

Ocular Manifestations and Human Immunodeficiency Virus Retinopathy in Patients with Acquired Immunodeficiency Syndrome in North India

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Aim: To evaluate the spectrum of eye diseases in patients with human immunodeficiency virus, with special reference to human immunodeficiency virus retinopathy and its risk factors.

Methods: All patient with human immunodeficiency virus attending the Infectious Disease Clinic at Sir Sunderlal Hospital, Institute of Medical Sciences, Banaras Hindu University, India, between January 2001 and December 2003 were enrolled. All patients underwent a thorough eye examination. Patients with acquired immunodeficiency syndrome retinopathy were analysed separately for predisposing factors. The risk factors analysed were positive C-reactive protein, low CD4 levels, associated central nervous system infections, and other eye diseases. Statistical analysis was done using Medcalc version 7.5.

Results: Of 460 analysable patients, 88 patients (19%) had some eye manifestations, and 54 patients had human immunodeficiency virus retinopathy. Univariate analysis disclosed that immunosuppression (CD4 levels, <200/ μ L), positive C-reactive protein, associated eye lesions, and any central nervous system pathology were significant risk factors for the development of human immunodeficiency virus/acquired immunodeficiency syndrome retinopathy.

Conclusions: Human immunodeficiency virus could be a risk factor for retinopathy as a significant number of patients did not have any other findings or risk factors for the development of retinopathy. However, it would be premature to draw definitive conclusions about the risk factors, as the number of patients analysed was small.

Key words: CD4-positive T-lymphocytes, Eye manifestations, HIV infections, India

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Introduction

Ocular manifestations in acquired immunodeficiency syndrome (AIDS) are varied and affect almost all the structures in the eye. The lifetime cumulative risk of at least one abnormal ocular lesion in patients with human immunodeficiency virus (HIV) ranges from 52% to 100%.¹⁻⁶ The first published data in India focusing on ocular manifestations in patients with HIV was from Sankara Nethralaya in 1995.⁴ However, there is no information on eye manifestations associated with HIV from eastern Uttar Pradesh and Bihar, the 2

most populous states in India. This study provides preliminary data on eye manifestations associated with HIV in this area and is one of the largest studies focusing on HIV retinopathy conducted to date in India. The results of this study were compared with those of other Indian studies and data from other countries.

Methods

Patients

All patients with HIV attending the Infectious Disease Clinic, Sir Sunderlal Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India, were enrolled in the study. Sir Sunderlal Hospital is a 1000-bed tertiary care teaching hospital with a catchment area of 5 states (Uttar Pradesh, Madhya Pradesh, Bihar, Jharkhand, and Chattisgarh). The annual number of new patients

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Eye Manifestations in Patients with Acquired Immunodeficiency Syndrome

Table 1. Baseline characteristics of patients with human immunodeficiency virus.

Characteristics	Patients with retinopathy (n = 54)	Patients without retinopathy (n = 108)
Age (SD) [years]	35.2 (12.6)	36.9 (13.6)
Male:female ratio	3.6:1	3.8:1
Duration of symptoms (SD) [months]	11.6 (1.9)	11.7 (2.2)
Time from diagnosis (SD) [months]	4.57 (0.74)	5.03 (0.59)
Patients receiving highly active antiretroviral therapy (%)	96	92

with HIV is approximately 150. Patients with HIV retinopathy were included as the study population. The control patients had HIV but did not have HIV retinopathy and were matched for age, sex, and duration of AIDS symptoms. The baseline characteristics of the study population and controls are shown in Table 1. Informed consent was provided by all patients prior to investigation. Patients were excluded from the study if they did not consent to enrollment, or if they had coexistent diabetes or hypertension, as the manifestations of HIV retinopathy and diabetic/hypertensive retinopathy overlap.

Design

The presumed risk factors included were positive C-reactive protein (CRP), low CD4 levels (<200/ μ L), associated central nervous system (CNS) infections, and other eye diseases.

HIV status was confirmed by antibody testing using enzyme-linked immunosorbent assay with 2 different antigens. CD4 count was performed by using fluorescent assisted cell sorter count (Becton Dickson, Singapore) as per the protocol given by the manufacturer. Ophthalmological examination included naked eye examination, visual acuity, indirect and direct ophthalmoscopy, and slit-lamp examination.

All the associated diseases were identified exclusively on the basis of clinical examination by their classical appearance. If patients had associated CNS lesions, the type of lesion was assessed by imaging, cerebrospinal fluid evaluation, culture, and serology.

Statistical Analysis

Analysis was done using Medcalc version 7.5. It was hypothesised that immunosuppression as evidenced by low CD4 level, active inflammation represented by positive CRP, associated CNS lesions, and eye diseases were independent risk factors for HIV retinopathy. The odds ratio for developing HIV retinopathy was calculated from matched pairs. Univariate analysis was done by means of McNemar's chi squared test. Conditional logistic regression was used for the analysis of presumed risk factors.

