Journal of Cardiovascular Disease Research

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

Original research article

CLINICAL PROFILE OF CYTOMEGALOVIRUS INFECTION IN HIV PATIENTS

[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

Cytomegalovirus is a genus of viruses in the order herpesvirales, in the family herpesviridae, in the sub family beta-herpesvirinae. Humans and monkeys serve as natural hosts.

Severity of cytomegalovirus infection is associated with its tropism for retina and central nervous system. It generally affects patients with major deficit in cellular immunity. A cross sectional observational study was conducted in Department of General Medicine and ART Centre. 50 consecutive adult HIV patients of either sex with CD4 T-cell count less than 100 cells/microliter were included in the study. 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.

Keywords: Cytomegalovirus, HIV Patients, Cd4 T-Cell count

Introduction

Cytomegalovirus disease is one of the serious opportunistic infections due to reactivation of previously latent infection or newly acquired infection which occurs frequently in immunocompromised patients by HIV infection, organ transplantation, malignancy etc.

It is uncommon in the developed nations with the widespread use of Highly Active Anti-Retroviral Therapy (HAART), but in developing countries, despite efforts made by public health programs to prevent the HIV infection, the diagnosis is still late; which lead to high rate of morbidity and mortality due to cytomegalovirus and other opportunistic infections like Toxoplasma, Rubella, Herpes Simplex etc. [1] Approximately 20-40% of adults developed CMV disease before the use of highly active antiretroviral therapy which has substantially decreased the occurrence of CMV

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

disease but, it is still a significant threat to immunocompromised patients as in HIV patients with CD4 T-cell count less than 100 cells/microliter [2]. A patient with AIDS has a 30% lifetime risk of developing CMV retinitis once the CD4 T-cell count drops below 50 cells/microliter [3].

Cytomegalovirus is a genus of viruses in the order herpesvirales, in the family herpesviridae, in the sub family beta-herpesvirinae. Humans and monkeys serve as natural hosts.

Severity of cytomegalovirus infection is associated with its tropism for retina and central nervous system. It generally affects patients with major deficit in cellular immunity.

Cytomegalovirus is a major debilitating opportunistic infection in patients with advanced HIV with CD4 T-cell count less than 100 cells/microliter [4]. Retinitis is a major manifestation (~15%) of the disease with insidious onset and symptoms of blurred vision, floaters and visual field defects which can result in blindness if untreated. The gastrointestinal tract is the 2nd most common (~10%) site of cytomegalovirus infection and colon is the most frequently affected organ. Other less common but serious manifestations are cytomegalovirus encephalitis, myeloradiculopathy, pneumonitis, hepatitis etc. [5, 6]

Cytomegalovirus infection is an AIDS-defining condition which is now very less common than in the past due to the extensive use of antiretroviral therapy which was approximately 40% of HIV infected patients with advanced immunosuppression previously. Cytomegalovirus is a cofactor for rapid HIV disease progression as it has been associated with inflammation, immune activation and it is a predictor of end organ damage which results in a significant exacerbation of morbidity and mortality [7].

Diagnosis of Cytomegalovirus infection can be achieved by clinical examination, dilated fundus examination with indirect ophthalmoscopy, cytomegalovirus IgM antibody test, pp65 antigenemia test, examination of formalin fixed, paraffin embedded tissue & immunohistochemistry, cytomegalovirus Quantitative DNA Polymerase chain reaction (PCR), tissue cultures etc.

Newer methods for detection of Cytomegalovirus viremia are Quantitative PCR and detection of Antigen pp65 by the antigenemia test in peripheral blood polymorphonuclear leukocytes.

High level of antigenemia test measured by the pp65 antigenemia test is correlated with clinical cytomegalovirus disease in HIV patients. But quantitative PCR testing is much quicker and more sensitive than the cytomegalovirus pp65 antigen assay.

