·Clinical Research·

Clinical spectrum of 15 patients with HIV-related ocular involvement in Tehran

Ali Abdollahi [1], Giv Heidari-Bateni [2], Reza Zarei [1], Parastou Kheirandish [3], Mohammadhosein Malekmadani [1], Minoo Mohraz [3], Maryam Abdollahi [1], Mohammad Taher Rajabi [1]

[1]Department of Ophthalmology, Eye Research Center, Farabi Hospital, Tehran University of Medical Sciences, Tehran, Iran
[2] Student of MD/MPH, Tehran University of Medical Sciences, Tehran, Iran
[3] Department of Infectious diseases, Iranian Research Center for HIV/AIDS, Tehran University of Medical Sciences, Tehran, Iran
Correspondence to: Mohammad Taher Rajabi. Department of Ophthalmology, Eye Research Center, Farabi Hospital, Tehran University of Medical Sciences, Tehran, Iran. mt_rajabi@yahoo.com
Received:2010-11-08 Accepted:2010-11-30

Abstract

• AIM: To determine the frequency of HIV-related ocular involvement and to describe the characteristics of involvement in a special clinic in Tehran.

• METHODS: In this cross sectional study, 141 patients (125 male and 16 female, 282 eyes) of HIV-infected patients with various stages of HIV infection that were referred to Center of behavioral diseases were evaluated during a period of 7 months. Every patient had a complete profile including demographic data, method of HIV transmission, recent CD4 T cell lymphocyte count, serological studies for common sexual or blood-born viruses and toxoplasmosis, history of antiretroviral therapy, and associated systemic disease.

• RESULTS: A total of 141 patients were evaluated. HIV-related ocular involvement was detected in 15 patients (10.6%), including 3 mycobacterium tuberculosis-related choroiditis, 2 cytomegalovirus retinitis, 2 retinal toxoplasmosis, 2 herpes simplex virus-related lesions, 1 HIV-associated retinopathy, 1 herpes zoster ophthalmicus, 1 undetermined vitritis, and 3 cases of cranial nerve involvement including 2 cases of gaze palsy and 1 case of papilitis. In our study, mean CD4 T cell lymphocyte count was fewer in patients with ocular involvement than in patients without ocular involvement (204.7±123.8 *vs*403.7±339.7, P= 0.029), but there was no difference in other possible associated factors between two groups.

• CONCLUSION: Mycobacterium tuberculosis-related choroiditis and neurophthalmic lesions are the most common HIV-related ocular involvements in Tehran that is different from those of recent publications in developed countries.

• KEYWORDS: HIV; ocular involvement; highly active anti-retroviral therapy
DOI:10.3980/j.issn.2222-3959.2010.04.13

Abdollahi A, Heidari-Bateni G, Zarei R, Kheirandish P, Malekmadani M, Mohraz M, Abdollahi M, Rajabi MT. Clinical spectrum of 15 patients with HIV-related ocular involvement in Tehran. *Int J Ophthalmol* 2010;3(4):331-336

INTRODUCTION

First description of HIV-related ocular involvement was reported more than two and a half decade ago. In the early epidemic of AIDS, presence of cotton-wool spots was the most common ophthalmic finding in AIDS patients. Since then, precise description of different form of ocular involvement in HIV-infected patients was made so that nowadays, diagnostic criteria for many form of ocular disease in HIV infected patients have been produced. Surveys on ocular involvement of HIV were conducted in few studies around the developing world. Putting these data together with those of developed countries reveals that the spectrum of HIV and AIDS-related ocular diseases is different in various parts of the world [1]. For example, Cytomegalovirus Retinitis is the most common cause of retinitis in HIV-infected patients in developed world although it seems less prevalent in developing countries.

On the other hand, after the introduction of highly active anti-Retroviral therapy (HAART), which became widely available in 1996, clinical features of ocular involvement associated with HIV infection have been changed and frequency of ocular involvement, which affects 70 to 80 percent of all HIV infected patients at some point during their illness, decreased dramatically. Based on the reported data, the HIV epidemic in Iran appears to be accelerating at an alarming trend [2]. According to the latest data, about 66 000 (36 000-160 000) people are living with HIV in Iran,

thus the prevalence rate is about 0.2% [0.1-0.4] among adults aged 15 to 49[2].

