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Original Article

Clinical study of ocular manifestations in hiv/aids and its correlation with cd4+ t cells

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ABSTRACT

Background: The ocular manifestations of HIV/AIDS may lead to visual impairment or blindness the ocular sequelae of HIV infection leading to an early diagnosis of AIDS, which along with an early and effective treatment might be able to reduce ocular and general morbidity and mortality in AIDS. **Objectives:** This study was undertaken to find out the prevalence of ocular manifestations in HIV/AIDS patients and to study the correlation between ocular complications of HIV/AIDS and the degree of immunodeficiency as determined by CD4+ T lymphocyte count of HIV infected individuals. **Methods:** This prospective study included 100 HIV positive patients, with or without AIDS, irrespective of treatment status. A detailed history and comprehensive ophthalmic examination was performed and findings were noted. The WHO clinical stage of HIV/AIDS, CD4+ T lymphocyte count and duration of disease were noted. The prevalence of ocular manifestations and their correlation with CD4+ T cell counts were determined. **Results:** The prevalence of ocular manifestations in HIV/AIDS patients was 46%, 97% had good vision but 7% patients had lost one eye to ocular complications and 1% patient was blind due to the disease. The most common manifestations were HIV retinopathy 12% and CMV retinitis 7%. The prevalence of ocular manifestations was significantly higher with lower CD4+ T lymphocyte counts in HIV infected individuals. **Conclusions:** The study concluded that CD4+ cell counts and WHO clinical stage of HIV disease are important predictors of occurrence of ocular morbidity in HIV positive individuals.

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1. Introduction

Since its discovery in 1981, Acquired Immunodeficiency Syndrome (AIDS) has emerged as a global health problem. It is a potentially lethal multisystem disorder caused by a retrovirus, Human Immunodeficiency virus (HIV).^{1,2}

Epidemiology: According to the UNAIDS 2009 AIDS epidemic update a total of 33.3 million (31.4 – 35.3 million) people are living with HIV with 2.6 million (2.3 – 2.8 million) being newly infected in 2009. The total number of deaths due to AIDS in 2009 was estimated to be 1.8 million (1.6 – 2.1).³

According to the NACO (National AIDS Control Organization) Annual Report 2009-2010 people living with HIV / AIDS in India are estimated to be 22.7 lakhs with an adult prevalence of 0.29%.⁴ India harbours the world's second largest burden of HIV infected with one in every six new HIV infections occurring in India and two Indians becoming HIV infected every minute.⁵

Up to 50-75% of HIV / AIDS patients have at least one ocular manifestation in their life time.⁶ It can involve any part of the eye from the adnexa and anterior segment to posterior segment.

The severity of ophthalmic sequelae of HIV infection increases as immunocompetency decreases, which is measured by CD4+ T cells count.⁷ Most importantly, ocular signs can be the initial manifestation of AIDS. Vision loss in AIDS patients is primarily due to cytomegalovirus (CMV) retinitis (10-20%).⁵ Introduction of highly active antiretroviral therapy (HAART), which is a combination antiretroviral therapy has reduced the risk of mortality, opportunistic infections and improved the quality of life of HIV / AIDS patients. On the contrary widespread use of HAART tends to increase the prevalence of HIV / AIDS because survival improves to a greater extent than decline in transmission of HIV infection.⁸ Thus HIV / AIDS is a major public health problem, especially in developing countries where approximately 97% of AIDS patients live.³

The need of the hour is an understanding of ocular sequelae of HIV infection leading to an early diagnosis of AIDS, which along with an early and effective treatment might be able to reduce ocular and general morbidity and mortality in AIDS.

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Thus, the present study is undertaken to determine the prevalence of ocular manifestations of HIV/AIDS and its correlation with immunodeficiency. It emphasizes on the need of developing a specific ophthalmic examination for the management of ocular sequelae in the care of HIV infected patients.

Objectives

- To study the prevalence of ocular manifestations in HIV / AIDS patients.

- To study the relationship between ocular complications in HIV infection and

the degree of immunodeficiency as measured by CD4+ T cell count.

2. Material and Methods

The present study titled 'CLINICAL STUDY OF OCULAR MANIFESTATIONS IN HIV/AIDS AND ITS CORRELATION WITH CD4+ T CELLS' was conducted in Department of Ophthalmology, J.J.M. MEDICAL COLLEGE, Davangere Karnataka India.

The present three year prospective study was conducted during November 2009 to August 2011 with a sample size of 100 Patients known to be positive for HIV infection with or without AIDS on treatment/without treatment, and have determined their CD4+T lymphocyte cell count. Outpatients attending clinics and admitted in inpatient wards at Medical/Ophthalmic departments, belonging to any age and of either gender at Chigateri General Hospital and Bapuji Hospital, attached to J.J.M. Medical College, Davangere were included in the study.