With the deterioration of immune system in HIV AIDS patients, the cytomegalovirus infection disseminates and cell free virus can be detected in serum and plasma by PCR. Cytomegalovirus establishes lifelong latency following primary infection. Thus, positive antibody test is often not helpful to distinguish reactivation from latent infection. Positive serology involves performing a Cytomegalovirus DNA PCR before starting HAART If CD4 T-cell count is less than 100 cells/microliter. PCR is also more sensitive than cultures and correlates with development of cytomegalovirus disease. Oral Ganciclovir can be used to prevent development of Cytomegalovirus disease in patients of HIV AIDS. Therefore, it is imperative to identify patients at high risk of developing cytomegalovirus at an early stage.

Acute lumbosacral polyradiculopathy, also known as cauda equine syndrome is an

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

uncommon but distinctive neurological syndrome that occurs in patients with advanced HIV disease. Patients usually presents with subacute onset bilateral lower motor neuron leg weakness, progressing to flaccid paraparesis, often associated with pain, paraesthesia areflexia and sphincter dysfunction. CSF studies show pleocytosis with a polymorphonuclear leucocyte predominance with raised protein. CMV in CSF can be identified by culture, in situ hybridization or the polymerase chain reaction (PCR).

Tuberculosis has surpassed HIV as the leading infectious cause of deaths worldwide. HIV patients are at high risk of developing TB and account for approximately 9% of new TB cases and nearly 300,000 TB related deaths worldwide. The incidence of TB has significantly decreased with widespread use of HAART in HIV patients however, the burden of TB remains high in this population. India has the third highest HIV burden and the highest TB burden globally with approximately 1 million new TB cases in HIV patients every year [8].

The most common fungal infection in among advanced HIV patients is cryptococcosis and its incidence is increasing with the rapid spread of the disease [9, 10]. Cryptococcosis is one of the most important risk factors associated with very high degree of morbidity and mortality in advanced HIV patients [9, 10].

Methodology

Study place: Department of General Medicine and ART Centre.

Study design: Cross sectional observational study.

Study group: Patients attending ART Centre.

Sample size: 50 consecutive HIV patients attending ART centre at Hospital with CD4 T-cell count less than 100/microliter.

Sample size

Formula: $n = (Z_{1-\alpha/2})2 * p * q/d^2$.

Where, $(Z_{1-\alpha/2})$ = 95% Confidence interval, p = Prevalence, q = 1-p, d = Allowable error. Chakravarti *et al*. [2] stated in their study that there is 25-40% occurrence of CMV disease in AIDS patients.

So, $n = (1.96)^2 * 40 * 60/(10)$

$= 92.19$

Sample size was calculated as 92. However, according to the data that is available with us about HIV patients with CD4 T-cell count less than 100 cells/microliter, we are likely to get around 50 patients during our study period. Therefore, we are taking 50 as a sample size of convenience.

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.

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

Results

Table 1: Distribution of age (years) of study subjects

Age (years)	Frequency	Percentage
18-30	16	32.00%
31-40	15	30.00%
41-50	9	18.00%
51-60	10	20.00%
Mean ± SD	38.38 ± 11.5	
Median (25th-75th percentile)	37(28.25-50)	
Range	19-60	

Table 2: Descriptive statistics of CD4 T cell count (/µL) of study subjects

Variable	Mean ± SD	Median (25th-75th percentile)	Range
CD4 T cell count(/µL)	59.48 ± 26.53	57.5(40-83.25)	8-99

Mean value of CD4 T cell count (/µL) of study subjects was 59.48 ± 26.53 with median (25th-75th percentile) of 57.5(40-83.25).
In present study, in 54.00% of patients, CMV DNA PCR was positive. CMV DNA PCR was negative in only 23 out of 50 patients (46.00%).

Table 3: Descriptive statistics of CMV DNA PCR (/mL) of study subjects

Variable	Mean ± SD	Median (25th-75th percentile)	Range
CMV DNA PCR(/mL)	8993.33 ± 15685.35	720(100-8950)	100-51000

Mean value of CMV DNA PCR (/mL) of study subjects was 8993.33 ± 15685.35 with median (25th-75th percentile) of 720(100-8950).