Recent attention to HIV epidemiology and programs for case detection and supportive care in Iran make it possible to find out the pattern of ocular involvement in this developing country in the era of highly active antiretroviral therapy. This cross sectional study was conducted as a part of a larger consulting and supportive program for behavioral diseases, which was holding in Imam Khomeini hospital and aimed to determine the frequency of ocular involvement and to describe the characteristics of involvements in Iranian patients with various stages of HIV infection referred to center of behavioral diseases in Tehran.

MATERIALS AND METHODS

Materials During Jun. 2006 to Dec. 2006, any case attended to the center for routine appointments, after giving an informed consent, was consequently included in the study. Participants were committed to attend in the eye examination program, which was held every week in the eye clinic established in the center. For all of these patients, diagnosis of HIV seropositivity had been proved by a positive enzyme linked immunosorbent assay (ELISA) and a positive immunoblotting (Western blot) test for HIV. All patients had a medical record including demographic data, method of HIV transmission, history of drug therapy, past medical history and results of systemic examinations for signs of opportunistic or any other systemic disease, which was completed in every appointment by an infectious disease specialist. In addition, serum analysis for hepatitis C virus antibody, hepatitis B surface antigen, toxoplasma antibody and necessary laboratory data including hematology and lymphocyte subset analysis were included.

Methods Patients are seen routinely every 3 months and at other times if they are ill. After obtaining the medical record, every patient underwent a complete ophthalmologic examination in the eye examination clinic. Registering of visual complains was performed by a trained eye nurse and visual acuity was checked with an E chart by an optometrist. Then pupils were dilated with 10g/L Tropicamide and 20-50g/L Phenylephrine. Two expert ophthalmologists examined the external eye and anterior segment with a slit lamp, and then examined the retina by indirect ophthalmoscopy. When there was an ophthalmic involvement, the patient was referred to Farabi Eye Hospital as a tertiary center and complementary diagnostic work up was performed there. The frequency and description of ocular involvements and comparison of associated factors between patients with eye involvement and those without involvement were investigated in this study.

Statistical Analysis Analysis was performed by software SPSS version 13. Statistical significance was determined by χ^2 analysis and Student's t test for categorical and numerical variables, respectively.

RESULTS

Systemic Findings During the study period, 141 HIV-infected patient underwent complete ophthalmic examination. The mean age ± standard deviation of patients was 37±9 years and none of them was aged more than 55 years. From those participated in the study, 125 patients were male (88.7%) and 16 were female (11.3%). The mean time between ophthalmic examination and HIV antibody detection by Western blotting was 4 years and 2 months (range: 2 months -16 years). Twelve patients had active or a recent history of pulmonary tuberculosis and 52.4% of patients had coinfection with hepatitis C virus. Table 1 lists the clinical characteristics of patients.

From all patients, 46.2% were taking highly active antiretroviral therapy (HAART) at the time of ocular examination and none of the patients had documentation for taking but discontinuing HAART at any time in the past. At the time of the eye examination, 25 of HIV-positives (17.7%) had CD4 T lymphocyte count of fewer than 200cells/mm^3 and eight patients had CD4 T Lymphocyte count of fewer than100cells/mm^3.

According to the 1993 Centers for Disease Control and Prevention case surveillance definition of AIDS, 39 patients were in AIDS phase (27.6%).

Ocular Involvement Blurred vision (low vision) was the commonest complain among HIV-infected patients and was seen in 106 eyes (37.6%). In fifteen eyes with blurred vision, this complaint considered to be due to HIV-related eye involvement (Table 2). However, refractive error was the most common cause of low vision (84.9%). Only one of the patients with low vision had cataract. After a complete eye examination, ocular involvement, regardless of cataract and refractive errors, was found in 18 patients (28 eyes). Cells in AC and Vitreous and multiple lesions of choroiditis were the most common involvements (Table 3). Ocular involvement in 15 patients (10.6%) was HIV-related.