Results

Of 460 patients enrolled in the study, there were more men than women, with a ratio of 3.7:1. There was no sex difference in the incidence of eye diseases. The mean age of the patients was

Table 2. Ocular manifestations in patients with human immunodeficiency virus.

Manifestation	Number of patients (%)*
Cytomegalovirus retinitis	1 (1.1)
Molluscum contagiosum of the eyelid	6 (6.8)
Conjunctivitis	12 (13.6)
Papilloedema	26 (29.4)
Blepharitis	34 (38.7)
Human immunodeficiency virus retinopathy	54 (61.4)
Impaired visual acuity (<6/24 uncorrected)	66 (75.0)

* Percent calculated from the total number of eye manifestations.

37.6 years (range, 2 to 60 years). The CD4 count was available for 375 patients. Eighty eight patients (19%) had some ophthalmological manifestations and 54 patients had HIV retinopathy. The various ophthalmological findings are shown in Table 2.

Among the patients with HIV retinopathy, 23 had CNS diseases — tubercular meningitis (8), cryptococcal meningitis (6), CNS toxoplasmosis (4), progressive multifocal leukoencephalopathy (2), and HIV encephalopathy (3) — 19 patients had other eye manifestations — molluscum contagiosum of the eyelid (6), blepharitis (10), and conjunctivitis (3) — and the remaining 12 patients had other diseases — pulmonary tuberculosis (8), *Pneumocystis carinii* pneumonia (3), and disseminated multi-dermatomal herpes (1). The mean blood pressure and blood sugar of patients with or without HIV retinopathy were tested because patients with hypertension or diabetes might have findings similar to HIV retinopathy, but these were not significantly different.

Univariate analysis showed that immunosuppression (CD4 level, <200/ μ L), positive CRP, other associated eye lesions, and any CNS pathology were significant risk factors for retinopathy. The analysis is shown in Table 3. However, when dichotomised CD4 levels, positive CRP, and other associated eye diseases were simultaneously analysed in conjunction with sex and age as potential confounding factors in a conditional logistic regression model, CD4 levels and CRP lost their significance, while associated diseases of CNS lesions or other ophthalmological diseases maintained their significance.

Discussion

The spectrum of ocular lesions in patients with HIV from this region of India is different to that from other regions in India⁵ and other parts of the world⁷⁻⁹ (Table 4).

Table 3. Univariate and multivariate analysis of risk factors for human immunodeficiency virus retinopathy.

Variable	Univariate analysis			Multivariate analysis		
	Odds ratio	95% Confidence interval	p Value	Odds ratio	95% Confidence interval	p Value
CD4*	7.2	2.0-24.8	0.000	2.0	0.5-10.3	0.43
C-reactive protein	3.8	1.6-9.3	0.001	1.2	0.4-6.9	0.78
Tubercular meningitis	3.7	1.8-12.3	0.05	4.7	0.9-22.0	0.07
Cryptococcal meningitis	16.9	2.4-141.0	0.001	30.0	2.9-318.0	0.001
Toxoplasmosis	4.9	0.6-6.8	0.07	15.0	2.6-108.8	0.003
Other eye lesions	23.2	6.8-72.8	0.000	47.0	8.7-238.6	0.000
Other central nervous system lesions	3.8	1.8-12.3	0.05	8.0	2.2-36.8	0.005

* CD4 levels dichotomised to >200/ μ L and <200/ μ L values

Table 4. Ophthalmological findings in various studies.

Characteristics	USA, 1995 ⁹	Kenya, 1996 ⁸	USA, 1997 ⁷	India, 1998 ⁵	Present study, 2004
Number of patients	781	102	30	100	460
Human immunodeficiency virus retinopathy	50	25	16	15	54
Blepharitis	0	0	—	2	34
Molluscum contagiosum	0	0	—	1	06
Cytomegalovirus retinitis	37	3	7	17	1
Kaposi's sarcoma	2	2	3	0	0
Other	1*	1*	—	0	12 [†]

* Toxoplasmosis of the eye.

† Conjunctivitis.

In India, the incidence of HIV in men is greater than in women.¹⁰ Due to the low educational status and poverty in the area, most people do not seek medical advice until the disease progresses to an advanced stage. Therefore, female patients and those with early HIV infection were under-represented in this study. Moreover, patients with HIV do not undergo routine eye examinations and were referred for an eye examination only if they had symptoms pertaining to vision. This could give a false impression of a high incidence of eye diseases in studies conducted at referral ophthalmic centres. To estimate the true incidence of eye disease in patients with HIV, the authors undertook routine examination of all patients with HIV, irrespective of their symptoms. Only 19% of patients with HIV had eye manifestations. This incidence was less than that in the USA (50%),⁹ Africa (66%),⁸ and other Indian studies (42.5%).⁵ The reason could be due to the large denominator of asymptomatic patients with HIV in the present study.

