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Optic nerve head morphology and visual field function in patients with AIDS and without infectious retinitis

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INTRODUCTION

HIV/AIDS continues to be a major public health problem in the United States and worldwide. The current prevalence of HIV infection in the United States is estimated to be over one million.¹ Treatment of HIV infection with combination antiretroviral therapy (cART) has increased survival and shifted the spectrum of HIV-associated morbidity and mortality from opportunistic infections toward a variety of other medical conditions.^{2,3}

It has been reported that even in the cART-era, patients with HIV/AIDS suffer retinal damage and vision loss.^{4,5} Modern retinal imaging has been crucial in demonstrating inner retinal damage, in particular nerve fiber layer (NFL) loss in HIV/AIDS patients without infectious retinitis. Optical coherence tomography (OCT) and scanning laser polarimetric studies of the peripapillary NFL show evidence of inner retinal damage, which seems cumulative in HIV/AIDS patients without any evidence of infectious retinitis and with a history of low CD4+ T-lymphocyte counts.^{6–9} Additionally, abnormalities in color vision and contrast sensitivity have been reported in HIV ocular disease contributing to the complex called HIV-associated neuroretinal disorder (NRD).^{10–13}

Nerve fiber layer loss is known to often precede visual field loss and glaucomatous optic nerve damage.¹⁴ Although there are numerous reports on NFL damage^{15,16} and subtle visual field loss^{17–19} in HIV/AIDS patients, there has been limited investigation of the optic nerve head topography.²⁰ Patients with AIDS, who during the course of their disease, never have developed ocular opportunistic infections (OOI) remain at risk of developing HIV/AIDS-associated NRD. It is possible that features of the optic nerve head could change over time in HIV/AIDS patients and if present, could be associated with the development of NRD. In

this study, we report an analysis of optic nerve head morphology from stereoscopic color fundus photographs and of visual field testing in patients with AIDS without retinitis over 5 years of follow-up in the Longitudinal Study of Ocular Complications of AIDS (LSOCA), with a particular interest in changes in cup-to-disc ratio (CDR). We also evaluated changes in visual field (VF) performance, changes in intraocular pressure (IOP) measurements, and the development of glaucoma.

METHODS

Participants

LSOCA is a prospective multicenter observational study of patients with AIDS.²¹ Patients were enrolled with or without CMV retinitis; however, this report focuses on patients without CMV retinitis or any other type of OOI. As of 31 December 2009, 1,750 patients with AIDS and without OOI had been enrolled into LSOCA. Of these patients, 246 had ONH photographs that met the criteria below and visual field data at enrollment and at 5-years follow-up. The data on contrast sensitivity (CS) in LSOCA patients was available from previously published studies and abnormal CS was defined as $\log CS < 1.5$ (lower 2.5th percentile for a normal control population).²² The study was conducted with approval from the appropriate institutional review boards at each participating Institution. Informed consent was obtained from all subjects, and the study was conducted in accordance with Health Insurance Portability and Accountability Act regulations.

Imaging studies

Stereoscopic serial photographs of the optic disc and macula were obtained from both eyes at each study visit, and de-identified photographs were sent to the reading center (Fundus Photograph Reading Center, Department of Ophthalmology and Visual Sciences at the University of Wisconsin-Madison) for evaluation.

All patients underwent pharmacologic pupil dilation followed by 9-field photography using 50 or 60 degrees field with specified capture and export settings. Images were obtained in film format and sent as color slides or as digital images and sent on CDs. The photographic procedure remained the same irrespective of the type of media. Film sets were viewed upon a standard light box (6500° K color temperature), using a Donaldson stereo viewer (5×) and digital images were viewed on calibrated computer monitors using hand held stereo viewers (Screen-Vu stereoscope, Portland, OR). For final analysis we included only film images.

Two trained ocular disease evaluators assessed the optic nerve head images, at enrollment and at year 5. The cup can be traced by directly visualizing its contour or by identifying its contour by following blood vessel patterns. Cup/Disc Ratio (CDR) is calculated as follows

$$\text{Cup Vertical} / \text{Disc Vertical} = \text{Vertical Cup Disc Ratio}$$

In some situations, where the diameters could not be measured due to poor photographic quality or due to media opacity obscuring the view of the fundus, then “cannot grade” is assigned to the eye at that visit. CDR was measured longitudinally, where the evaluator had access to the enrollment images and grading data for the patient, during evaluation of follow up images. Additional variables assessed were the presence of optic nerve pallor, splinter

hemorrhages on the disc, and notching of the cup, which are suggestive of glaucomatous optic nerve damage. Quality control of RC grading was performed by repeat grading of a random set of images at both visits. For quality control assessments, images were graded without access to the previous visit images or grades assigned.

