Original Article

Microbiology Section

The Reactivation of the Cytomegalovirus (CMV) Infection in HIV Infected Patients

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ABSTRACT

Background: CMV is a virus of paradoxes and can be a potential killer or a silent companion lifelong. The CMV infection in immunocompromised patients carries high morbidity and mortality. In most people with a fully functional immune system, an initial infection with CMV may cause a mild flu like illness and later the virus remains dormant. A damaged immune system permits CMV reactivation. The magnitude of this problem in India has not been adequately investigated and it is still a major health problem, warranting strong preventive measures.

Aims: We planned to study the prevalence of the CMV infection, re infection and the reactivation of the CMV infection in persons who were infected with HIV and AIDS and to correlate the reactivation of this disease with the CD 4 cell count in these patients.

Settings And Design: This study was planned on patients who attended the ICTC center and it was conducted over a period of six months.

Methods And Material: This study was conducted on 94 patients who were reactive for the HIV1 and/or HIV2 antibodies. The serum samples were tested for the IgG and IgM antibodies which were directed against CMV by ELISA.

Results: Among the 94 cases, IgG antibodies were detected in 84 (89.4%) and IgM in 10(10.6%) cases. Among the 84 IgG cases, 42 were males and 42 were females. The IgM antibodies were positive in 4 (9.52%) out the 42 cases of AIDS and in 6 (11.5%) out of the 52 seropositive healthy individuals.

Statistics: Percentage and Chi square tests were applied.

Conclusion: As there is a high seroprevalence of the CMV infection in HIV positive patients and as there is a reactivation of CMV in healthy and immuno suppressed HIV positive patients, the early diagnosis of the CMV IgM antibodies help in the early detection of the reactivation of the virus before the development of the clinical manifestations. They improve the survival and protect the patients from the development of end organ disease.

Key Words: CD4 count, CMV, HIV

KEY MESSAGE

- The CMV active infection might be a marker of extremely severe immunosuppression which may ultimately lead to a fatal outcome in the patients.
- This reactivation is indicated by presence of IgM antibodies in such persons.
- The presence of the IgM antibodies may be due to reactivation or reinfection by CMV.
- There is a reactivation of the CMV in healthy and immuno suppressed HIV positive patients the early diagnosis of the CMV IgM antibodies help in the early detection of the reactivation of the virus before the development of the clinical manifestations.

INTRODUCTION

Cytomegalovirus (CMV) is a ubiquitous herpes virus that generally causes asymptomatic or mildly symptomatic infections in immunocompetent hosts. In contrast, the CMV infection in immunocompromised patients carries high morbidity and mortality [1].

The CMV infection is endemic throughout the world. The infection with CMV is more common in the developing nations and among the people who belong to the lower socioeconomic section of the society. The seroprevalence varies greatly with a variety of epidemiological factors such as age, geographical distribution, socioeconomic status, marital status and parity. In different parts of India, serological surveys have shown an 80-90% prevalence of the CMV IgG antibodies in healthy individuals, indicating a past exposure to the virus [2-8].

In most people with a fully functional immune system, the initial infection with CMV may cause a mild flu like illness and later the virus may remain dormant. A damaged immune system permits the reactivation of CMV. A synergistic effect may worsen the immunological profile and could potentially translate into a more rapid disease progression in HIV infected persons [3]. The tumour necrosis factor (TNF)-α -mediated stimulation of the host cell leads to the intranuclear accumulation of the nuclear factor kB and causes the activation of the CMV DNA replication. This might explain the high prevalence of the CMV reactivation in HIV infection [1].

During advanced AIDS, CMV can produce debilitating end-organ disease (EOD) including retinitis, colitis, and pneumonitis. Previous to the HAART (highly active antiretroviral therapy) era, some studies observed that the rates of the CMV EOD among the patients

with advanced HIV infection were approximately 40% or greater. With the advent of HAART, the incidence of the CMV EOD has reduced [9-10].

The CMV IgG antibodies are present in long standing CMV seropositive people but the clinical manifestations of the CMV disease do not generally present until the CD4 count drops below 100 cells/cmm [11]. The Enzyme Linked Immunosorbent Assay (ELISA) is the most commonly available test for measuring the antibodies to CMV. Measuring the CMV IgG antibodies indicates that the person had exposure to CMV in the past. The CMV IgM antibody testing indicates the presence of a recent or the reactivation of the CMV infection [8].

The magnitude of this problem in India has not been adequately investigated and it is still a major health problem, warranting strong preventive measures. We planned to study the prevalence of the CMV infection, re infection and the reactivation of the CMV infection in persons who were infected with HIV and AIDS and to correlate the reactivation of the disease with the CD 4 cell counts in these patients.

MATERIALS AND METHODS

This study was conducted on 94 patients who attended the ICTC center, who were reactive for the HIV1 and/or the HIV2 antibodies. This study was conducted over a period of six months at the Mamata Medical College, Khammam, Andhra Pradesh. All the patients were from rural areas and they belonged to the lower socioeconomic group. A majority of them were farmers and labourers. Patient consent was taken and clearance from ethical committee of college was obtained. The patients were in the age group which ranged from 20 to 60 years.

The serum samples were tested for the IgG and IgM antibodies which were directed against CMV. The antibodies were detected by a third generation ELISA method and the kit was supplied by Equipar Lilac Medicare Private Limited (US FDA approved). The assay was performed as per the manufacturer's instructions. The CD4 + T lymphocyte count of all the patients was obtained.

