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Research Article

Retinal Manifestations in Acquired Immuno Deficiency Syndrome: A Clinical Study and their Relationship to CD_4 Cell Count

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Abstract

Background: HIV is a multisystem disorder causing a wide spectrum of diseases. Ocular manifestations which occur in 70-80% of HIV patients may be the initial presentation of a systemic infection in an asymptomatic patient. HIV-related ocular symptoms can vary depending on CD_4+ T lymphocyte levels.

Aim: To analyze the retinal manifestations of HIV/AIDS patients and to evaluate its association with CD_4 cell counts.

Material and Methods: HIV patients with CD_4T cell count < 200 cells/mm^3 and WHO stage 4 disease irrespective of CD_4 cell count were included in the study. Detailed history and ocular examination were undertaken along with systemic evaluation.

Observations: Out of total 306 patients examined, 86 (28%) had retinal manifestations. Majority of patients belonged to age group 20-40 yrs (69%). Most common retinal manifestations were HIV retinopathy (19%), then CMV retinitis (6%). Retinal manifestations were more among those with CD_4 count < 50 cells/mm^3. In HIV positive patients with retinal manifestations, HIV retinopathy seen as comparatively early manifestation, while CMV retinitis seen as a late manifestation. There is increased risk for CMV retinitis in those with CD_4 cell count <50 cells/mm^3 which is statistically significant with p value <0.0001. HIV retinopathy is seen more in those with CD_4 cell count between 50-200 cell/mm^3 (26%) and this is statistically significant with p value < 0.045

Conclusion: Most common retinal manifestations in AIDS patients were HIV retinopathy and CMV retinitis, which has an inverse association with CD_4 cell count of the patient. Our study highlights the importance of ophthalmological examination in HIV patients especially with low CD_4 count, which can help in early diagnosis and management, which will considerably decrease the visual morbidity in such patients.

Keywords: HIV Infection; AIDS; Ocular Manifestations; HIV Retinopathy; CMV Retinitis

Introduction

Acquired immunodeficiency syndrome (AIDS), is a potentially fatal multisystem illness marked by a significant immune system disruption and susceptibility for several opportunistic infections and neoplasms. Infection with HIV results in selective loss of CD_4 T cells initiated by the specific binding of the HIV envelops glycoprotein, gp120 to the CD_4+receptor [1]. Progressive depletion of CD_4+cells provide the best surrogate marker of immune dysfunction in HIV infection.

Ocular lesions usually occur in the late phase of HIV infection but can be an early manifestation also. Most common ocular finding in AIDS is HIV related non-infectious retinal vasculopathy, consisting of cotton wool spots or intraretinal hemorrhages and it is seen in approximately 50% of patients with AIDS [2]. CMV

retinitis is the most common ocular opportunistic infection and the leading cause of blindness associated with AIDS and its incidence vary considerably from 6-38% [3,4]. CMV retinitis is typically a late manifestation of AIDS associated with low CD_4 count [5].

CD_4 T lymphocyte count has been used to predict the onset of certain ocular infections in patients who are HIV positive. CD_4 cell count less than 500 cells/mm^3 is associated with Kaposi's sarcoma, lymphoma and tuberculosis. CD_4 count less than 250 cells/mm^3 is associated with pneumocystosis and toxoplasmosis. Less than 100 cells/mm^3 is associated with retinal or conjunctival microvasculopathy, CMV retinitis, VZV retinitis, mycobacterium avium complex infection, cryptococcosis, microsporidiosis, HIV encephalopathy and progressive multifocal leukoencephalopathy [5].

Aim

Aim of our study was to analyze the retinal manifestations of HIV/AIDS patients and to evaluate its association with CD_4 cell counts.

Materials and methods

This cross sectional study was done to evaluate various retinal diseases in a south Indian population of HIV infected persons, in association with their CD_4 count which reflects the immune status of the patients. HIV seropositive patients attending the ART center, Government Rajaji Hospital Madurai, during the period of January 2013 - September 2014 were selected for the study. Their HIV status was confirmed by ELISA/TRI DOT test at Voluntary Counseling and Testing center, under Institute of Microbiology, Madurai Medical College, Madurai. Eligible patients attending ART centre will be referred to Department of Ophthalmology by ART Medical Officer, after confirming their HIV status, CD_4 cell count results and clinical staging of HIV according to WHO staging criteria. Diagnosis of HIV infection is done by ELISA test and CD_4 cell count by FACS caliber machine, at Institute of Microbiology, Madurai Medical College, Madurai. We included all the HIV positive patients with CD_4 T cell count < 200 cells/mm^3 and those with WHO stage 4 disease irrespective of CD_4 cell count in this study. Patients on ART, those with CD_4T cells > 200 cells/mm^3 other than stage IV disease and seriously ill patients who cannot co-operate for ophthalmological examination were excluded from the study.