HIV retinopathy was the commonest eye manifestation in patients with HIV in this region. HIV retinopathy was also the commonest eye manifestation in other series with an incidence ranging from 25% to 75%.^{6,11,12} Retinopathy is a form of microvasculopathy of obscure aetiology, represented by retinal cotton wool spots that rarely interfere with vision. The cotton wool spots can also be seen in patients with diabetes, hypertension, systemic lupus erythematosus, leukaemia, and various other systemic illnesses.¹³⁻¹⁵ Microscopic examination of the cotton wool spots in patients with AIDS shows pathological features identical to those seen in association with other disorders. The proposed mechanisms include

ischaemic injury to the nerve fibre layer of the retina, leading to focal interruption to the axonal flow (trafficking of cargoes of organelles and molecules between the cell body) and accumulation of subcellular material. Attempts have been made to investigate the causes of and possible risk factors for HIV retinopathy.^{6,16,17} Earlier speculation that these spots represent *P carinii* infection or cytomegalovirus (CMV) have been unsubstantiated.^{16,17} Attempts to isolate HIV from these lesions have also been largely unsuccessful.⁶ However, some authors have demonstrated HIV antigen in microvascular tissue near the cotton wool spot.⁶ This is likely to be due to the following factors:

- active inflammation leads to vaculitis and consequent ischaemic injury (represented by CRP)
- the innate immune status (CD4) of the patients (as the virus was not proven to be causative in all patients)
- other CNS lesions that might interrupt axonal flow
- other eye diseases that may stimulate local inflammation and consequent changes that may trigger pathogenesis of cotton wool spots as major risk factors.

The univariate analysis disclosed that immunosuppression, positive CRP, other associated eye lesions, and any CNS pathology were significant risk factors. However, when dichotomised CD4 levels, positive CRP, and other associated diseases were simultaneously introduced in conjunction with sex and age as potential confounding factors in a logistic regression model, CD4 levels and CRP lost their significance, while associated diseases such as CNS lesions or other ophthalmological manifestations maintained

their significance. These findings were difficult to interpret as the number of patients in this study was low.

The apparent implication of immune status and CRP, as observed in the univariate analysis, could be secondary to the associated opportunistic infections; it has been shown that opportunistic infections occur in the setting of low immunity (represented by low CD4 count) and will trigger an inflammatory reaction (represented by positive CRP). It is also probable that, even if the CD4 levels are low, it is the absolute decline in the host defence as represented by any opportunistic infection, or an actively ongoing inflammation secondary to the infection (represented by CRP) that makes a patient with HIV likely to develop retinopathy. However, since a detailed evaluation was not performed for these patients, any conclusions would be inappropriate. This point is also reinforced by the observation that, although the majority of these patients had AIDS, only 15% had retinopathy compared with 56% of patients with CNS lesions. The presence of positive CRP could also be explained by this theory.

CMV retinitis is one of the most commonly reported opportunistic infections of the eye, with a prevalence ranging from 15% to 45%.^{1-3,5,18} The incidence of CMV retinitis decreased steeply (up to 80%) with the advent of highly active antiretroviral therapy in developed countries.¹⁹ However, the incidence remains high in developing countries. Surprisingly, only 1 patient with CMV retinitis was encountered in this study during the 2-year study period. As this is a preliminary study, further studies are required to ascertain whether this pattern is consistent in this part of India. Other diseases encountered in the study included molluscum contagiosum, an occasionally reported DNA pox virus disease.²⁰ Several patients had a single small lesion affecting the eyelid but 1 patient had a large number of bilateral lesions.

Neuro-ophthalmic manifestations such as papilloedema, neuritis, and gaze palsies constituted 10% to 15% of all eye manifestations in patients with HIV in one of the largest Indian studies.⁵ In the present series, 29.5% of patients had papilloedema but the other manifestations were not found. It is possible that severe blepharitis was due to both immunosuppression and poor hygiene. The frequency of conjunctivitis in this study did not appear to be high compared with the general population and could be due to seasonal eye diseases. *Toxoplasma gondii*,⁷ *P. carinii*,²¹ *Varicella zoster*,²² and Kaposi's sarcoma⁶ are rare in the Indian context.

The commonest eye lesion in this study was HIV retinopathy. CMV retinitis, molluscum contagiosum, and blepharitis were uncommon. The implication of HIV in the development of retinopathy

could be in the pathogenesis of retinopathy because there was a significant number of patients who did not have any other findings or risk factors for the development of retinopathy. However it would be premature to make any conclusions on the risk factors as the number of patients analysed was small.

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