Visual field studies

Visual field testing was obtained using a Humphrey Visual Field Analyzer (model 620; Carl Zeiss Meditec, Dublin, California). Standard automated perimetry (SAP) with a full threshold 24-2 program 24-2 and routine settings was utilized for evaluating visual fields. Trial frames with the appropriate refraction were used to maximize patient's performance. The examination was paused for a while before evaluating the second eye. Only reliable VFs, defined as those with less than 33% false-positives, less than 33% false-negatives, and less than 20% fixation losses, were analyzed. Naïve visual fields were not analyzed; fields were included only after initial practice.

Statistical analysis

Summary statistics were obtained for enrollment characteristics. Crude and adjusted linear regression models utilizing robust variance were employed to assess the magnitude and significance of changes after five years of follow-up for the main outcomes. Proportion of eyes with secondary ONH characteristics and visual function parameters prevalent at enrollment and incident at follow-up were computed with associated 95% confidence intervals. Pearson product-moment correlation and Bland-Altman coefficient of repeatability were computed to assess intra-grader agreement of 19 images at baseline. All analyses were performed using SAS (version 9.2, SAS Institute, Cary, N.C.) and Stata (version 11, Stata Corp., College Station, TX).

RESULTS

Enrollment characteristics of the study sample are shown in Table 1. About one half of the patients (49.2%) had experienced a nadir CD4 + T cell count of $< 50 \mu\text{L}$, and 211 (85.8%) were receiving cART. Low contrast sensitivity, a surrogate for NRD and as previously defined, was recorded in 9.7% of patients in this cohort. The Pearson correlation for intra-grader measurement of CRD was 0.85 (95% CI: 0.64, 0.94). The Bland-Altman coefficient of repeatability was 0.12. Hence, there is 95% probability that repeat CDR measurements are within 0.12 of each other.

As assessed by an unadjusted linear regression model (Table 2), the mean CDR at 5-years of follow-up was statistically significantly greater than the mean CDR at enrollment (mean change = 0.004; 95% CI = 0.0001, 0.009; $P = 0.04$) (Figures 1 and 2). Immune status at enrollment (CD4+ T cells $< 50 \text{ cells}/\mu\text{L}$ versus CD4+ T cells $> 50 \text{ cells}/\mu\text{L}$) did not modify the change in CDR at 5-years of follow-up (P for interaction = 0.66). The 5-year change in CDR did not vary for subsets of patients at different ages at baseline (results not shown). Statistically significant changes in mean deviation score (mean change = 0.93 dB; $P < 0.001$), and pattern standard deviation score (mean change = -0.29 dB ; $P = 0.02$) also were observed at 5 years of follow-up. However, these changes in the two visual field domains

were not significant when 5-year data were compared to 1-year follow-up data (mean change = 0.28 dB; $P=0.21$; and mean change = -0.05 dB; $P=0.71$; respectively), suggesting a practice effect in the first year of follow-up. Similar results were obtained when we eliminated eyes with cataract progression (mean change = 0.29 dB; $P=0.22$; and mean change = -0.10 dB; $P=0.48$; respectively). No statistically significant change was observed in IOP after 5-years of follow-up. The direction and significance of these four outcomes remained unchanged when tested in a multivariable model controlling for age, time since AIDS diagnosis, and cART use at enrollment (results not shown).

