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Research Article

Risk Factors for Premature Nuclear Cataract Formation in Human Immunodeficiency Virus (HIV) Infected Individuals Receiving Antiretroviral Therapy

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Abstract

Background: Antiretroviral therapy (ART) has resulted in a dramatic decrease in AIDS-associated morbidity and mortality including ocular opportunistic infections. However, despite its advantages, the use of ART has been associated with metabolic and end organ dysfunction, with ocular complications remaining ill-defined in this group.

Methods: A retrospective chart review was performed in an outpatient HIV clinic to include all patients receiving ART who had ophthalmologic evaluation between January 2006 to November 2010. All had a CD4 count and HIV viral load within six months preceding or 1 month after the visit. The selected charts were evaluated for demographic information, ocular diagnosis and any medical comorbidities. Statistical analysis identified independent variables in patients with and without cataracts. Unadjusted and adjusted prevalence odd ratios and 95% confidence intervals were calculated for correlates associated with nuclear cataracts.

Findings: A total of 102 patients were identified, the majority of whom (80%) were African American and had a median CD4 count of 441 cells/μL. 41.2% (42/102) were diagnosed with nuclear cataracts while infectious etiologies were low. Comorbidities significantly associated with cataract diagnosis included hypertension ($p<0.0283$), diabetes mellitus ($p<0.0249$), and HIV retinopathy ($p<0.0490$). There was no statistically significant association between ART regimen, CD4 count or race with the development of nuclear cataracts. Cataract development was 15-fold higher than the general US population amongst patients aged 40-49 years.

Interpretation: Premature nuclear cataract formation is common amongst HIV-infected persons receiving ART and may warrant more regular ophthalmologic evaluation in this patient group.

Introduction

Persons infected with human immunodeficiency virus (HIV) have longer life expectancies now than anytime previously with use of combination antiretroviral therapy (ART) and opportunistic infection (OI) prophylaxis.1-3 The widespread use of ART has allowed HIV infected persons to live well into their fifth, sixth, and seventh decades and beyond and therefore nationally, the HIV cohort is aging. According to the Centers for Disease Control (CDC), persons aged 50 and older accounted for 27% of persons living with HIV in 2013.4 However, despite decreased mortality, there have been numerous observations which have demonstrated that the chronic inflammation associated with HIV infection may directly affect the aging process of this patient population. 5,6 Specifically, they are experiencing typical age-related comorbidities such as neurocognitive decline, frailty, malignancy, cardiovas-

cular disease, metabolic syndrome, and end organ dysfunction at younger ages than HIV uninfected individuals [5,6]. The exact etiology of this premature or accelerated aging phenomena that has been observed in HIV infected persons on ART remains unclear, but most likely is multifactorial. The combination of the chronic inflammation associated with HIV infection and the mitochondrial toxicity associated with the use of nucleoside reverse transcriptase inhibitors (NRTIs) as part of an ART regimen is a possible explanation.[7]

The potential effects of HIV on the eyes are many, including retinitis, uveitis, vasculitis and optic neuropathy. In the pre-ART era, the lifetime incidence of any ocular disorder in HIV-positive patients was 70%-80%, with cytomegalovirus (CMV) retinitis being the most common manifestation [3,8]. CMV continues to contribute to ocular morbidity, accounting for 40% of vision loss in AIDS patients.9 However, the incidence of ocular manifestations such as CMV retinitis and other ocular OIs have decreased dramatically because of the use of ART. We have demonstrated previously that during a 1 year observation period where we noted a high incidence of ocular syphilis in HIV infected persons receiving ART, we observed no cases of CMV retinitis.10 As such, the pattern and prevalence of ocular manifestations in HIV infected persons is changing. As age related visual complications are common in the general population, we undertook this retrospective study to determine the most common ocular complications in HIV infected persons receiving ART. Our objective was to evaluate ocular disease in HIV patients in an urban study population on ART presenting for dedicated ophthalmologic care and to address the patients' comorbidities and ART regimen as a possible risk factor for ocular disease.