Table 4: Descriptive statistics of complete blood count of study subjects

Complete blood count	Mean ± SD	Median (25th-75th percentile)	Range
Hemoglobin (gm/dL)	9.41 ± 1.98	9.15(7.925-10.575)	6-13.6
Total leucocyte count (/cumm)	7003.6 ± 4778.78	5400(4300-7950)	2000-26550
Platelets (in lakhs) (/cumm)	1.62 ± 0.6	1.7(1.3-1.938)	0.1-3.5
Red blood cell count ($X10^6$ per cumm)	3.28 ± 0.6	3.14(2.825-3.875)	2.15-4.4

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

PCV (%)	28.58 ± 5.74	27.65(24.05-32.675)	19-41
MCV (fl)	87.13 ± 11.95	85.5(79-94.3)	68-126.8
MCHC (%)	33.02 ± 2.65	33.95(32-34.6)	23.5-38

Table 5: Distribution of peripheral smear of study subjects

Peripheral smear	Frequency	Percentage
Macrocytic RBCs	7	14.00%
Normal leukocytes	40	80.00%
P. falciparum gametocytes	1	2.00%
Platelet adequate	39	78.00%
Leukocytosis	5	10.00%
Leukopenia	5	10.00%
Reduced platelet	12	24.00%
Microcytic RBCs	10	20.00%
Normocytic Normochrommic RBCs	33	66.00%

Table 6: Descriptive statistics of glycaemic parameters of study subjects

Glycemic parameters	Mean ± SD	Median (25th-75th percentile)	Range
FBS (mg/dL)	92.08 ± 7.94	90(86-97)	80-114
PPBS (mg/dL)	135.2 ± 10.52	134.5(128.25-139.75)	117-167

Table 7: Descriptive statistics of kidney function test parameters of study subjects

Kidney function test parameters	Mean ± SD	Median (25th-75th percentile)	Range
Urea (mg/dL)	26.58 ± 11.19	24(20-29)	7-69
Serum creatinine (mg/dL)	0.64 ± 0.24	0.6(0.5-0.775)	0.2-1.41
Uric acid (mg/dL)	3.63 ± 0.96	3.4(3.025-4.075)	1.8-6.2

Table 8: Descriptive statistics of liver function test parameters of study subjects

Liver function test parameters	Mean ± SD	Median (25th-75th percentile)	Range
SGOT(IU/L)	42.06 ± 50.83	29(20.25-37)	7-328
SGPT(IU/L)	37.92 ± 25.6	30(22.25-38.75)	13-130
ALP(IU/L)	127.24 ± 110.27	96.5(78-120.75)	50-628
Serum bilirubin(mg/dL)	1.41 ± 2.7	0.9(0.52-1.1)	0.15-18.8

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

Table 9: Distribution of urine R/M of study subjects

Urine R/M	Frequency	Percentage
Normal	42	84.00%
Trace protein	3	6.00%
1+ protein	4	8.00%
2+ protein	1	2.00%
Total	50	100.00%

Table 10: Distribution of ECG findings of study subjects

ECG findings	Frequency	Percentage
Normal sinus rhythm	50	100.00%
Total	50	100.00%

Table 11: Distribution of chest X-ray PA view of study subjects

Chest X ray PA view	Frequency	Percentage
Normal	44	88.00%
Pleural effusion	3	6.00%
Consolidation	1	2.00%
B/L Infiltrates	2	4.00%
Total	50	100.00%

Table 12: Distribution of USG W/A findings of study subjects

USG W/A findings	Frequency	Percentage
Pleural effusion	3	6.00%
Splenic granuloma	1	2.00%
Hepatomegaly	9	18.00%
Splenomegaly	19	38.00%
BL kidney raised cortical echogenicity	1	2.00%
Mesenteric lymphadenopathy	5	10.00%
Omental thickening	1	2.00%
Hepatosplenomegaly	4	8.00%
Ascites	4	8.00%
Periampullary carcinoma	1	2.00%

Table 13: Descriptive statistics of HIV viral load (/mL) of study subjects

Variable	Mean ± SD	Median (25th-75th percentile)	Range
HIV viral load(/mL)	65518 ± 36055.47	64750(39750-87900)	10000-150000

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

Mean value of HIV viral load (/mL) of study subjects was 65518 ± 36055.47 with median (25th-75th percentile) of 64750(39750-87900).