Vertical CDR also was examined as a binary outcome, classifying patients with a CDR ≤ 0.6 or less (Table 3). The proportion of eyes at enrollment with CDR > 0.6 was 4.9%. None of these eyes had a clinical diagnosis of glaucoma. During the 5-year follow-up period, 0.4% new cases of glaucoma were observed. The prevalence of optic nerve head pallor, hemorrhage, notching, and papillary swelling were 1.6%, 0.0%, 0.0% and 6.5%, respectively. The cumulative incidences of these characteristics after 5-years of follow-up were 0.8%, 0.4%, 0.0%, and 4.3%, respectively. There were 2.0% of patients who had vision worse than 20/40 at enrollment and 1.7% who developed vision worse than 20/40 after 5 years of follow-up. 0.4% of patients reported having cataract surgery at time of enrollment and 6.5% had myopia at enrollment. The cumulative incidence of cataract surgery was 0.0%, and that of myopia was 0.9%. CDR was not significantly different between patients with low and normal contrast sensitivity at baseline ($p=0.846$) or at 5 years ($p=0.876$).

DISCUSSION

In this study we compared longitudinal data from fundus photographs and visual fields from enrollment to year 5 of follow-up in eyes of patients with AIDS but without OOI. The medians of CD4+ T-cell nadir and duration of AIDS defines this group as high risk for developing HIV-associated NRD. Patients with similar systemic profiles have been shown to have the subtle visual dysfunction observed with HIV-associated NRD in this cohort and others.^{4,10–13} We observed a small, statistically significant increase in mean CDR at 5 years of follow-up independent of incident glaucoma and other structural changes in ONH morphology such as optic disc hemorrhage, notching, pallor or swelling. The increase in CDR was not associated with any increase in IOP or with ocular hypertension over the 5 years of follow-up.

Possible reasons for an increase in CDR include diseases such as glaucoma, toxic, ischemic, or traumatic neuropathies as well as typically small increases in CDR due to the normal aging process. LSOCA collects data on the development of optic neuropathies at each study visit. Of the 246 eyes studied, one eye developed a clinical diagnosis of glaucoma based on VF and intraocular pressure changes. No eyes developed an optic neuropathy of any other cause including no cases of drug-related optic neuropathy, which has been reported to occur with several HIV-related medications. The loss of nerve fiber layer (NFL) is a contributory mechanism leading to increase in CDR. Race can be a factor influencing morphology of ONH; however the reported differences are observed typically in disc area rather than CDR.^{23,24} A few studies have reported NFL loss^{25,26} and increase in ONH cupping with

aging.^{27–30} The affects of age on optic nerve head morphology are generally considered small. The amount of increase in CDR in our patients (0.0008/year) was similar to previous reports by Bengtsson (0.002/year)²⁷, Garway-Heath et al. (0.0037/year),²⁸ by Sung et al. (0.0037/year),³⁰ and by Harju et al. (0.0015/year).³¹

Stereoscopic optic nerve head photography has been shown effective in evaluating morphologic changes such as in glaucoma. It is a well-established documentation of basic clinical examination and progression. Its validity has been verified in large randomized clinical trials.^{32–34} Recently, new technology has been applied to study optic nerve head morphology such as Heidelberg Retina Tomography or optical coherence tomography (OCT). LSOCA did not collect OCT data; however, in several reports, the diagnostic accuracy for differentiating healthy eyes from early glaucomatous eyes has been similar between optic nerve head stereophotography and newer imaging modalities.^{35–37}

We also observed small but statistically significant changes in mean deviation score and pattern standard deviation score on VF testing at the 5-year follow-up visit. Interestingly however, these changes point toward improvement of VF performance over time. In fact, the improvement was observed primarily at the 1-year follow-up visit. Indeed, after controlling for the improvement in VF testing from the baseline to the year 1 VF (e.g., a practice effect as most of our patients had never received VF testing prior to enrolling into LSOCA), the observed changes were not significantly different. If the small increases in CDR that we observed in our cohort were due to glaucoma, we would have expected to observe VF deficits consistent with glaucoma, which we did not. The interpretation of VF assessment is affected by the quality of patient's performance. The learning effect is an essential part of this performance, especially for full threshold testing and is most commonly observed in the first few visits.^{38,39} As the majority of this cohort did not have clinical glaucoma at the time of enrollment it is likely that our patients had little to no experience with VF testing and therefore, the small improvements that we observed in VF testing in the first year after enrollment are likely attributable to a learning effect.

Limitations of this study include the relatively small number of eyes, imaging grading technique and survivor bias. The number of eyes was decreased because we included only film stereophotography and no other imaging media. However, validated epidemiologic studies with comparable observation period have used similar number of patients/eyes.^{40,41} We acknowledge that advanced imaging technology such as HRT may give more precise information than human assessment from fundus photos but this technology has not been a part of SOCA Study. As stated previously, fundus stereo-photography has been shown comparable with HRT technology.^{35,36} We also have not used OCT technology to measure retinal NFL as the technology became available after the original SOCA protocol. Survivor bias in context of this study means that we cannot evaluate the rate of change in AIDS patients who have died in the course of the study.