Methods

This was an IRB-approved retrospective chart review of Infectious Diseases and Ophthalmology clinic patient databases at an urban academic center. The electronic medical record system was queried for all "active" (living) patients in the Ryan White Clinic database of the HIV clinic at the MedStar Washington Hospital Center in Washington D.C.. Inclusion was defined within this group as also concurrently having been seen at the Washington National Eye Center ophthalmology clinic between January 1, 2006 and November 1, 2010. This included 250 potential patients.

As inclusion criteria, all patients were on antiretroviral therapy at the time of the visit and had a CD4 count measured within six months preceding the visit, or one month following the visit. 102 patients met these criteria. These selected charts were then evaluated for demographic information, ocular diagnosis, medical and HIV related comorbidities, medications including ART and concomitant corticosteroid use.

The most common ocular diagnoses were determined, and based on these results, further statistical analyses were performed. Statistical analysis included a chi square test to identify independent variables in patients with and without cataracts. Unadjusted and adjusted prevalence odd ratios and 95% confidence intervals were calculated for correlates (age, race, gender, chief complaint, ocular diagnosis, medical co-morbidity, antiretroviral regimen, CD4 count) associated with nuclear cataracts within the study population. Those variables found statistically significant were incorporated into a multivariable model.

Results

Of the 102 patients who met pre-determined study criteria, the median age was 46 years, ranging from 18 to 71 years. Approximately half (51%) were male and the majority (80%) were African-American. All patients were receiving ART at the time when they were being evaluated for their ocular complaint. Median CD4 count was 441 cells/μL (range 15-1712). 52% of patients had undetectable viral load. (Table 1).

Characteristic	HIV-infected Individuals, n=102 (%)
Age, median (years)	46 (18-71)
Male	52 (51%)
Race	
African-American	82 (80%)
Other	19 (19%)
Antiretroviral Therapy	102 (100%)
Median CD4 Lymphocyte Count	441 cells/μL

Table 1: Study population Demographics.

The primary presenting complaint was decreased visual acuity, accounting for 48% of visits. The next most common reason for ophthalmologic evaluation of these patients was for routine screening (31%).

In the study population, there were 44 different ocular diagnoses made. The most common included refractive error in 58 patients (56.9%), and cataracts in 45 patients (44.1%); 93.3% (42/45) of patients with cataracts had nuclear cataracts. A total of 10 patients had HIV or other infectious complications which included 5 with HIV retinopathy, 4 with Varicella Zoster infection, and 1 with endocarditis. Another three patients were diagnosed with an inflammatory uveitis. (Table 2).

Diagnosis	Number of Patients* (%)
Refractive Error	58 (56.9%)
Cataract Nuclear cataracts Posterior subcapsular cataract	45 (44.1%) 42 (41.2%) 3 (2.9%)
Glaucoma	13 (12.7%)

Dry Eye	10 (9.8%)
Epithelial Erosion	6 (5.88%)
Blepharitis	5 (4.9%)
Hypertension Retinopathy	4 (3.9%)
Primary Open Angle Glaucoma	3 (2.9%)
Other	22 (21.6%)
*Some patients were documented to have more than one diagnosis	

Table 2: Ophthalmic Diagnoses.

Further statistical analyses with regards to the diagnosis of nuclear cataracts were performed to determine risk factors and associations with other variables. The peak incidence of cataract diagnosis occurred at age 50 in our study population (p<0.0001). A multivariable analysis identified only one ocular diagnosis significantly associated with development of nuclear cataracts which was HIV retinopathy (p=0.0490). Among medical co-morbidities, a history of diabetes mellitus (p=0.0249) or hypertension (p=0.0283) was associated with cataract development. Comorbid presence of chronic kidney disease was statistically significant in the unadjusted prevalence odd ratio but was not significant in the final multivariable adjusted odd ratio. (Table 3).