Table 14: Distribution of CSF CMV PCR of study subjects

CSF CMV PCR(n=7)	Frequency	Percentage
Negative	6	85.71%
Positive	1	14.29%
Total	7	100.00%

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.

Table 15: Distribution of TORCH profile of study subjects

TORCH Profile	Frequency	Percentage
CMV+	12	24.00%
Negative	38	76.00%
Total	50	100.00%

In present study, in majority (76.00%) of patients, TORCH profile was negative. TORCH was CMV+ in only 12 out of 50 patients (24.00%).

Table 16: Distribution of CMV manifestations of study subjects

CMV manifestations(n=-27)	Frequency	Percentage
Retinitis	5	18.52%
Polyradiculopathy	1	3.70%

In present study, in 18.52% of patients, CMV manifestation was retinitis. CMV manifestation was radiculopathy in only 1 out of 27 patients (3.70%).

Discussion

HIV patients with low CD4 T-cell counts are prone to wide variety of opportunistic infections that includes Tubercular, Bacterial, Fungal, Parasitic, Viral etc. Tuberculosis, bacterial pneumonia, herpes zoster, oropharyngeal candidiasis etc. can occur in HIV patients with CD4 T-cell count less than 500/microliter. Patients with CD4 T-cell count less than 100 cells/microliter are prone to pneumocystis jiroveci pneumonia, oesophageal candidiasis, toxoplasmosis, cryptococcal meningitis, cryptosporidiosis etc. Patients with CD4 T-cell count less than 50/microliter can be infected with mycobacterium avium complex, cytomegalovirus etc.

Cytomegalovirus infection is associated with wide variety of clinical presentations

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

which includes Retinitis, Colitis, Myeloradiculopathy, Encephalitis, Pneumonia etc. in HIV patients with CD4 T-cell count less than 100 cells/microliter and more common with less than 50 cells/microliter.

A study group included a total of 50 HIV patients with a mean age of 38.38 ± 11.5 years, ranging from 19 years to 60 years. The median age was 37 years and male to female ratio was approximately 3:1. Mean CD4 T cell count was 59.48 ± 26.53/microliter, ranging from 8-99/microliter.

Out of 50 HIV patients, 27(54%) patients had positive CMV DNA PCR report and 23(46%) patients had negative CMV DNA PCR report. Mean CMV viral load was 8993.33 ± 15685.35/ml among positive CMV DNA PCR patients, ranging from less than 100-51000/ml. Out of 27 CMV DNA PCR positive patients, only 5(18.52%) had some manifestations of CMV infection. 5(18.52%) of CMV DNA PCR positive patients had retinitis and 1(3.70%) of those 5 patients also had CMV infection related myeloradiculopathy. 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.

Chakravarti A *et al*., said in Indian journal of microbiology that the risk of Cytomegalovirus is highest when CD4 counts are below 50 cells/microliter and is rare with more than 100 cells/microliter.[2] The mean CD4 T-cell count(/µL) of CMV DNA PCR positive patients in our study is 50.22, ranging from 8-97/microliter. 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 without CMV manifestations which is 55.55 ± 24.1. (p value=0.019)

Jacobson MA *et al*., quoted in their study that chorioretinitis most commonly occurs with CD4 counts less than 50 cells/microliter [11]. In a Retrospective study conducted by Guobao Huang *et al*. [12] with 67 AIDS patients, they found that the CD4 T-cell count was 0-141 cells/microliter when cytomegalovirus retinitis developed. Of all, the CD4 T-cell count of 77.9% cases was less than 50 cells/microliter, 50-100 cells/microliter in 14.7% cases and more than 100 cells/microliter in 7.4% cases. In our study, the mean CD4 cell count of patients with chorioretinits is 26.8 cells/microliter ranging from 8 to 52 cells/microliter. This finding corresponds with this study.

