & scintillations. Patients with CD4 T-cell count less than 100/microliter should undergo ophthalmological examination every 3-6 months as majority of CMV retinitis occur in patients with CD4 T-cell count less than 50/microliter. CMV reactivation has dropped to close to 2% in the cART era which was seen in 25-30% patients with AIDS prior to the availability of cART. Induction therapy with IV ganciclovir for 3 weeks is followed by maintenance therapy with oral valganciclovir. Intravitreal ganciclovir is useful in CMV disease limited to the eye. Maintenance therapy is given until CD4 T-cell count remains more than 100/microliter for more than 6 months [4].

There are 2 forms of CMV encephalitis in HIV patients: one resembles HIV encephalitis and presents as progressive dementia and the other one is a ventriculo-encephalitis presenting with cranial nerve palsies, nystagmus, disorientation, lethargy and ventriculomegaly. In advanced HIV patients, CMV can also cause subacute progressive polyradiculopathy, a reversible condition if diagnosed early and treated immediately [5, 6].

Methodology

This study was an observational cross-sectional study, conducted at the Department of Medicine and ART centre in collaboration with the Department of Microbiology and Department of Ophthalmology. More than 18 years old HIV patients with CD4 T-cell count less than 100 cells/microliter were included in the study.

The patients were evaluated as per the standard protocol specially concentrating on-

- Age.
- Gender.
- Socioeconomic status.
- Detailed history with examination.

Baseline routine investigations were done for all the enrolled patients. HIV viral load, TORCH profile, anti-HCV and HBsAg and peripheral blood CMV PCR were

ISSN:0975 -3583,0976-2833 VOL13, ISSUE 05, 2022

performed for all the patients. Patients who had symptoms of encephalopathy or myeloradiculopathy were admitted and CSF CMV DNA PCR along with other infectious encephalopathy investigations were performed and baseline NCCT head was done. India ink staining and cryptococcal antigen assays in CSF were also performed.
Indirect ophthalmoscopy and fundus photography were performed for all the enrolled patients in the ophthalmology department.
Sputum CMV PCR and TB PCR examinations were done for the patients with respiratory tract infections. Cryptococcal antigen assay and India ink staining of sputum or pleural fluid were done as per indications.

- Cytomegalovirus Quantitative DNA polymerase chain reaction by 'artus CMV PCR kit Qiagen' in peripheral blood.
- Patients who have serum PCR positive for CMV were advised for admission and CSF PCR for CMV was done after their consent.
- HIV viral load by TaqMan plasma (Quantitative) method.
- CSF cytology/biochemistry/culture/ADA/CMV DNA PCR/Rubella PCR/Herpes Simplex Virus PCR/India ink in patients with features of encephalitis.
- Sputum for CMV PCR and TB PCR if patient had features of pneumonia.
- Anti HCV and HBsAg.
- TORCH (Toxoplasmosis, Others, Rubella, Herpes Simplex) profile to rule out other opportunistic infections.

Patients with high peripheral blood CMV PCR load or fundus examination suggestive of CMV retinitis or CMV myeloradiculopathy were started on IV Ganciclovir Induction Therapy followed by oral Valganciclovir Maintenance Therapy and they were followed up till recovery.

Inclusion criteria

Adult HIV patients of either sex with CD4 T-cell count less than 100 cells/microliter.

Exclusion criteria

Patients previously treated or existing on treatment for cytomegalovirus infection.

Results

Table 1: Correlation of CD4 T cell count (/µL) with CMV DNA PCR (/mL)

Variables	CMV DNA PCR (/mL)
CD4 T cell count(/µL)	
Correlation coefficient	-0.554
P value	0.003

Pearson correlation coefficient

Significant negative correlation was seen between CD4 T cell count (/µL) with CMV DNA PCR (/mL) with correlation coefficient of -0.554.