The following data was collected from each patient. General symptoms, eye symptoms, history of tuberculosis, risk factors such as sexual promiscuity, sexually transmitted diseases, blood transfusion and intravenous drug abuse. A systemic examination was performed to rule out any systemic disease including examination of the skin and mucous membranes, central nervous system, cardiovascular system, respiratory system, and GI system. After completing the above check, the patients were fixed at WHO stage.

All the patients underwent a comprehensive eye examination also which includes visual acuity with Snellen's chart, slit-lamp bio-microscopy, tonometry, color vision with Ishihara pseudo-chromatic chart, central visual field with tangent screen, amslers grid, automated perimetry field testing to those who are suspected to have field defects, fundus examination with indirect ophthalmoscopy, and fundus photography in those with findings. Statistical analysis was done using chi-square test.

Observation and results

Out of 306 patients, 86 had retinal manifestations (28%). Majority of the patients in this study were in the age group of 31-40 (41%) and 21-30 (28%) corresponding to the sexually active, high risk group. Among total 306 patients, 186 were males (61%) and 120 were females (39%) with a ratio of 1.5:1. 63 in 186 males (73%) and 23 in 120 females (27%) had retinal findings.

Majority of virus transmission occurred through sexual contact which accounts to 96% of cases (293 patients). Major source of infection was commercial sex workers in case of males and for females their husbands. Blood transfusion accounted for 4 cases (1%) and trans placental transmission in 9 cases (3%).

Pulmonary tuberculosis was the most common systemic disease associated with HIV infected patients 96 (31%). Others were anemia 67 (22%) and oral candidiasis 48 (16%). Majority of the patients included in this study belonged to stage III of the disease, which accounts to 69% of study group and 73% of patients with retinal disease also belong to this group.

In our study group majority of patients belong to 150-100 category but maximum retinal findings were found in 100-50

CD 4 cell count	No. of patients/%	No of patients with retinal disease/%
> 200	48 (16%)	3 (3%)
200-150	59 (19%)	8 (9%)
150-100	82 (27%)	18 (21%)
100-50	69 (22%)	36 (42%)
< 50	48 (16%)	21 (25%)
Total	306	86

Table 1: Showing distribution of HIV patients with retinal manifestations based on their CD_4 count.

cell count group, next is those having CD_4 cell count < 50 cells/mm^3 (Table 1). Majority of the patients were asymptomatic. Most common ocular symptoms were defective vision followed by ocular irritation and seeing flashes or floaters. Major retinal manifestations were HIV retinopathy, followed by CMV retinitis and Toxoplasma retinochoroiditis. Comparison of different retinal manifestations based on CD_4 count is illustrated in table 2 and 3.

Retinal disease group	Total N = 306 No. %	Absolute cells/mm^3		
		Mean	Median	Range
No retinal disease	220 (71%)	138	112	2 - 192
HIV retinopathy	58 (19%)	89	74	4-212
CMV retinitis	17 (6%)	9	4	2-63
Toxoplasmosis	2 (1%)	138	138	108-168
Others		57	73	2-148

Table 2: Showing comparison of absolute CD4 count by retinal disease group.

CD4 Count	Total No of patients	HIV Retinopathy		CMV Retinitis	
Cells/mm^3	No	No	%	No	%
0-50	48	4	8%	16	33%
51-200	210	54	26%	1	<1%

Table 3: Showing comparison of retinal disease group by absolute CD_4 count.

Discussion

The incidence of ophthalmic manifestations in HIV infection has been reported on various studies to occur in as high as 50% - 100% of patients [3]. Almost all HIV patients develop ocular manifestations at some point in the course of their disease. Retinal disease is the most frequent form of ocular involvement in HIV infected individuals. This study is directed towards the retinal manifestations in 306 sero-positive individuals in a tertiary eye care hospital in south India and 28% of these patients were found to have retinal findings.

Majority of the patients in this study were in the age group of 20-40 (69%), which is comparable to the WHO estimates (62.39%). This is attributed to the fact that this being the sexually active age group; the risk of exposure is very high. The increased awareness of the disease and early reporting in this age group could also be a contributing factor.