In the study conducted by Bowen *et al*., Quantitative analysis of CMV PCR-positive patients showed that viral load at entry of study was 3.64 to 5.66 log10 copies/ml and at presentation of CMV disease it was ranged from 4.51 to 7.05 log10 copies/ml [13]. In another prospective study carried by Casado *et al*., Mean CMV load was significantly higher with 3700 copies per ml in those patients who developed CMV retinitis and 384 copies per ml in those who did not develop CMV retinitis. Shinkai M *et al*., conducted a natural history study with median baseline CD4 count of 54/microliter found that 41 out of 94 patients were CMV PCR-positive and out of those 24 developed documented CMV disease who had a median of 473 CMV DNA copies/microliter compared to 17 other patients who never developed disease with median of 35 CMV DNA copies/microliter [14]. In our study 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

Conclusion

- In present study, in 54.00% of patients, CMV DNA PCR was positive. CMV DNA PCR was negative in only 23 out of 50 patients (46.00%).
- 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.

References

1. El Fane M, Sodqi M, EL Rherbi A, Chakib A, Oulad Lahsen A, *et al*. Cytomegalovirus Disease in Patient with HIV infection. J Antimicro. 2016;2:108.
2. Chakravarti A, *et al*. Human Cytomegalovirus infection among patients living with AIDS in a tertiary level hospital in India. J Int Assoc Physicians AIDS care (Chic.). 2010;9(2):94-7.
3. Jabs DA. Cytomegalovirus retinitis and the acquired immunodeficiency syndrome-bench to bedside: LVII Edward Jackson Memorial Lecture. Am J ophthalmol. 2011;151(2):198-216.
4. Gemma GM, Parea M, Percivalle E, *et al*. Human Cytomegalovirus Viraemia in HIV-1 seropositive patients at various clinical stage infection. AIDS. 1990;4:1027-31.
5. Mills JM. Serious Cytomegalovirus disease in the AIDS. Ann Intern Med. 1988;108:585-94.
6. Jabs DA, Green WR, Fox R, Polk BF, Bartlett JG. Ocular manifestations of AIDS. Ophthalmology. 1989;96:1092-99.
7. R. P, Vergara A, Monclus E. Cytomegalovirus infection in HIV-infected patients in the era of combination antiretroviral therapy. BMC infect Dis. 2019;19:10-30.
8. Gupte AN, Kadam D, Sangle S, Rewari BB, Salvi S, Chavan A. Incidence of tuberculosis in HIV-infected adults on first-and second-line antiretroviral therapy in India. BMC Infect Dis, 2019, 19(1).
9. Jain S, Singh AK, Singh RP, Bajaj JK, Damle AS. Spectrum of opportunistic fungal infections in HIV-infected patients and their correlation with CD4+ counts in western India. Journal of Medical Microbiology and Infectious Diseases. 2014;2(1):19-22.
10. Pfaller MA, Diekema DJ. Progress in antifungal susceptibility testing of Candida spp. by use of Clinical and Laboratory Standards Institute broth microdilution methods, 2010 to 2012. J Clin Microbiol. 2012;50(9):2846-56.
11. Jacobson MA, Mills J. Serious cytomegalovirus disease in the acquired immunodeficiency syndrome (AIDS). Ann Intern Med. 1988;108:585-94.
12. Guobao Huang, Qiang Jiang, Mei Li, Yong Lu, Zhen Wang. Retrospective study of Cytomegalovirus retinitis complicated with Acquired immunodeficiency syndrome. Int. J Clin Exp Med. 2015;8(6):9537-42.
13. Bowen, Frances E, Sabin, Caroline A, Wilson Pauline, Griffiths Paul D, *et al*. Emery; Vincent C. AIDS: 1997;11(7):889-93.
14. Shinkai M, Bozzette Sam Powderly W, Frame P, Spector SA. Utility of urine and leukocyte culture and plasma DNA polymerase chain reaction for identification of AIDS patients at risk for human cytomegalovirus disease, J infect Dis. 1997;175:502-8.

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

Accepted on 26/05/2022