All patients who are sero-positive to HIV with or without AIDS in whom CD4+T cell count has been determined were included.

Patients who are not compliant or have not given consent for examination and with similar ocular manifestations secondary to immunosuppression due to other causes were excluded.

Methodology

After obtaining the informed consent, patients were enrolled in the study. Detailed evaluation of the patient including a detailed history by personal interrogation either with the patient or his/her relative in case patient was unconscious, was noted. Emphasis was given to elicit history of high risk behaviour, blood transfusion, intravenous drug abuse and other habits. Family history, status of

the spouse if married and children if present, whether dead or alive and the cause of death were noted. History regarding ocular complaints was enquired in detail. General physical examination and systemic examination were done. The clinical stage of the disease was defined using World Health Organisation (WHO) clinical staging criteria. The HIV status of all the patients was verified and the CD4+ T cell count was obtained from the ART centre attached to Chigateri General Hospital, Davangere recognised by NACO. The duration of HIV disease since first diagnosis was also noted. The CD4+T cell subset analysis was performed by using a standard technique for dual-colour immunofluorescence staining of the peripheral whole blood. The percentage of CD4+ T lymphocyte count was calculated by multiplying the percentage of

CD4+ T lymphocytes obtained from single platform flow cytometry using Cy Flow Counter by Partec, by the absolute lymphocyte count obtained from complete blood cell count with differential.

The ophthalmic evaluation was done in Ophthalmic OPD in all the patients except for those who were too ill to be moved to the OPD, in whom bed side evaluation was done. Visual acuity was recorded by Snellen's test chart. In few patients where visual acuity could not be recorded by Snellen's test chart due to poor general condition, it was determined clinically by recording patient's ability to count fingers at a certain distance. Ability to count fingers at 6 meters was considered clinically good. Anterior segment examination was performed in all conscious and cooperative patients with the Slit lamp biomicroscope or torch light while examining the patient bed-side. The pupils were dilated with Phenylephrine 5% and Tropicamide 0.8% combination eye drops. Direct and indirect ophthalmoscopy was performed in all patients to study the posterior segment of the eye. Documentation of relevant findings of the ocular adnexa and eye were made in the form of external photography, fundus diagrams and fundus photography. The relevant treatment for ocular complaints was instituted, along with the consultation with the physician for systemic condition, when required.

Main parameters studied :

1. Prevalence rate of ocular manifestations in HIV/AIDS patients.

2. Association between CD4+T lymphocyte cell count and ocular manifestations of HIV/AIDS.

STATISTICAL ANALYSIS:

• Prevalence rate of ocular manifestations of HIV/AIDS was determined as the percentage of the total patients examined, having ocular manifestations of HIV/AIDS.

• Association between ocular manifestations of HIV/AIDS & CD4+T cell count was analysed using Chi-square (χ^2) test.

3. Results

The patients who had their CD4+ T lymphocyte count were enrolled in the study. The prevalence rate of ocular disease in HIV/AIDS patients and the correlation of CD4+ T cell count with ocular manifestations of HIV/AIDS were studied. The data was tabulated as follows:

Table 1: age and sex distribution of patients studied (n=100)

Age group (years)	Total Number of patients	Males	Females
0-9	7	2	5
10-19*	-	-	-
20-29	12	4	8
30-39	42	15	27
40-49	29	18	11
50-59	7	6	1
60-69	3	1	2
Total	100	46	54

* No patients enrolled in the study were in this age group.

In our study, the mean age of the patients was found to be 36.4 years ranging from 1 year 3 months to 68 years with a SD of 11.6 years. Majority of patients, 42(42%) were within the age group of 30-39 years. The no. of males studied were 46 (46%) and the no. of females were 54 (54%). The majority of males i.e., 18 (39%) were in the age group of 40-49 years and the majority of females i.e. 27 (50%) were in the age group of 30-39 years. Our study found sexual route as the most common mode of transmission of HIV seen in 81% of patients, of which heterosexual was the most common mode seen in 79 patients (79%). Seven patients acquired the infection perinatally (7%) and in one patient it could possibly be traced to blood transfusion (1%). Eleven patients denied any of the above routes of exposure (11%). The number of patients having systemic manifestations of HIV in our study was 46%. The most common systemic involvement seen in our cohort of HIV infected patients was the respiratory system which was affected in 21 of the 46 patients (21%). Out of these 21 patients, 18 had tuberculosis, making it the most common cause of respiratory system involvement in our HIV infected cohort. The next most common organ system involved in our study was the oropharynx and gastrointestinal tract, which was seen in 9 patients (9%), with candidiasis being the most common cause seen in 8 patients. CNS was involved in 6 patients (6%) with 4 of them having meningitis. Others had dermatologic (7%) and genitourinary (3%) complications. Our study showed the prevalence of ocular manifestations among HIV positive patients as 46%.

