CD4 counts: a strong indicator of retinal and ocular lesions in HIV disease

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INTRODUCTION

Human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) is a global pandemic, with cases reported from practically every country. The recent World Health Organization (WHO) estimate of the total HIV burden in the world is 33.2 million (30.6–36.1 million).¹ India is categorised as a low prevalence nation but a major concern is that in view of the large population size, a mere 0.1% increase in prevalence rate would increase the numbers of patients living with HIV infection by over half a million.²

The aetiological agent of AIDS, HIV, belongs to the family of human retroviruses and the subfamily of lentiviruses. Ocular lesions mainly involve the posterior segment, which include HIV vasculopathy, infectious retinopathy or choroidopathy, and rare neoplasms. Also, HIV vasculopathy or microangiopathy is the most common manifestation (40–60%) of AIDS in developed countries which includes retinal haemorrhages, cotton-wool spots, microaneurysms, ischaemic maculopathy and telangiectatic vessels while large vessels disease is rarely seen.^{3–5}

Cytomegalovirus (CMV) retinitis is the most common (15–40%) cause of infectious retinopathy in AIDS and its complications (immune recovery uveitis (IRU) and retinal detachment) are the most common cause of visual morbidity.³ The involvement of the anterior segment is less and includes complicated cataract, anterior uveitis, fungal keratitis, herpes simplex and zoster keratitis, peripheral ulcerative keratitis and bacterial keratitis.^{4–6}

The majority of information and studies regarding ophthalmic manifestations in India reflects the pre-HAART (highly active anti-retroviral therapy) era.^{7,8} India may be going through an intermediate stage where the spectrum of the ophthalmological manifestations may be changing significantly. This study was conducted to evaluate ophthalmic manifestations predominantly of the posterior segment in HIV-infected service personnel.

MATERIALS AND METHOD

The study was carried out between September 2005 and November 2007 at the ophthalmology outpatient department of a service tertiary care hospital as well as at a premier apex Government of India medical institute. This was a cross-sectional study to evaluate ophthalmic (predominantly posterior segment) manifestations in HIV infection and AIDS patients. The aim was to evaluate about 125 HIV-infected patients. Patients suffering from diabetes, any type of glaucoma, or any other pre-existing retinal disorder were excluded to avoid any overlap of retinal findings. Human immunodeficiency virus testing along with CD4 and CD8 T lymphocyte counts as well as viral loads were the prerogative of the treating physician. After the collection of demographic data, a detailed ophthalmic evaluation was carried out.

The HAART was defined as a combination of anti-retroviral therapy with a minimum of three drugs containing at least one protease inhibitor and two nucleoside reverse transcriptase inhibitors.⁹ The most common ocular lesions in numerous studies have been CMV retinitis and HIV microvasculopathy.¹⁰ Severe intra-ocular inflammatory reactions can develop in eyes with CMV retinitis following initiation of HAART if immune reconstitution occurs, which is referred to as IRU.¹¹ Cytomegalovirus retinitis (Figure 1) was diagnosed clinically by the characteristic appearance of a necrotising retinitis with either oedematous white borders or granular white border with or without haemorrhage while HIV microangiopathy (Figure 2) was diagnosed when a patient presented with cotton-wool spots, retinal haemorrhages, microaneurysms, telangiectatic vessels, and ischaemic maculopathy.^{3–5}

The findings of the study were evaluated and statistically analysed.

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Figure 1 Cytomegalovirus retinitis.

Figure 2 Human immunodeficiency virus microangiopathy.

Table 1 Ophthalmic symptoms in relation to CD4 counts.

	CD4 counts		
	<100 cells/ μ L	100–200 cells/ μ L	>200 cells/ μ L
Total HIV-positive patients	21	41	63
Patients with ocular lesions	16	17	10
Patients with ocular symptoms	16	15	6
Ocular lesions without symptoms	–	2	4
Ocular symptoms in HIV patients (%)	76.2	36.6	9.5
Ocular symptoms in HIV patients with ocular lesions (%)	100	83.3	60

$\chi^2=35.02$, $df=2$, $P<0.001$ is statistically highly significant for ocular symptoms with number of patients in the various CD4 count groups.

RESULTS

A total of 125 patients who were HIV positive were examined. CD4 and CD8 counts were done for all patients while viral loads could be estimated only in 23 patients (18.4%). Eighteen patients had received HAART or treatment with at least two anti-retroviral drugs. There was wide variation in ocular examination in relation to duration of HIV positivity, from two weeks to over nine years. CD4 counts of <100 cells/ μ L were found in 21 patients (16.8%), between 100 and 200 cells/ μ L in 41 patients (32.8%), and >200 cells/ μ L in 63 patients (50.4%).