ISSN:0975 -3583,0976-2833 VOL13, ISSUE 05, 2022

Table 2: Association of CD4 T cell count (/µL) with CMV Manifestations

	CMV Manifestations			
CD4 T cell count(/µL)	**No(n=22)**	**Yes(n=5)**	**Total**	**P value**
Mean ± SD	55.55 ± 24.1	26.8 ± 17.14	50.22 ± 25.37	0.019*
Median (25th-75th percentile)	54.5 (42-68.25)	22 (17-35)	52 (32-62)	
Range	8-97	8-52	8-97	

*Independent t test

Mean ± SD of CD4 T cell count (/µL) in patients with CMV manifestations was 26.8 ± 17.14 which was significantly lower as compared to patients with CMV Manifestations (55.55 ± 24.1). (p value=0.019)

Table 3: Association of HIV viral load (/mL) with CMV Manifestations

	CMV Manifestations			
HIV viral load(/mL)	**No(n=22)**	**Yes(n=5)**	**Total**	**P value**
Mean ± SD	72054.55 ± 34990.93	110100 ± 14302.1	79100 ± 35315.57	0.027*
Median (25th-75th percentile)	67000 (54750-79000)	104000 (100000-120000)	74000 (59150-98500)	
Range	10000-150000	96500-130000	10000-150000	

*Independent t test

Mean ± SD of HIV viral load(/mL) in patients with CMV manifestations was 110100 ± 14302.1 which was significantly higher as compared to patients without CMV manifestations (72054.55 ± 34990.93).(p value=0.027)

Table 4: Association of CD4 T cell count (/µL) with CMV DNA PCR

	CMV DNA PCR			
CD4 T cell count(/µL)	**Negative(n=23)**	**Positive(n=27)**	**Total**	**P value**
Mean ± SD	70.35 ± 24.06	50.22 ± 25.37	59.48 ± 26.53	0.006*
Median (25th-75th percentile)	80 (52-89)	52 (32-62)	57.5 (40-83.25)	
Range	19-99	8-97	8-99	

*Independent t test

Mean ± SD of CD4 T cell count(/µL) in negative CMV DNA PCR was 70.35 ± 24.06 which was significantly higher as compared to positive CMV DNA PCR (50.22 ± 25.37). (p value=0.006

ISSN:0975 -3583,0976-2833 VOL13, ISSUE 05, 2022

Table 5: Association of HIV viral load (/mL) with CMV DNA PCR

	CMV DNA PCR			
HIV viral load(/mL)	**Negative(n=23)**	**Positive(n=27)**	**Total**	**P value**
Mean ± SD	49573.91 ± 30484.95	79100 ± 35315.57	65518 ± 36055.47	0.003*
Median (25th-75th percentile)	43000 (22850-70200)	74000 (59150-98500)	64750 (39750-87900)	
Range	12000-120000	10000-150000	10000-150000	

*Independent t test

Mean ± SD of HIV viral load(/mL) in positive CMV DNA PCR was 79100 ± 35315.57 which was significantly higher as compared to negative CMV DNA PCR (49573.91 ± 30484.95). (p value=0.003)

Table 6: Correlation of CMV DNA PCR (/mL) with HIV viral load (/mL)

Variables	**HIV viral load(/mL)**
CMV DNA PCR (/ml)	
Correlation coefficient	0.537
P value	0.0001

Pearson correlation coefficient

Significant positive correlation was seen between CMV DNA PCR (/ml) with HIV viral load (/mL) with correlation coefficient of 0.537.

Table 7: Association of CMV DNA PCR (/mL) with CMV Manifestations

	CMV Manifestations			
CMV DNA PCR(/mL)	**No(n=22)**	**Yes(n=5)**	**Total**	**P value**
Mean ± SD	4378.18 ± 10920.91	29300 ± 18451.29	8993.33 ± 15685.35	0.036*
Median (25th-75th percentile)	120 (100-1975)	34000 (12000-41000)	720 (100-8950)	
Range	100-47000	8500-51000	100-51000	

*Independent t test

Mean ± SD of CMV DNA PCR(/mL) in patients with CMV Manifestations was 29300 ± 18451.29 which was significantly higher as compared to patients without CMV Manifestations (4378.18 ± 10920.91).