Table 2 : Ophthalmic manifestations in anterior segment of hiv / aids patients

Parts of the eye	Diseases	No. of patients
LIDS	a) Molluscum contagiosum	1
	b) Herpes zoster ophthalmicus	42
	- Active	
	- Healed	
	d) Preseptal cellulitis	1
	e) Blepharitis	1
CONJUNCTIVA	f) Recurrent hordeolum	2
	a) Conjunctival microvasculopathy	1
	b) Dry eye	3
EPISCLERA / SCLERA	a) Scleritis	1
CORNEA	a) Varicella zoster keratitis	22
	Healed	
	b) Fungal keratitis	2
	c) Herpes simplex keratitis	12
	- Active	
ANTERIOR UVEA	- Healed	
	a) Anterior uveitis	21
	- Active	
ORBIT	- Healed	
	a) Orbital cellulitis - Active	1

In the present study, majority of patients i.e., 62 (62%) belonged to WHO clinical stage 1 and 2. Thirty eight (38%) patients belonged to WHO clinical stage 3 & 4. The majority of HIV infected patients with ocular manifestations belonged to stage 3 & 4.

Chi-square analysis showed that prevalence of ocular manifestations associated with HIV was significantly higher in patients in clinical stages 3 & 4. The median CD4+ T cell count was 236 cells/ml ranging from 17-1287 cells/ml. In our study, the majority of HIV infected patients with ocular manifestations i.e., 13 (92.9%) had CD4+ T cell counts < 100 cells /ml. The rest of the patients had CD4+ cell counts between 100 and 500 cells /ml and only 1 patient (7.1%) had CD4+ T cell count > 500 cells /ml. Chi-square analysis was done which showed significant correlation (p = 0.001) between ocular manifestations in HIV and lower CD4+ T cell counts

4. Discussion

SOCIO-DEMOGRAPHIC CHARACTERISTICS OF STUDY PARTICIPANTS:

Age and sex distribution of patients studied:-

In the present study the mean age of the participants was 36.4 years, standard deviation (SD) 10.87 years, ranging from 1 year 3 months –68 years. Majority i.e. 42 (42%) participants were in the age group of 30-39 years. 46 (46%) patients were males and 54 (54 %) patients were females. The majority of males i.e. 18 (39%) were in the age group of 40-49 years and the majority of females i.e. 27 (50%) were in the age group of 30-39 years. In this series the highest prevalence is in the 4th and 5th decade with the mean age of 36.4 years. Pattern of age distribution but shows an almost equal to higher infection rate in females (54% compared to 46% in males).

Distribution of cases by mode of transmission:-

The present study shows the most common risk of exposure is sexual route which is observed in 81 (81 %) participants, of which only two people acquired the infection by homosexual route, the rest having acquired the infection by heterosexual contact. Seven children (age 0-9 years) had acquired the infection perinatally and in 1 (1%) patient the mode of acquiring infection could possibly be traced to blood transfusion. Rest of the 11% denied revealing the route of infection. This series shows heterosexual route of transmission as the major route of transmission in India.

CLINICAL PROFILE OF THE PARTICIPANTS

Clinical stage:-

In our study, 38 (38%) patients belonged to WHO clinical stage 3 and 4 and 62 (62%) patients belonged to stage 1 and 2.

OCULAR MANIFESTATIONS:

The visual status in HIV/AIDS patients:

In our study, 97 (97%) patients had good vision (6/6 – 6/18 in the better eye), 2 (2%) patients had low vision (6/24 – 3/60 in the better eye) attributable to cataract and 1 (1%) patient was blind (as classified by WHO). 31 (31%) patients had uncorrected refractive error. The percentage of one eyed patients in our study was 7%. Three patients had only perception of light in one eye, attributable to retinal detachment secondary to Cytomegalovirus retinitis in 2 and orbital cellulitis following lid abscess in 1 patient. The remaining 4 patients had one phthisical eye with no perception of light, attributable to retinal detachment following CMV-retinitis, ARN, pan uveitis secondary to ocular tuberculosis and fungal endophthalmitis

respectively. One patient had cortical blindness secondary to Cryptococcal meningitis. In our study majority i.e. 97 (97%) had good vision. This shows that diminution of vision is rarely complained of by the patients suffering from HIV infection because of the good vision in the better eye. It is important to note that 31 (31%) of the patients had uncorrected refractive error. HIV/AIDS may be an important factor for the patients not seeking treatment which could be attributed to the stigma of the disease as well as the disabling illness associated with HIV/AIDS. The prevalence of the blindness due to HIV/AIDS may be underestimated in a study like ours as many of them spend last days of their lives in their homes. So visual acuity cannot be taken as the indicator of the ophthalmic manifestation. Routine screening is the only way to detect the ophthalmic manifestations of HIV infection.