A total of 37 (29.6%) patients had ophthalmic symptoms. Diminution of vision without floaters was the commonest symptom in 17 (13.6%) patients followed by diminution of vision with floaters in 14 (11.2%) patients, redness in four (3.2%) patients, and only floaters and pain in one patient each (0.8%). The incidence of ophthalmic symptoms in relation to the CD4 counts of the patients is given in Table 1.

It was found that of the total 21 patients in this group, all 16 patients with ocular lesions having CD4 counts <100 cells/ μ L had ocular symptoms (100%). Of a total of 63 patients, 15 of the 17 patients with ocular lesions with CD4 counts between 100 and 200 cells/ μ L (41 patients) had ocular symptoms (88.23%), while only 60% (six out of 10 patients with ocular lesions) had ocular symptoms in the group with ocular lesions >200 cells/ μ L counts. These clinical findings of ocular symptoms with the

Table 2 Ocular lesions in various CD4 count groups.

	CD4 counts	
	<200 cells/ μ L	>200 cells/ μ L
Total patients	62 (100%)*	63 (100%)
Patients with ocular findings	33 (53.23%) [†]	10 (15.87%)
Patients without ocular findings	29 (46.77%) [#]	53 (84.13%)

*21 in <100 cells/ μ L group and 41 in 100–200 cells/ μ L group.

[†]16 in <100 cells/ μ L group (76%) and 17 in 100–200 cells/ μ L group (43.9%).

[#]5 in <100 cells/ μ L group (23.8%) and 24 in 100–200 cells/ μ L group (56.1%).

$\chi^2=19.32$, $df=1$, $P<0.001$, OR=6.03, 95% CI of OR=2.43–15.32 when considering the number of patients with ocular lesions in <200 cells/ μ L and >200 cells/ μ L groups with those without ocular lesions in the above groups.

CD4 counts was statistically analysed using the χ^2 tests and $P<0.001$ was found to be statistically very significant.

Out of the 125 patients, a total of 43 patients had ophthalmic manifestations. Amongst those who had CD4 count <100 cells/ μ L, 76.2% (16 of 21 patients) had ocular lesions. In patients with CD4 count between 100 and 200 cells/ μ L, 43.9% (17 of 41 patients) had ocular lesions while in those patients with CD4 count >200 cells/ μ L, only 15.9% (10 of 63 patients) had ocular lesions as shown in Table 2. For the purpose of ease in statistical analysis, the subjects were also regrouped as having CD4 counts <200 cells/ μ L and >200 cells/ μ L. Ocular lesions were

Table 3 Presence of ocular manifestations with CD4 count range.

Patients with ocular lesions (N)*	CD4 counts		
	<100 cells/ μ L	100–200 cells/ μ L	>200 cells/ μ L
Total patients	21 (16.8%)	41 (32.8%)	63 (50.4%)
Patients with ocular lesions	16 (76.2%)	17 (41.5%)	10 (15.8%)
Patients without ocular lesions	5 (23.8%)	24 (58.5%)	53 (84.1%)
CMV retinitis (15) [†]	8 (38.1%)	6 (14.6%)	1 (1.6%)
Active CMV retinitis (7)	5 (23.8%)	2 (4.9%)	–
HIV vasculopathy (14) [†]	6 (28.6%)	5 (12.2%)	3 (4.8%)
Uveitis (6) [†]	2 (9.5%)	3 (7.3%)	1 (1.6%)
Chorioretinitis (4) [†]	1 (4.8%)	2 (4.9%)	1 (1.6%)
Acute retinal necrosis (1) [†]	1 (4.8%)	–	–
Toxoplasmosis (1) [†]	–	1 (2.4%)	–
Neuro-ophthalmological manifestations (14)	5 (23.8%)	4 (9.8%)	5 (7.9%)
Anterior segment manifestations (12)	4 (19.1%)	4 (9.8%)	4 (6.4%)
Extra-ocular manifestations (4)	1 (4.8%)	2 (4.9%)	1 (1.6%)

*Some patients had more than one ocular lesion ($\chi^2=43.56$, $df=2$).