The gender incidence in our study is 1.5:1 (Male: female). This male predominance is explained by their high risk of exposure due to their nature of work and economic freedom. According to WHO estimates among the adults living with AIDS/HIV, 59% are male and 41% are female. In this study it is 61% and 39% respectively, which correlates well with the WHO reported incidence. The mode of transmission in all cases except for cases in the age group 0-10 yrs and 4 adults who had history of blood transfusion were trans-sexual. The most common source of infection among males was from commercial sex workers, and the predominant source of infection in females was their husbands.

Most common systemic disease observed in association with HIV/AIDS was pulmonary tuberculosis in 96 patients, approximately 31% of the study group, and 4 had extra pulmonary tuberculosis followed by anemia at 22% and oral candidiasis at 16%. Others include herpes zoster, HSV2 infection, pneumocystis carinii infection, and cryptococcal meningitis.

Out of 306 HIV patients in the study group, 210 patients (69%) belonged to WHO stage III, of which 63 (30%) had retinal manifestations, which made up for the 73% of total patients affected with retina disease in the study group (86). In stage IV, out of 36, 23 (63%) had retinal manifestations, which accounts for 27% total affected. This observation confirms that retinal manifestations are seen more in advanced stages of the disease.

CD_4+ T-cell count is an important predictor of immune suppression in HIV/AIDS patients. The bulk of the patients in our study group, belonged to the CD_4 + T cells > 50 cells/mm^3 group (258 patients [84%]), whereas 48 (16%) patients belonged to the <50 cells/mm^3 group. This means that severe immune-suppression was comparatively less in our study population. In 258 patients with CD_4 count > 50 cells/mm^3, 65 patients (25%) had retinal diseases. This made up for 75% of the total afflicted, which could be explained with the majority of the study group population (84%) belonged to CD_4 count > 50 cell/mm^3. Of the remaining 48 patients with CD_4 count < 50 cells/mm^3, 21 patients (43%) had retinal disease, which made up for 25% of the total afflicted. This observation concludes that the CD_4 count and retinal disease in HIV patients is inversely related; with increase incidence in patients with CD_4 count < 50 cells/mm^3.

In terms of ocular symptoms, majority of the patients were asymptomatic with only 53 patients (17%) among 306 patients had ocular symptoms. Defective vision being the predominant symptom. Patients with CMV retinitis and toxoplasmosis were symptomatic with complaints of defective vision if macular region was involved, while majority of HIV retinopathy patients were asymptomatic. Those few patients with HIV retinopathy who complained of defective vision, either had a refractive error or pathology unrelated to the retinal disease.

Retinal manifestations encountered in our study were HIV related non-infectious retinal vasculopathy, CMV retinitis, Toxoplasmosis, acute retinal necrosis, CRAO, pale disc, peripheral vasculitis and pneumocystis carini choroiditis. Predominant retinal manifestation in our study was HIV retinopathy (Figure 1) or non-infectious retinal vasculopathy 58 (67%) out of 86 affected patients had cotton wool spots with or without hemorrhage. This comes to 19% of total patients examined. World literature reports an incidence of 40-50% in full blown AIDS patients[6] while incidence in asymptomatic individuals is 3-4%. Since this study included symptomatic AIDS patients and asymptomatic HIV seropositives, a figure in between is explainable.

Figure 1: Cottonwool spots and retinal haemorrhages in HIV retinopathy.

The median CD_4 count for group of patients with HIV retinopathy was 74 cells/mm^3 compared to 112 cells/mm^3 for the patients with no HIV retinopathy. The literature documents that when CD_4 count decreases, the prevalence of HIV retinopathy increases [7]. In this study, only 8% of those <50 cells/mm^3 had disease. This may be because majority of study group belong to > 50 cells/mm^3.

Clinical diagnosis of CMV retinitis was made in 20% (17) of total patients with retinal diseases. Classical form (Figure 2) was seen in 15 patients and 2 had non hemorrhagic granular indolent lesion in the periphery. Various literature gives incidence of CMV retinitis as high as 6-40% [3,4,8]. But in our study, incidence was 6%. The higher incidence in literature may be because the studies were conducted dealt with full blown cases of AIDS, while our study was a mixture of asymptomatic cases with fewer cases of AIDS.

Figure 2: Classical form of CMV retinitis.

The median CD_4 count for those with CMV retinitis was 4 cells/mm^3 with a range of 2-63 cells/mm^3. Out of 17 patients, only one patient had CD_4 count > 50 cells/mm^3 and all others were having < 50 cells/mm^3. This means CMV retinitis is more prevalent in severely immune-suppressed state as reflected by CD_4 cells < 50 cells/mm^3 with statistically significant p value of 0.0001.