	Unadjusted pOR (95% CI)	p-value	Adjusted pOR (95% CI)	p-value
Age				
	1.13 (1.06 – 1.19)	<0.0001	1.20 (1.10 – 1.30)	<0.0001
Race				
Black	1.00		1.00	
Unknown	2.97 (1.06 – 8.36)	0.0391	4.89 (1.12 – 21.40)	0.035
Gender				
Male	1.00		1.00	
Female	0.91 (0.41 – 2.00)	0.8129	2.24 (0.72 – 6.98)	0.1652
Chief Complaint				
Irritation/FBS	0.27 (0.03 – 2.39)	0.2379	--[b]	
Stable	2.00 (0.79 – 5.04)	0.1428	3.49 (0.94 – 13.00)	0.0626
Ocular Diagnosis				
Blepharitis	2.23 (0.36 – 13.97)	0.3914	-- [b]	
Eye misalignment	2.23 (0.36 – 13.97)	0.3914	-- [b]	
Glaucoma, confirmed	2.95 (0.26 – 33.64)	0.3836	-- [b]	
Glaucoma, suspected	0.60 (0.17 – 2.08)	0.4181	0.27 (0.04 – 0.99)	0.1552
HIV retinopathy	0.34 (0.04 – 3.17)	0.3445	0.06 (0.004 – 0.99)	0.049
Hypertensive retinopathy	4.83 (0.93 – 25.25)	0.0618	-- [b]	
Keratitis	0.45 (0.09 – 2.35)	0.3434	-- [b]	
Medical Co-morbidity				
Cerebrovascular Accident	2.00 (0.42 – 9.44)	0.3815	5.58 (0.54 – 57.31)	0.1482
Chronic Kidney Disease	9.83 (1.14 – 84.98)	0.0378	-- [b]	
Coronary Artery Disease	2.95 (0.26 – 33.64)	0.3836	-- [b]	
Diabetes Mellitus	0.50 (0.13 – 2.01)	0.3288	0.09 (0.01 – 0.74)	0.0249
Hepatitis C	2.60 (0.96 – 7.08)	0.0614	-- [b]	
Hyperlipidemia	3.00 (0.93 – 9.72)	0.0669	-- [b]	
Hypertension	1.77 (0.68 – 4.66)	0.245	5.24 (1.19 – 23.00)	0.0283
Syphilis	4.83 (0.93 – 25.25)	0.0618	4.78 (0.49 – 46.58)	0.1776
Tuberculosis	2.95 (0.26 – 33.64)	0.3836	-- [b]	
Antiretroviral Regimen				
Triple class regimen	0.34 (0.04 – 3.17)	0.3445	0.08 (0.004 – 1.69)	0.1051
CD4 Count (cells/uL)				
	1.00 (0.99 – 1.00)	0.6371	-- [b]	
POR: Prevalence Odds Ratio; CI: Confidence Interval				
[a]Model began with all variables listed on this table.				
[b]Eliminated from final model because p-value > 0.20.				

Table 3: Unadjusted and adjusted prevalence odds ratios and 95% confidence intervals for correlates associated with Nuclear Cataracts among a study population of HIV infected persons receiving ART.

There was no significant association between nucleoside reverse transcriptase inhibitor (NRTI) use or protease inhibitor (PI) use and development of nuclear cataracts. No ART regimen used within the study population was significantly associated with or protective from development of cataracts. (Table 4) We performed a detailed statistical analysis of the five most common ART regimens in the study population but were unable to find any association with the development of nuclear cataracts and a specific ART regimen. (Data not shown) Corticosteroid use was uncommon in our study patients; only 3 patients without nuclear cataracts were on concomitant corticosteroids, and 1 patient with nuclear cataracts was receiving concomitant corticosteroids.