ISSN:0975 -3583,0976-2833 VOL13, ISSUE 05, 2022

Discussion

In our study, only 12 patients out of 27 of those peripheral blood CMV PCR positive patients had IgM antibody against CMV positive by ELISA method. It clearly suggests that CMV PCR is far more sensitive in detection of CMV viremia than serology. Quantitative PCR is much more helpful for detecting viral load and its correlation with disease activity as well as to monitor response to treatment by determining decreasing titres of viral load along with clinical improvement.

Min Zhao *et al*. found that 808 HIV/AIDS patients were detected CMV infection (29.05%) of which, 77.02% patients had a CD4 count less than 50/microliter and quantitative level of HIV-RNA in CMV infected group was higher than that of CMV uninfected group.[7] In our study, Mean ± SD of HIV viral load (/mL) in patients with CMV manifestations was 110100 ± 14302.1 which was significantly higher as compared to patients without CMV manifestations which was 72054.55 ± 34990.93 with p value of 0.027.

In our study we have found that Mean ± SD of CD4 T cell count(/µL) in positive CMV DNA PCR was 50.22 ± 25.37 which was significantly lower as compared to negative CMV DNA PCR (70.35 ± 24.06). (p value=0.006). Therefore, we can say that the risk of CMV infection increases with reduction of CD4 T-cell counts.

R F Miller *et al*. in their retrospective study found that out of 17 HIV patients with acute lumbosacral polyradiculopathy, infection with CMV was confirmed by polymerase chain reaction amplification in 15 patients, by culture in 1 patient and by clinical objective clinical response to anti-CMV treatment in one patient [8]. In present study, in majority (85.71%) of patients, CSF CMV PCR was negative. CSF CMV PCR was positive in only 1 out of 7 patients (14.29%) and that was the only patient presented with radiculopathy. CMV radiculopathy was seen in only 1 out of 27 serum CMV DNA PCR positive patients (3.70%).

In this study cohort, mean value of HIV viral load (/mL) of study subjects was 65518 ± 36055.47 with median (25th-75th percentile) of 64750 (39750-87900). Mean ± SD of HIV viral load(/mL) in positive CMV DNA PCR was 79100 ± 35315.57 which was significantly higher as compared to negative CMV DNA PCR (49573.91 ± 30484.95) with p value of 0.003. Mean ± SD of HIV viral load (/mL) in patients with CMV manifestations was 110100 ± 14302.1 which was significantly higher as compared to patients without CMV manifestations (72054.55 ± 34990.93) with p value of 0.027. So, we can say that the incidence of CMV infection as well as its different clinical manifestations significantly increase with high HIV viral load in these patients.

Cytomegalovirus infection is an AIDS-defining condition which is now becoming less common than in the past due to the extensive use of highly active antiretroviral therapy (HAART) which was approximately 40% of HIV infected patients with advanced immunosuppression previously. In present study, in 27 (54.00%) patients, CMV DNA PCR was positive. CMV DNA PCR was negative in only 23 out of 50 patients (46.00%). Out of those 27 positive patients, only 5 (18.52%) patients had significant clinical manifestations of CMV infection.

All the 5 patients with CMV infection related manifestations were admitted in our institute and “Induction Treatment” with IV Ganciclovir 5 mg/kg two times per day for 21 days was given followed by that they were put on Oral Valganciclovir 900 mg once a day “Maintenance Treatment” until adequate resolution CMV retinitis and the CD4

ISSN:0975 -3583,0976-2833 VOL13, ISSUE 05, 2022

T-cell count remained more than 100 cells/microliter for more than 6 months with regular monthly follow ups [9].

There is a variable prevalence of tuberculosis as an opportunistic infection in HIV like, a study conducted by Kumarasamy *et al*. [10] observed 46% patients with pulmonary tuberculosis while 15% patients had extra pulmonary tuberculosis. Similarly, Srirangaraj *et al*. [11] observed prevalence of 68.83% of pulmonary tuberculosis and 31.17% prevalence of extra pulmonary tuberculosis. In our study, 12% patients had tuberculosis out of which 8% had abdominal tuberculosis while 4% had pulmonary + abdominal tuberculosis. So, the prevalence of extra pulmonary tuberculosis was more in our study subjects [12].