When comparing the incidence of HIV retinopathy and CMV retinitis, HIV retinopathy was seen more in the patients with CD_4 count 50 - 200 cells/mm^3. CMV retinitis was seen more in those with CD_4 for cell count < 50 cells/mm^3. Both are significant statistically with p value of < 0.045 and < 0.0001 respectively. From this we can conclude that HIV retinopathy can be an early manifestation in HIV disease, while CMV retinitis a late one.

Toxoplasmosis was seen in 2 patients and both had old healed multifocal lesions in both eyes. They had CD_4 count of 108 and 168 cells/mm^3. Serological tests were not done due to lack of facility. Other retinal manifestation included 5 cases of acute retinal necrosis. Two cases of disc pallor; secondary optic atrophy due to CRAO, one case of pneumocystis carini infection and one peripheral vasculitis.

In literature Biswas., *et al*. reported an incidence rate of 21.4% and 12.8% for CMV retinitis and HIV retinopathy respectively [9]. Incidence of retinal disease in AIDS in the present study is comparable with the study of Biswas., *et al*. with reference to HIV retinopathy (19%) but not with CMV retinitis (6%). The difference may be due to difference in the study group as our study contained more asymptomatic HIV patients.

Study of Baruch D. Kuppermann., *et al*.						
Retinal Disease group	**Total No of Patients -132**		**Absolute CD4 count (cells/mm^3)**			**P value**
	No	%	Mean	Median	Range	
No retinal disease	70	53%	70.9	57	0-198	-
HIV retinopathy	36	27%	30.9	14	0-160	0.0001
CMV retinitis	16	12%	7.4	8	0-21	0.0001
Present Study						
Retinal Disease group	**Total No of Patients -306**		**Absolute CD4 count (cells/mm^3)**			**P value**
	No	%	Mean	Median	Range	
No retinal disease	220	71%	138	112	2-192	-
HIV retinopathy	58	19%	89	74	4-212	0.045
CMV retinitis	17	6%	9	4	2-63	0.0001

Table 4: Comparative Analysis of absolute CD_4 count by retinal disease group.

Comparing with the observations of Kuppermann., *et al*. [10] only median CD_4 count of CMV retinitis is comparable (Table 4). This could be explained by the difference in study population. Our study group contained only 48(16%) patients with CD_4 count <50 cells/mm^3, while the study group of Kuppermann., *et al*. had 87 (65%) patients.

According to Baruch D Kuppermann, CMV retinitis was detected in 30% of patients with CD_4 count < 50 cells/mm^3 [10]. Our study showed that 33% of patients with CD_4 count < 50 cells/mm^3 had CMV retinitis. This can be compared with the documented study. Regarding HIV retinopathy 45% of those with CD_4 count < 50 cells/mm^3 had CWS, while only 16% of those > 50 cells/mm^3 had the same. In present study it is 8% and 26% respectively. This is also due to difference in the study group.

From the present study we can conclude that HIV retinopathy occurs more in those with a better CD_4 count (50-200 cells/mm^3) and CMV retinitis ocular in those with severe immunosuppression, with CD_4 count < 50 cells/mm^3. Both are statistically significant with p value < 0.05.

Conclusion

Ophthalmic manifestations of HIV disease are increasingly being recognized in present era due to increased longevity of patients after HAART. Our study confirms that most common retinal manifestations in AIDS patients are HIV retinopathy and CMV retinitis, which has an inverse association with CD_4 cell count of the patient. HIV retinopathy is seen more commonly in late stages of HIV disease (stage III and IV) with CD_4 count 50-200 cells /mm^3. It is seen much earlier than CMV retinitis, which occurs usually with CD_4 count < 50 cells/mm^3.

There is increased incidence of opportunistic infections when CD_4 count is < 200/mm^3. Hence it is imperative that patients undergo ophthalmologic examination every 6 months in those with CD_4 count < 200 and once in 3 months for those with < 50 cells/mm^3. Screening for retinal diseases can be done at home by patients themselves using Amsler's grid test once weekly by which they can detect scotomas in central field. This would favour an early diagnosis and treatment, hence better visual prognosis.

Chemoprophylaxis for CMV retinitis in HIV patients with CD_4 count < 50 cells/mm^3 would prevent vision threatening infection. Our study highlights the importance of ophthalmological examination in HIV patients especially with low CD_4 count, which can help in early diagnosis and management, which will considerably decrease the visual morbidity in HIV patients.

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None.

Conflicts of Interest

Nil.

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