Prevalence of ocular manifestations :-

In our study the ocular manifestations of HIV/AIDS was found in 46 (46%) patients.

Ocular manifestations in HIV/AIDS patients:-

Posterior segment manifestations in HIV:-

HIV Retinopathy:

In the present study, 12 (12%) patients had HIV retinopathy as the most common ocular finding. Of these 12 patients, 9 (75%) had cotton wool spots (CWS) i.e. 8 having only CWS and 1 having both CWS and dot haemorrhages. 3 (25%) patients had retinal hemorrhages only in the form of flame shaped and dot haemorrhages. No patient had visual impairment attributable to HIV retinopathy.

These are usually asymptomatic and thus can be missed unless looked for specifically in HIV infected patients. It is proved that in absence of Diabetes mellitus and Hypertension, presence of even a single CWS in an otherwise normal fundus is suggestive of HIV infection.¹¹

CMV Retinitis:

In the present study Cytomegalovirus retinitis was found in 7 patients (7%) with one patient returning to us with Immune Recovery Uveitis after 8 months of initial diagnosis of indolent CMV retinitis. It is the second most common ocular finding and the most common ocular opportunistic infection in our series. Three patients among the 7 had retinal detachment secondary to CMV retinitis (42.9%). Immune recovery uveitis (IRU) is the new entity among ocular manifestations of AIDS resulting from response to HAART therapy in patients with inactive lesions like indolent CMV retinitis as is shown in one case in our study. The proportion of patients who had CMV retinitis in our series is 7%.

Ocular Tuberculosis:

In the present study 4 (4%) out of the 18 patients with tuberculosis had ocular tuberculosis. One patient had nodular scleritis with co-existent pulmonary TB for which anti-tubercular therapy (ATT) was started. Another patient presented with pan uveitis and retinal detachment in the left eye and a solitary choroidal tubercle in the right eye. Subretinal abscess was seen in one patient following which ATT was started but the patient was

lost to follow up. One case presented with bilateral lateral rectus palsy due to meningitis which was proved to be due to tuberculosis by CSF analysis.

Neuro-ophthalmic manifestations:

In our study 6 (6%) patients had neurological abnormalities. Of the 6 patients, 4 (4%) patients had neuro ophthalmic abnormality. They included papilledema in 1 (1%) patient with meningitis and cranial nerve palsies in all 4 (4%) patients.

Other posterior segment manifestations:

Other posterior segment manifestations in our study included ARN in 1 (1%) patient, Toxoplasmic retino-choroiditis in 1 (1%) patient, Cryptococcal choroiditis in 1 (1%), 1 (1%) case of central retinal vein occlusion and 1 (1%) case of non-specific viral retinitis.

Anterior segment manifestations of HIV:-

Our study showed comparatively less occurrence of adnexal and anterior segment manifestations as compared to the posterior segment findings in HIV/AIDS. In the present study Molluscum contagiosum of the eye lids was found in 1 (1%) patient. Herpes zoster ophthalmicus was seen in 6 (6%) patients, being the initial manifestation of HIV in 3 of them. Preseptal cellulitis and blepharitis were seen in 1 (1%) patient each. Recurrent hordeolums were complained of by 2 patients (2%). Conjunctival microvasculopathy was noted in 1 patient (1%) and dry eye was documented in 3 cases (3%). Corneal involvement was noted in 4 cases of Varicella zoster keratitis (4%), 3 patients with Herpes simplex keratitis (3%) and fungal keratitis in 2 cases (2%), making it the most common structure involved in the anterior segment. Anterior uveitis was seen in 3 patients (3%). One patient with a lid abscess developed orbital cellulitis rapidly. The organism isolated from the pus after incision and drainage of abscess was found to be *Staphylococcus aureus*. There were no cases of Kaposi's sarcoma in this study which is in agreement with the similar studies in India and is thought to be due to low seroprevalence of HHV-8 (causative organism of Kaposi's sarcoma) in our population.¹⁰

Association between clinical stage of HIV disease (according to WHO) and eye involvement:-

In the present study, majority of the patients i.e. 62 (62%) patients belonged to WHO clinical stage 1 and 2. Thirty eight percent patients belonged to clinical stage 3 and 4. Two patients (9.5%) in stage 1 and 15 patients (36.6%) in stage 2 disease had ocular lesions. Fifteen patients (65.2%) in stage 3 and 14 patients (93.3%) in stage 4 had ocular lesions. Chi-square analysis showed that the prevalence of ophthalmic manifestations associated with HIV was significantly higher in those with WHO clinical stages 3 or 4 (p value < 0.05).