Ocular tuberculosis (TB) was diagnosed in 7.7% of patients in AIDS phase and 2.1% among HIV-infected patients in our study. Three of 12 patients with recent or history of previous TB reactivation had TB ocular involvement. All of them had CD4 T-cell count of fewer than 200cells/mm^3. One of them was a 48 year-old man on HAART with previous history of active TB infection who was under isoniazid prophylaxis and with a CD4 count of 150cells/mm^3. The other one was a 26 year-old man with active TB infection who was on anti-TB treatment regimen. His CD4 count was 123cells/mm^3. The last patient was a 37 year-old man with active TB infection

Table 1 Clinical and demographic characteristics of HIV-positive patients

Variable	With eye involvement[1]	Without eye involvement	Total
Number of patients	15 (10.6%)	126 (89.4%)	141 (100%)
Mean age	34.5±9.0	37.0±8.7	36.7±8.8
Presence of a systemic infection	25.0%	13.6%	14.9%
IV drug use	56.2%	50.4%	51.1%
HBS antigen positive	6.2%	6.4%	6.4%
HCV antibody positive	68.8%	50.4%	52.4%
Toxoplasma seropositivite	31.2%	23.2%	27.2%
HAART	50.0%	44%	44.7%
Mean CD4 T cell count	204.7±123.8[a]	403.7±339.7[a]	369.1±322.8
Mean Refraction			
Right eye	-0.35±1.02	-0.26 ±1.73	-0.27±1.65
Left eye	-0.39±1.09	-0.26 ±1.09	-0.28 ±1.08

[1]Patients with only ocular symptoms but no ophthalmic sign were categorized in patients without eye involvement. Patients with diagnosis of blepharitis, glaucoma and refractive errors were also excluded from those with eye involvement. [a]$P = 0.029$.

Table 2 Frequency of ocular symptoms in 282 eyes of HIV+ patients

Symptoms	Right	Left	Total
Redness	3	2	5
Pain	3	1	4
Blurred vision	55	53	106
Scotoma	3	2	5
Diplopia[1]	2		
Purulent discharge	5	5	10
Burning sensation	3	2	5
Photopsia	2	1	3

[1] Two persons suffered from diplopia

Table 3 Frequency of ocular involvements and final diagnosis in 141 HIV-infected patients

Type of lesion	Right	Left	Final diagnosis
Cotton wool spots	1	1	HIV related Retinopathy (n=1)
Area of full thickness retinal necrosis	2	1	
Retinal detachment	1	0	
Dendritic scars on cornea	1	0	Undetermined vitritis (n=1)
disciform keratitis and necrotizing stromal keratitis	0	1	TB choroiditis (n=3)
Multiple or focal lesions of choroiditis	3	3	CMV retinitis (n=2)
Superficial retinal necrosis	1	1	chorioretinal toxoplasmosis (n=2) herpes keratitis (n=2)
Intraretinal hemorrhage	2	1	
AC and/or vitreous inflamation	5	5	
Horizontal gaze paresis	2	1	Horizontal Ophthalmoplegy (n=2)[1]
Vertical gaze paresis	0	1	Vertical Ophthalmoplegy (n=1)
Papilitis	1	0	Undetermined papilitis (n=1)[2]
Periocular vesicular lesions	1	0	Herpes Zoster Ophthalmicus infection (n=1)
Inflammation of eyelids	2	2	blepharitis (n=2)
Elevated cup to disc ration	1	2	Possible cases of glaucoma (n=2)

[1] One patient had horizontal ophthalmoplegy in right eye and vertical in the contralateral eye.

[2] With elevated cup to disk ratio in the contralateral eye

and CD4 count of 100cells/mm^3.

Visual acuity was spared in the latter two patients but the first one had visual acuity of counting fingers in both eye.

CMV retinitis was diagnosed in only two patients and three eyes (point prevalence of 1.4% among HIV-infected patients). Considering patients in AIDS phase, CMV retinitis

were seen in 5.1% of them. One of them was a 36 year-old woman with area of full thickness retinal necrosis, intraretinal hemorrhage and signs of retinal detachment in her right eye. Here CD4 count was 105cells/mm^3. She had sign of blepharitis on her left eye.