RESULTS

Out of the 94 cases, IgG antibodies were detected in 84 (89.4%) and IgM antibodies in 10(10.6%) cases. Among the 84 IgG cases, there were 42 males and 42 females. The IgM antibodies were positive in 4 (9.52%) out the 42 cases of the AIDS patients and in 6 (11.5%) out the 52 seropositive healthy individuals. The Chi square test was applied and the two-tailed P value equalled to 1.0000. The association between the CD 4 count and the IgM antibodies was considered to be statistically not significant.

DISCUSSION

CMV is a virus of paradoxes and it can be a potential killer or a silent companion lifelong. It is probably one of the most common infections which are known to humans and is characterized by a self limiting infection in healthy individuals. The infection with CMV is more common in the developing nations and in the people who belong to the lower socio-economic sections of the society.

CD4 count	IgG Positive	IgM Positive	Total
< 200cells/mm^3	38	4	42
> 200cells/mm^3	46	6	52
Total	84	10	94

[Table/Fig-1]: Showing number of IgG and IgM positive patients and their CD 4 cell count

After CMV infection in immunocompetent individuals, a disease occurs in a small number of cases and it is usually manifested as an infectious mononucleosis-like syndrome. It is different from what happens with immunodeficient patients where different clinical manifestations are associated with the CMV disease such as retinitis, colitis and encephalitis. In these patients, the disease frequently occurs as a reactivation of the latent virus in CMV seropositive patients. The risk of the CMV disease is highest when the CD 4 count is < 50 cells /cmm and it is rare when the count is > 100 cells/cmm. Likewise, it has been shown that the CD4 lymphocyte levels below 50 cells/cmm are important markers in the prognosis of the clinical manifestations of CMV and that they also indicate a disease phase which is frequently defined as advanced AIDS [3,12].

The CMV reactivation in AIDS patients is due to the tumour necrosis factor (TNF α) mediated stimulation of the host cells, leading to intranuclear accumulation and the activation of the CMV DNA replication [13]. HIV patients who are unable to control CMV replication have an increased risk of HIV disease progression and death. Both symptomatic and asymptomatic CMV infections are associated with an increased risk of death in the AIDS patients this might be due to organ failure which is related to the CMV end organ disease [14,15].

The CMV active infection might be a marker of extremely severe immunosuppression, which may ultimately lead to a fatal outcome in the patients. This reactivation is indicated by the presence of IgM antibodies in such persons. The presence of the IgM antibodies may be due to reactivation or reinfection by CMV. The CMV IgG antibodies are present in long standing CMV seropositive people. The high incidence (89.7%) of the IgG antibodies in our study indicates that these persons have been previously infected by CMV. This fact is in accordance with the high rates of CMV infection in the Indian scenario. This high incidence may be attributable to a common factor of high risk behaviour for HIV and the CMV infection.

Positivity for IgM was seen in 4(9.52%) cases of the AIDS patients, whereas it was seen in 6(11.5%) cases of the healthy seropositive individuals. The incidence of the IgM positivity correlates with those of other Indian studies in which they have observed positivity rates of about 3–10 % [3,16, 17, 18]. We have applied the Chi square test for the correlation of the CD4 count with the presence of the IgM antibodies in these patients. The value of p was 1.0000. It can be concluded that there was no significant correlation between the CD4 counts and the presence of the IgM antibodies thus, the reactivation of CMV occurs even if the CD4 counts are above 200cells/cmm. Surprisingly, in healthy seropositive persons, the incidence of the IgM antibodies was 11.5 %.

There are a few reports which are available on the CMV infection in Indian patients with HIV/AIDS, which are based primarily on the evaluation of clinical findings or autopsy [17]. As there is paucity of literature regarding such studies in the Indian perspective, further studies with larger sample sizes are required to know the effectiveness of these diagnostic modalities for a better management of these life threatening complications of CMV.

In India, the better care of the HIV infected persons and the affordability of HAART have changed the scenario in patients who live with HIV/AIDS [16]. The evaluation of the IgM antibodies by ELISA is easier to perform and less expensive. Some studies

have doubts about the effectiveness of the detection of the IgM antibodies by ELISA because of the less sensitivity of this test [16,17]. This is because, in immunocompromised patients, there may be delayed antibody formation, thus reducing the sensitivity of the test. The PCR (polymerase chain reaction), pp65 assays are highly specific for the diagnosis of the CMV reactivation, but considering the resource poor centers in India, the detection of the IgM antibodies by ELISA can be cost effective for a better management of the persons who live with HIV/AIDS.

It is important to know the CD4 cell count values in the staging of the HIV patients so that an effective antiretroviral treatment can be initiated at an appropriate time during the surveillance of the HIV-infected population.[18]

As there is a high seroprevalence of the CMV infection in HIV positive patients and as there is a reactivation of CMV in healthy and immuno suppressed HIV positive patients, the early diagnosis of the CMV IgM antibodies can help in the early detection of the reactivation of the virus before the development of the clinical manifestations. It also improves the survival and protects them from the development of end organ disease.

LIMITATIONS OF THE STUDY

We have not followed up these patients after antiretroviral therapy. Hence, we could not know as to how many patients have developed end organ disease or the progression of the CMV infection.

The study was limited by its small size sample.

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