We observed 2% prevalence of cryptococcal meningitis and 4% prevalence of cryptococcal pneumonia in our study subjects. 2 patients with CSF findings suggestive tuberculous meningitis were also found to have hydrocephalus and anti-TB drugs were started for them. During the study, 1 patient was found to have Giardia enterica infection and appropriate treatment was given.

Conclusion

- CMV viral load was higher in patients with CMV infection related manifestation. Therefore, it is also a useful tool for determining the extent of infection and disease activity as well as to monitor the response to the treatment of CMV infection.
- Mean CD4 T-cell counts were comparatively low and Mean HIV viral load was significantly higher in patients with CMV infection related manifestations. So, advancement of HIV infection will also increase the risk of CMV related organ damage. It shows the importance of early and aggressive start of Highly Active Anti-Retroviral Therapy (HAART) as soon as the diagnosis of HIV is made.

References

1. Naumnik B, Malyszko J, Chyczewski L, Kovalchuk O, Mysliwiec M. Comparison of serology assays and polymerase chain reaction for the monitoring of active cytomegalovirus infection in renal transplant recipients. Transplant. Proc. 2007;39(9):2748-50.
2. Rasmussen L, Kelsall D, Nelson R, Carney W, Hirsch M, Winston D, *et al*. Virus-specific IgG and IgM antibodies in normal and immunocompromised subjects infected with cytomegalovirus. J Infect. Dis. 1982;145(2):191-9.
3. Kim DJ, Kim SJ, Park J, Choi GS, Lee S, Kwon CD, *et al*. Realtime PCR assay compared with antigenemia assay for detecting cytomegalovirus infection in kidney transplant recipients. Transplant. Proc. 2007;39(5):1458-60.
4. Mhiri L, Kaabi B, Houimel M, Arrouji Z, Slim A. Comparison of pp65 antigenemia, quantitative PCR and DNA hybrid capture for detection of cytomegalovirus in transplant recipients and AIDS patients. J Virol. Methods. 2007;143(1):23-8.
5. Seehofer D, Meisel H, Rayes N, Stein A, Langrehr JM, Settmacher U, *et al*. Prospective evaluation of the clinical utility of different methods for the detection of human cytomegalovirus disease after liver transplantation. Am J Transplant. 2004;4(8):1331-37.
6. Sonnenberg P, Glynn JR, Fielding K, Murray J, Godfrey-Faussett P, Shearer S.

ISSN:0975 -3583,0976-2833 VOL13, ISSUE 05, 2022

How soon after infection with HIV does the risk of tuberculosis start to increase? A retrospective cohort study in South African gold miners. J Infect Dis. 2005;191:150-8.

7. Zhao M, Zhuo C, Li Q, Liu L. Cytomegalovirus (CMV) infection in HIV/AIDS patients and diagnostic values of CMV-DNA detection across different sample types. Ann Palliat 2020;9(5):2710-15.
8. Miller RF, *et al*. Acute lumbosacral polyradiculopathy due to cytomegalovirus in advanced HIV disease: CSF findings in 17 patients. Journal of Neurology, Neurosurgery and Psychiatry 1996;61:456-60.
9. Stewart MW. Optimal management of cytomegalovirus retinitis in patients with AIDS. Clin Ophthalmol. 2010;4:285-99.
10. Kumarasamy N, Solomon S, Paul SAJ, Venilla R, Amalraj RE. Spectrum of opportunistic infections among AIDS patients in Tamil Nadu, India. Int J STD AIDS. 1995;6(6):447-9.
11. Srirangaraj S, Venkatesha D. Opportunistic infections in relation to antiretro-viral status among AIDS patients from south India. Indian J Med Microbiol. 2011;29(4):395-400.
12. Kaur R, Dhakad MS, Goyal R, Bhalla P, Dewan R. Spectrum of opportunistic fungal infections in HIV/AIDS patients in tertiary care hospital in India. Can J Infect Dis Med Microbiol. 2016;1:1-7.

Accepted on 28/05/2022