The other was a 33-year-old man with a CD4 count of 110cells/mm^3 with the same lesions in both eyes. Both patients had a reduced visual acuity in the affected eyes. Chorioretinal toxoplasmosis was diagnosed in two patients, with complaints of photopsia and scotomoas and blurred vision. Both patients had positive serum immunoglobulin G levels to *Toxoplasma gondii* Two cases of herpetic lesions (a case of herpetic keratitis and a case of stromal corneal herpes) a case of undetermined vitritis and an HIV-infected patient with herpes zoster ophthalmicus were also found. Both patients with herpatic lesions were in AIDS phase (5.1% of AIDS patients). HIV-related retinopathy was diagnosed in both eyes of only one patient.

Neurophthalmic involvement was primarily diagnosed in three patients. There were two cases with gaze palsies. One of them was a 25 years man with right eye horizontal gaze palsy with a CD4 count of 534cells/mm^3. The other person was a 34 years man with a horizontal gaze palsy of right eye and a vertical gaze palsy of the contra lateral eye. He had a visual acuity of 2/10 in the right eye and 1/10 in the left. He was on HAART with a CD4 count of 326cells/mm^3.

Optic nerve papilitis was primarily diagnosed in a 34-year man with CD4 count of 218cells/mm^3, unfortunately complementary work up was not achieved in the patient due to discontinuation of consulting from the side of patient.

Analysis of data between patients with eye involvement and those without involvement (regardless of presence or absence of ocular symptom) showed that in patients with ocular involvement the mean ±standard deviation of CD4 positive T cells were 204.7 ±123.8cells/mm^3. This was significantly fewer than those without ocular involvement in which mean±standard deviation count of CD4 T cells were 403.7±339.7cells/mm^3(P=0.029). No association were found between ocular involvement and variables such as mean age, method of HIV transmission, proportion of seropositive patients for HBS antigen, HCV antibody and Toxoplasma antibody.

DISCUSSION

Our study was conducted to find out the frequency of ocular involvement in a developing country. Based on our observation, 10.6% of HIV-infected patients had ocular involvement, which was HIV-related and mycobacterium tuberculosis was the most common causative agent. Data investigating burden of HIV disease in Asia before HAART showed that HIV-infected patients in Asia were mostly in early stages of HIV infection and presented with diseases such as pneumococcal pneumonia, invasive salmonella, and tuberculosis.

The spectrum of HIV ocular involvement seems to be dependent to the burden of disease and therefore in developing countries, it is potentially different from those in developed ones. This altered pattern was investigated in few studies all of them conducted before HAART era. This altered spectrum of ocular involvement in HIV-infected patients in developing countries is not only related to the higher frequencies of exposure to causative infectious agents but also to the higher rates of death early in the course of disease. In our study, overall 44.7% of patients were on HAART regimen. Something that is comparable to recent ocular surveys on HIV-infected patients around the world. In the report of enrollment data from The Longitudinal Study of the Ocular Complications of AIDS (LSOCA), 77.9% of patients were under HAART although all of them were in AIDS phase. It is necessary to emphasize that our study was conducted on patients in all stages of disease and only 27.6% of our patients were in AIDS phase. The most common ocular symptom in our study was blurred vision and this was compatible with pre HAART result in developing countries. In a study in Uganda main reason for low vision was cataract, but in our study refractive error was the most common underlying etiology.

None of our patients was more than 55 years old and cataract was not a common finding in our study. The most common ocular involvement in our series was TB choroiditis. Today, tuberculosis is the most common opportunistic infection among HIV-infected patients in Iran[3]. Nowadays, in the era of global HIV epidemics, the incidence of ocular tuberculosis has increased as part of the total increase in the number of patients with extra pulmonary tuberculosis. All of our ocular TB cases had documentation of ongoing or previous active TB in their medical records and CD4 T lymphocyte count of all three, were fewer than 200cells/μL. According to the literature, ocular involvement in TB can present in many different ways, including choroiditis and anterior uveitis (the most common presentations), choroidal tubercles, papillitis, retinitis, vitritis, scleritis, keratitis, dacryoadenitis and a lid mass.