	Nuclear Cataracts	p-value	Adjusted pOR (95% CI)	p-value
Diagnosis				
N = 42	1.13 (1.06 – 1.19)	<0.0001	1.20 (1.10 – 1.30)	<0.0001
n (%)	No Nuclear			
Cataracts	1.00		1.00	
Diagnosis	2.97 (1.06 – 8.36)	0.0391	4.89 (1.12 – 21.40)	0.035
N =60				
n (%)	Total		1.00	
N = 102	0.91 (0.41 – 2.00)	0.8129	2.24 (0.72 – 6.98)	0.1652
n (%)	p-value			
ARV regimen				
NNRTI based	15 (35.71)	18 (30.00)	33 (32.35)	0.54381
NRTI only regimen	1 (2.38)	1 (1.67)	2 (1.96)	0.83282
PI based	21 (50.00)	31 (51.67)	52 (50.98)	0.86841
Dual class regimen	4 (9.52)	5 (8.33)	9 (8.82)	0.71642
Triple class regimen	1 (2.38)	4 (6.67)	6 (4.90)	0.64632
NRTI = 3 nucleoside reverse transcriptase inhibitors				
NNRTI = 2 nucleoside reverse transcriptase inhibitors + 1 non-nucleoside reverse transcriptase inhibitor				
PI based = 2 nucleoside reverse transcriptase inhibitors + 1 protease inhibitor				
Dual class regimen = Use of 2 classes not meeting above criteria				
Triple class regimen = Use of an NRTI, NNRTI and a PI				

Table 4: Correlation of Nuclear Cataract Formation and Antiretroviral Therapy.

Discussion

In the era of effective ART, the primary care focus of the HIV-infected patient has shifted dramatically toward the management of comorbidities related to accelerated aging and premature end organ dysfunction. While this has been well-established in regards to dyslipidemia, insulin resistance, reduced bone mineral density, accelerated cardiovascular disease, and other conditions, less has been published regarding the potential ocular comorbidities and the relationship to the chronic inflammation associated with HIV infection.

We have observed that the pattern of ocular complications in HIV infected persons has changed significantly in the post-ART era with a shift from ocular opportunistic infections such as cytomegaloviral (CMV) retinitis toward more typical ocular diagnoses that are widely present in the general population seeking ophthalmologic consultation. Although age related cataract may be nuclear, cortical or posterior subcapsular in location, the latter are associated with topical or systemic steroid use and thus were excluded from our multivariate analysis. Most notably, in our study population, there were no cases of CMV retinitis and only 9.8% had complications related to infection, including HIV.

Previous studies examining ophthalmic complication rates have found overall relatively low rates of cataract formation in HIV-infected individuals, with a 2% incidence in Japanese and US cohorts.11, 12 A Danish nationwide cohort had a higher risk of cataract surgery among HIV-infected patients than among a non-infected cohort, particularly among patients with CD4 cell count ≤ 200/μL.13 In a longitudinal prospective US cohort of HIV infected individuals, Kempen and colleagues observed a 1.9% incidence of visually significant cataract or prior cataract surgery at the time of enrollment into the study with a yearly incidence of 0.37% per eye-year which was estimated to be higher than the general population. 12 As expected, the incidence of cataract formation increased with patient age, however, was found to be significantly higher among HIV-infected cohort patients aged 40-49 years as compared with an HIV-negative group.

Similarly, our findings demonstrate that HIV infected patients on ART appear to be predisposed to premature nuclear cataract formation. Among the 40-49 year old age group, there was a 15-fold higher rate of cataract diagnosis compared to the general population. Likewise, in the 50-59 year olds there was nearly a 10-fold higher rate. (Table 5).

Age (years)	Number of Study Patients with Nuclear Cataracts	Number of Study Patients in Age	% of Study Patients with Cataracts	National %
40-49	17	45	37.80%	2.50%
50-59	17	26	65.40%	6.80%
60-69	6	8	75%	20%
70-79	1	1	100%	43%
(Source: National Eye Institute: www.nei.nih.gov/eyedata/pbd_tables.asp)				

Table 5: Age at Cataract Diagnosis in National vs. Study Populations.