[†] $P<0.001$ is statistically significant for ocular lesions of the posterior segment.

present in more than three-fourth of the patients with CD4 counts <100 cells/ μ L in comparison to just over 15% in patients with CD4 counts >200 cells/ μ L. As CD4 count increases, the number of patients with ocular lesions decreases. These clinical findings of ocular lesions with the CD4 counts was statistically analysed using the χ^2 software system ($\chi^2=19.32$, $OR=6.03$) and $P<0.001$ was found to be statistically very significant.

The most common ophthalmic manifestation in this study was CMV retinitis, which was present in 12% (15 of the 125 patients) of all HIV-infected patients, of which active CMV retinitis was present in seven patients. Cytomegalovirus retinitis was more common when CD4 count was <100 cells/ μ L (38.1%) as eight out of the total of 15 CMV retinitis patients had counts <100 cells/ μ L. Similarly, six of the total of 14 patients of HIV microangiopathy (vasculopathy) manifested in CD4 counts <100 cells/ μ L which amounts to 28.6%. A summary of the ophthalmic manifestations and relation with CD4 count is given in Table 3. These clinical findings of posterior segment ocular lesions with the CD4 counts was statistically analysed using the χ^2 software system ($\chi^2=43.56$, $df=2$) and $P<0.001$ found was to be statistically very significant.

DISCUSSION

The study population consisted of 100% males, all service personnel with more than 55% in the fourth decade age group. Forty-three patients out of a total of 125 had ocular lesions (34.4%). The prevalence of ocular lesions is marginally lower compared to other studies which can perhaps be explained by the fact that many of our patients were recently diagnosed.¹⁰ The demographic patterns of our cases were quite similar to those noted in the national statistics of HIV disease in general, except that all our patients were males.

Only six (4.8%) patients had ocular lesions without any ophthalmic symptom. Of them, the most common (50%) cause was HIV microangiopathy seen in three patients. Four of these patients had CD4 counts >200 cells/ μ L while the remaining two had CD4 counts between 100 and 200 cells/ μ L and none <100 cells/ μ L. The high incidence of ocular symptoms in patients with low CD4 counts probably signifies the gravity of the ocular disease. Moreover, 76.2% of all patients whose CD4 counts was <100 cells/ μ L had ocular lesions, while 41.5% had ocular lesions in CD4 counts between 100 and 200 cells/ μ L and only 15.8% had ocular lesions in counts >100 cells/ μ L. This data is quite comparable to the other series from the published literature. All ophthalmic manifestations were much more common when the CD4 count was <200 cells/ μ L, than being above.

Low CD4 count is strongly related to the increased prevalence of ocular lesions as well as ocular symptoms. Cytomegalovirus retinitis is much more common in low CD4 counts. Fourteen of the 15 cases of CMV retinitis which included all the active cases had CD4 counts <200 cells/ μ L. Again, 11 of the 14 cases of HIV vasculopathy had CD4 counts <200 cells/ μ L and only three had CD4 counts >200 cells/ μ L. Similarly both anterior segments, extra-ocular, and neuro-ophthalmological manifestations were more common in patients with CD4 counts <200 cells/ μ L. Both the cases of IRU had CD4 counts <200 cells/ μ L while the only case of acute retinal necrosis had CD4 count of <100 cells/ μ L.

It is recommended that all patients with low CD4 counts should undergo a detailed and comprehensive ocular evaluation as the possibility of occurrence of ocular lesions is very high. Guidelines for eye care, screening, and follow-up of HIV-infected patients need to be evolved, preferably related to the CD4 counts. The primary care clinician and the ophthalmologist should work in conjunction to manage ocular opportunistic infections in HIV-infected persons. Those with low CD4 counts should be screened and followed more frequently and intensely.