The clinical feature in our patients was bilaterally multiple lesions of choroiditis in two patients and two focal sites of choroiditis in the other patient. Mild to moderate cells and flares in both AC and vitreous were also seen.

Two of 141 patients in our study were found to have CMV retinitis. Although CMV retinitis was the most common cause of retinitis in the literature before the HAART era, studies from developing countries showed that in these

countries CMV retinitis is not as common as developed world with a prevalence of 0-8.5%. Introduction of HAART led to an estimated 80% decrease in the incidence of CMV retinitis[4].

Ignoring the mild reduction in the severity of disease, It seems that introduction of HAART does not change the basic clinical features of CMV retinitis[5,6]. In our study, both patients had the basic clinical characteristics of CMV retinitis. However, none of them had CD4 T lymphocyte count of less than 50cells/μL. Low frequency of CMV retinitis in our study was compatible with previous surveys in developing countries. Considering the fact that CMV retinitis mostly occurs in those HIV-infected individuals with severe levels of immunodeficiency, as manifested by CD4+ T-lymphocyte counts of less than 50cells/μL. One can presume that HAART was effective in declining the number of patients with low count of CD4 T cells in Iran and introduction of HAART has declined the number of opportunistic ocular infection like CMV retinitis. On the other hand, it should be taken in to consideration that in Africa, most of HIV infected patients die before ocular opportunistic infections occur.

This fact may be true in any other developing countries like Iran. Conclusively, it is not clear that low frequency of CMV retinitis is due to effective role of HAART or occurrence of death before presenting the disease. In the report of enrollment data from The Longitudinal Study of the Ocular Complications of AIDS (LSOCA), the most frequent ocular diagnosis was CMV retinitis, affecting 22.1% of patients. This study suggests that new cases of CMV retinitis continue to occur and there is a population of patients with long-standing retinitis who will require management.

In LSOCA survey, all of the patients were in AIDS phase. Considering only the patients in AIDS phase, CMV retinitis accounted for 5.1% of patients in our study. In a study in rural Uganda, none of the HIV infected patients had ocular signs of CMV in preHAART era. Low prevalence of HIV associated retinopathy was also seen in our study. There was only one case with both eye involvements with CD4 count of more than 200cells/μL. CD4 count in this patient is not compatible with other literatures in which CD4 count in HIV-related retinopathy is fewer than 200cells/μL.

In HIV-related retinopathy, the most commonly observed manifestations include cotton-wool spots, intraretinal hemorrhages, and retinal microaneurysms. Multiple cotton wool spots and intraretinal hemorrhage were seen in our patient.

VZV keratitis was consisted two of our 15 HIV-related ocular involvement in our study. We deliberately exclude two patients with blepharitis from HIV-related involvements in our results. Because we did not know whether this finding was because of HIV induced immunocompromisation or a randomly associated findings in these patients, particularly those with blepharitis had CD4 count of more than 500cells/μL in our study.

The frequency of blepharitis in Iranian society is not known so it did not make sense for us if we included blepharitis as one of HIV-related lesions in the study, although it has mentioned in literature. Evidence number of VZV or HSV keratitis were considerable in our series and there was a case of herpes zoster ophthalmicus (HZO). HZO can be associated with conjunctival injection, epithelial keratitis, stromal keratitis, scleritis or episcleritis and inflammation of iris. Although there is some controversy about the greater incidence of HSV keratitis among HIV-infected patients but it has been suggested that HZO affects HIV-infected patients more common than non-infected individuals.

In LSOCA the frequency of active keratitis and corneal scars reached to 1.2% together and herpes zoster ophthalmicus prevalence was 0.1% of AIDS stage patients. Comparing with LSOCA results, 5.1% of our patients in AIDS phase had HSV-induced keratitis.

Toxoplasma chorioretinitis was another HIV-related ocular involvement which was seen in 2 patients in our survey.