Cataracts are known to have an association with diabetes mellitus and cigarette smoking. In our study population, a comorbid diagnosis of diabetes was significantly associated with higher risk of cataract diagnosis. Hypertension was also significantly associated with increased incidence of cataract development. The medical records did not uniformly quantify a tobacco use history, so this data was not included in our analysis. However, it is estimated that 50 -70% of all HIV-infected patients smoke cigarettes, and therefore may also be a predisposing risk factor for premature cataract formation in our patient cohort.14 Interestingly, although NRTIs and PIs are known to cause mitochondrial toxicity and metabolic dysregulation, respectively, there was no association

between these medications or any antiretroviral regimen and the development of nuclear cataracts. The comorbidities of diabetes and hypertension associated with increased cataract diagnosis may further define a population at increased risk that warrants ophthalmologic screening at a younger age than HIV-negative patients with similar comorbidities.

In our study which included a predominantly African American HIV-infected patient population with well preserved immune function we observed that 41.2% of our patients were diagnosed with nuclear cataracts. Our cohort is the first examining cataract prevalence among a predominantly African American HIV-infected patient group. It is interesting to note that among non-HIV infected patients, African Americans have higher rates of cataract development than the Caucasian population, but this is predominantly due to cortical cataract formation, and not nuclear cataracts which were the most common type of cataract in our study population.15 There were no statistically significant racial differences with regards to nuclear cataract formation in our patient cohort, consistent with prior epidemiological data. Another unique characteristic of our study population is relatively well persevered immune function, reflected by a median CD4 cell count of 441 cells/μL. Unlike the previously studied cohorts, our population differed in that they had a median CD4 well above their cited at-risk cutoff of $\leq 200/\mu L$, and we were unable to correlate a CD4 count cutoff with the development of cataracts.

In the era of the use of potent-ART, durable virologic suppression can be achieved in the majority of adherent HIV infected patients. As a result, HIV practitioners have shifted their focus to the management of the chronic complications associated with drug toxicity and the metabolic complications associated with HIV infection. The observation of accelerated aging in HIV infected persons may be a consequence of drug-induced mitochondrial toxicity and chronic inflammation associated with HIV replication.2,6 Additionally, active viral replication can take place within the eye, causing inflammation and uveitis.16,17 Based on our observations, we postulate that the presence of premature cataract formation in our HIV infected study population receiving ART may represent another manifestation of the accelerated aging process in HIV infected persons.

The limitations of our study include its retrospective nature, as well as being performed at a single center. Our patient demographics, while representative of HIV-infected persons in the District of Columbia, may not be reflective of all other HIV patient groups. Our study population included patients currently on active treatment for HIV. While we did not identify any association between CD4 count and development of premature cataracts, other studies have linked a low CD4 count or initiation of antiretroviral therapy to increased incidence of cataract diagnosis. As our study population has a baseline higher incidence of cataract diagnosis but were already on HIV therapy, we cannot comment on any potential role of immune reconstitution. This data suggests, however, that high CD4 and longstanding use of antiretrovirals are not protective against development of premature cataracts. This study took place largely before integrase inhibitor based therapy was widely used, so was not included in the regimens for any association with or protection from development of cataracts.

Currently, the 2013 Infectious Diseases Society of America guidelines for primary care of HIV-positive patients recommend ophthalmologic examination every 6 to 12 months for patients with CD4 count <50/ μL.18 While undoubtedly patients with CD4 count <50/μL should have baseline and regular ophthalmologic follow-up to rule out opportunistic ocular disease, our data supports increased screening for all HIV-1 infected patients regardless of CD4 count. Although our study population presented to an ophthalmology clinic, not all had symptoms to suggest cataracts or other ocular diagnosis, highlighting the need for routine screening rather than waiting for ocular symptoms to develop prior to presentation. Based on our observations, ophthalmologic screening may be warranted for all HIV-infected individuals regardless of CD4 count. In particular, it appears that HIV-infected persons on ART with comorbidities that include diabetes, hypertension and a known diagnosis of HIV retinopathy may be at the highest risk for premature cataract formation. Therefore as a part of routine health maintenance for otherwise stable HIV-infected individuals on ART, HIV primary care providers should consider routine ophthalmologic evaluation for their patients beginning at age 40.

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