CONFLICTS OF INTEREST

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REFERENCES

1. Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO), *AIDS Epidemic Update* Geneva: UNAIDS 2007. Available at: http://www.who.int/hiv/epi-update2005_en.pdf (accessed 25 August 2011).
2. Simon V, Ho DD, Karim QA. HIV/AIDS epidemiology, pathogenesis, prevention, and treatment. *Lancet* 2006;368:489–504.
3. Vrabec TR. Posterior segment manifestations of HIV/AIDS. *Surv Ophthalmol* 2004;49:131–157.
4. Jabs AD. Ocular manifestations of HIV infections. *Trans Am Ophthalmol Soc* 1995;93:623–683.
5. Tay Kearne ML, Jabs DA. Ophthalmic complications of HIV infection. *Med Clin North Am* 1996;80:1471–1492.
6. Ryan M, Pavan-Langston D, Durand M. AIDS and anterior segment. *Int Ophthalmol Clin* 1997;8:241–264.
7. Biswas J, Madhavan HN, George AE, Kumarasamy N, Solomon S. Ocular lesions associated with HIV infection in India: a series of 100 consecutive patients evaluated at a referral center. *Am J Ophthalmol* 2000;129:9–15.
8. Biswas J, Joseph AE, Raizada S, Kumarasamy N, Solomon S. Ophthalmic manifestations of acquired immunodeficiency syndrome in India. *Ind J Ophthalmol* 1999;47:87–93.
9. Jabs DA, Van Natta ML, Kempen JH, et al. Characteristics of patients with cytomegalovirus retinitis in the era of highly active antiretroviral therapy. *Am J Ophthalmol* 2002;133:48–61.
10. Gharai S, Venkatesh P, Garg S, et al. Ophthalmic manifestations of HIV infections in India in the era of HAART: analysis of 100 consecutive patients evaluated at a tertiary eye care centre in India. *Ophthalmic Epidemiol* 2008;15:264–271.
11. Nguyen QD, Kempman JH, Bolton SG, et al. Immune recovery uveitis in patients with AIDS and cytomegalovirus retinitis. *Am J Ophthalmol* 2000;129:634–639.

Journal scan

Lee WJ, Chong K, Ser KH, Lee YC, Chen SC, Chen JC, et al. Gastric bypass vs sleeve gastrectomy for type 2 diabetes mellitus: a randomized control trial. *Arch Surg* 2011;146:143. DOI: 10.1001/archsurg.2010.326

Recently gastrointestinal metabolic surgery has been proposed as a new treatment modality for obesity-related type 2 diabetes mellitus (T2DM) in patients with a BMI <35. This is the first randomised trial published that evaluates surgical treatment of non-morbidity obese patients (BMI <35) with poorly controlled T2DM.

The study has evaluated two procedures namely, sleeve gastrectomy (SG) performed laparoscopically by resecting the greater curvature and complete fundus from the distal antrum (4 cm proximal to the pylorus) to the angle of His and gastric bypass (GB) where a long sleeved gastric tube approximately 2 cm wide is created along the less curved side and anastomosed to a loop gastroenterostomy approximately 120 cm distal to the ligament of Treitz.

The authors have studied a total of 60 patients (out of 209 volunteers) with 30 patients in each arm. The study was a double-blinded randomised trial on non-morbidity obese patients (mean BMI = 31) with poorly controlled T2DM (mean haemoglobin A_{1c} [HbA_{1c}] = 10.5%). The primary end point of the study was glycaemic control at 12 months after randomisation as determined by fasting glucose levels and HbA_{1c} <6.5% without medications. The secondary end-points were improvement in the metabolic disorders, i.e. lipid profile changes, blood pressure, waist-hip circumference, etc.

Resolution of T2DM was significantly better in the GB group than in the SG group (93% vs 47%; $P = 0.2$). The mean reduction in the HbA_{1c} level was 3.0% (SG group) and 4.2% (GB group),

respectively, at the end of 12 months after surgery. Weight loss after surgery was same in both groups at the end of third and sixth months but was better in the GB group at the end of 12 months. The GB group had a significantly lower BMI, waist circumference, glucose, HbA_{1c}, and blood lipid levels than the SG group at 12 months after surgery. Both GB and SG were effective in the treatment of patients with T2DM in whom current medical treatment had failed. However, resolution rate of 93% and success rate of 57% for T2DM treatment in the GB group were superior to 47% and 0% in the SG group at 12 months after surgery.

The authors have reasoned that in this study of diabetic patients, the result strongly supports the findings that the duodenum may play a role in T2DM resolution after bariatric surgery. Although GB is more effective in control of diabetes, SG should still be considered as the first choice in patients with good pancreatic reserve. Gastric bypass also avoids possible delayed micronutrient deficiency and may be a better option in patients with metabolic syndrome or hyperlipidaemia.

The study is limited by lack of both the gut hormone data and long-term follow-up to confirm durability of DM remission. However, it is a path-breaking randomised controlled trial (RCT), which evaluates the two different types of metabolic surgery in the non-morbidity obese T2DM patients. The authors conclude that GB is more effective than SG for the surgical treatment of poorly controlled T2DM and control of metabolic syndrome; duodenum exclusion plays a role in T2DM remission.

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