Ocular toxoplasmosis affected 1 to 2 percent of HIV-positive patients in pre HAART era, and it was often diagnosed by the occurrence of anterior-chamber and vitreous inflammation, pigmented chorioretinal scars and a relative absence of retinal hemorrhage. Involvement in both cases in our study was unilateral and both had the typical presentation of disease. $CD4^+$ T lymphocyte count was 200-500cells/μL in both cases. External ocular manifestations of HIV-related neurophthalmic abnormalities occurred in about 7% of AIDS patients prior to the introduction of HAART. Considering our study as an investigation on HIV-infected patients and not just those in AIDS phase reveals that neurophthalmic involvement included a significant proportion of ocular involvement in our study. Unfortunately, complementary work up for a patient with unilateral papilitis failed, and the diagnosis of the patient remained unknown. In our study, two of our patients suffered from elevated cup to disk ratio. Association of chronic open angle glaucoma with HIV infection was not seen in any literature. Ultimately, we found that, the mean count of CD4 T lymphocyte were significantly fewer in HIV-infected with eye involvement than those without involvement. Low CD4 count was a reliable predictor for ocular complications in HIV patients. Our study failed to find any other possible risk factor for prediction of risk of ocular complication in HIV-infected individuals.

In conclusion, our finding was compatible with that of previous findings in developing countries. Ocular complications of tuberculosis, toxoplasmosis, herpes zoster, and particularly HSV keratitis were more prevalent in our survey. These findings seem to be due to higher frequencies of exposure to these causative infectious agents.

Although antibodies to CMV are widespread in the general population of Asian adults, but CMV retinitis was lower in frequency in comparison with recent surveys in developed countries. There is no evidence from ocular involvement from pre-HAART era in Iran, but frequency of ocular involvement observed in this study was lower than available pre-HAART literatures through out the world, which suggests the dramatic effect of HAART on the prevalence of HIV-related ocular involvement. Fewer CD4 count in the HIV-infected patients with ocular involvement in this study in comparison with those without involvement shows that ocular involvement is related to degree of immunocompetency in the HIV-infected patient. Considering TB choroiditis as the most diagnosis in this survey suggests that periodic ocular examination in HIV-infected with TB superimposition or history of TB infection even if there were no visual complaints is mandatory. This study was the first survey of ocular burden of HIV in Iran. There was no control group in this survey. So, some of our findings could not be interpreted as HIV-related involvement, like cases of blepharitis or association of high number of refractive errors with HIV. Although the method of patient selection was the best achievable way for conducting a cross-sectional study in our settings, but some caution must be kept in mind while interpreting data from this study. Undoubtedly, the patients were not the exact representatives of the general population of HIV-infected in Tehran. In particular, those participated in the follow up appointment of center of behavioral diseases were patients selected for compliance with follow-up visits.

REFERENCES

1 Belfort R Jr. The ophthalmologist and the global impact of the AIDS epidemic LV Edward Jackson Memorial Lecture, *Am J Ophthalmol* 2000;129(1):1-8

2 UNAIDS/WHO epidemiological fact sheets on HIV/AIDS and Sexually Transmitted Infections 2006

3 Sharifi-Mood B, Alavi-Naini R, Salehi M, Hashemi M, Rakhshani F. Spectrum of clinical disease in a series of hospitalized HIV-infected patients from southeast of Iran. *Saudi Med J* 2006;27(9):1362-1366

4 Jacobson MA, Stanley H, Holtzer C, Margolis TP, Cunningham ET. Natural history and outcome of new AIDS-related cytomegalovirus retinitis diagnosed in the era of highly active antiretroviral therapy. *Clin Infect Dis* 2000;30(1):231-233

5 Jabs DA, Van Natta ML, Kempen JH, Reed Pavan P, Lim JI, Murphy RL, Hubbard LD. Characteristics of patients with cytomegalovirus retinitis in the era of highly active antiretroviral therapy. *Am J Ophthalmol* 2002;133(1):48-61

6 Holland GN, Vaudaux JD, Shiramizu KM, Yu F, Goldenberg DT, Gupta A, Carlson M, Read RW, Novack RD, Kuppermann BD; Southern California HIV/Eye Consortium. Characteristics of untreated AIDS-related cytomegalovirus retinitis: II Findings in the era of highly active antiretroviral therapy (1997 to 2000). *Am J Ophthalmol* 2008;145(1):12-22