Our study showed that prevalence of ocular lesions associated with HIV was significantly higher in patients belonging to WHO clinical stages 3 or 4.

Association between CD 4 + T cell counts and eye involvement in HIV:

In our study, the majority of patients with ocular manifestations i.e. 13 (92.9%) had CD4+ T cell counts <100 cells/ μ l. Rest of the patients had CD4+ T cell count between 100 and 500 cells/ μ l and only 1 patient (7.1%) had CD4+ T cell count >500 cells/ μ l. Chi square analysis of the data revealed p value of 0.001 which is highly significant.

In our study we found a significant association between ocular manifestations and lower CD4+T cell count (0-100 cells/ μ l).

5. Conclusion

The present study is a hospital based prospective study representing the patients with HIV infection.

The study concluded that HIV/AIDS is a significant cause of ocular disease with 46 (46%) patients having HIV/AIDS related eye disease. Though majority of the patients had good vision, 7% had lost one eye due to the opportunistic infections occurring with falling immunity in HIV infected patients. Unless treated promptly, these patients are at a high risk of losing vision by involvement of the second eye. HIV/ AIDS may be an important cause limiting the patients from seeking medical care for visual impairment and patients with early disease have few or no ocular symptoms. Thus, screening for ocular complaints is not a reliable method to identify those with ocular morbidity. Comprehensive ophthalmic examination of all HIV infected patients with AIDS, at regular intervals, will help in identifying ocular morbidity early. The commonest ocular lesions observed were the posterior segment manifestations such as HIV retinopathy and CMV retinitis. The less common ocular manifestations seen were the adnexal and the anterior segment manifestations such as Herpes zoster ophthalmicus and viral keratitis. The study shows that the spectrum of the ocular lesions associated with HIV infection in India is different from elsewhere in the world. The prevalence of CMV retinitis is lower and there have been no cases of Kaposi's sarcoma. There is still a great need for the definitive diagnosis of the ocular lesions in HIV positive patients. The cases of atypical ophthalmic manifestations as an initial presentation of HIV infection highlights the need for increased index of suspicion for HIV infection in young patients. With the advent of HAART, there is an increase of atypical presentations of ocular diseases. The recognition and treatment of the Immune Recovery Inflammatory Syndrome, due to immune reconstitution in patients on treatment, poses a new challenge. Therefore ophthalmologists need to recognize ocular lesions in HIV infection along with careful and pertinent systemic evaluation with timely referral. This will help in earlier diagnosis and prompt treatment of these cases, failing which there may be serious consequences on vision. The prevalence of ocular manifestations correlated significantly with HIV/AIDS WHO clinical stage 3 and 4. The association between the prevalence of the ocular manifestations and the WHO clinical stages suggest that ocular involvement in HIV infected patients is related to the progression of the disease. Thus patients with clinical stages 3 and 4 need to be screened thoroughly for ocular manifestations and treated accordingly to protect them against loss of vision.

We found a significantly high correlation of ocular manifestations of HIV/AIDS with lower CD4+ T lymphocyte counts. This suggests that HIV related ocular disease is related to the degree of immunosuppression in HIV infected patients. The availability and cost of drugs such as Ganciclovir and follow-up for ocular diseases like CMV retinitis limit the visual outcome in patients with

higher degree of immunosuppression. With HAART being made widely available to the Indian population by NACO, the resultant immune recovery has led to a decline in the occurrence of dangerous, vision threatening complications of ocular diseases seen in AIDS.

Strengths of the study:

- All the patients had CD4+ T cell counts done by a standard method single platform flow cytometry using CyFlow system by Partec.

- All the patients underwent a comprehensive ophthalmic examination irrespective of the visual complaints.

Limitations of the study:

- The limited sample size, broad spectrum of diseases, follow-up of selective cases and a lack of control group for comparison are a few limitations of the present study.

A larger sample size with emphasis on specific sub-group of ocular disease in HIV/AIDS, with inclusion of patients willing to come for regular follow-up are required to find the correlation between degree of immunosuppression and each subgroup of ocular disease in HIV infected patients.

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