In summary, clinically minimal structural changes in ONH were observed in eyes of patients with AIDS and without OOI after 5 years of follow-up. These changes, most likely, are commensurate with aging changes described previously in studies of healthy volunteers. During the disease course there is no worsening of visual function performance on perimetry

testing. Our cohort is demographically comparable to the entire non-OOI cohort in LSOCA. Additionally, LSOCA is representative of AIDS patients in the United States hence our findings are applicable to the general AIDS population.

As such, this high-risk group of patients for HIV-associated NRD does not show clinically relevant ONH changes. This is a differentiating feature between them and HIV-negative patients with nerve fiber layer thinning who develop ONH changes such as glaucoma. HIV-associated NRD is therefore a specific entity not affecting the ONH. Advanced imaging technology should be applied in longitudinal studies to investigate detailed structure of optic nerve head and nerve fiber layer in AIDS patients.

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Figure 1.
Color fundus photo image of an HIV+ patient at enrollment showing few small drusen. CDR using was classified as 0.40.

Figure 2.
Color fundus photo image of the same eye at year 5 showing also few small drusen. CDR was classified as 0.45.

Table 1

Enrollment characteristics of patients with AIDS and without infectious retinitis

Characteristic	Total (N = 246)	
Age, years		
Median (25 th , 75 th quartiles)	43.0	(37.0, 49.0)
Gender, n (%)		
Male	204	(82.9%)
Female	42	(17.1%)
Race, n (%)		
White, non-Hispanic	113	(45.9%)
Black, non-Hispanic	91	(37.0%)
Hispanic	38	(15.4%)
Asian/Pacific Islander	2	(0.8%)
American Indian/Alaskan Native	0	(0.0%)
Other	2	(0.8%)
HIV exposure category, n (%)		
Men having sex with men (MSM)	135	(54.9%)
Injection drug use	8	(3.2%)
MSM and injection drug use	5	(2.0%)
Heterosexual contact	61	(24.8%)
Other	37	(15.0%)
Years since AIDS diagnosis		
Median (25 th , 75 th quartiles)	4.9	(1.5, 7.3)
Missing, n (%)	6	(2.4%)
Nadir CD4+ T-cells		
Median (25 th , 75 th quartiles), cells/μL	49.0	(14.0, 120.0)
n (%)		
100 cells/μL	75	(30.5%)
50 – 99 cells/μL	44	(17.9%)
< 50 cells/μL	121	(49.2%)
Missing	6	(2.4%)
CD4+ T-cells		
Median (25 th , 75 th quartiles), cells/μL	207.0	(123.0, 325.0)
n (%)		
100 cells/μL	201	(81.7%)
50 – 99 cells/μL	19	(7.7%)
< 50 cells/μL	25	(10.2%)
Missing	1	(0.4%)
HAART[*], n (%) yes	211	(85.8%)
Self-reported systemic comorbidities[†], n (%) yes		
High blood pressure requiring medication	43	(17.5%)

Characteristic	Total (N = 246)	
Hepatitis	97	(39.4%)
Diabetes mellitus	18	(7.3%)
Hyperlipidemia	71	(28.9%)
Renal disease	16	(6.5%)
Co-infections/systemic opportunistic infections[†], n (%) yes		
CMV disease	5	(2.0%)
Pneumocystis Pneumonia (PCP), probable or possible	33	(13.4%)
Mycobacterium Avium Complex (MAC)	16	(6.5%)
Tuberculosis	1	(0.4%)

* Highly active antiretroviral therapy.

[†] Categories are not mutually exclusive.

Table 2

Optic nerve head and visual field characteristics over time in 246 HIV positive eyes without CMV retinitis.

Outcome	Enrollment Median (Q1, Q3)*	1-yr follow-up Median (Q1, Q3)	5-yr follow-up Median (Q1, Q3)	5-yr follow-up vs. enrollment Mean change [†] (95% CI) [†] P [†]	5-yr follow-up vs. 1-yr follow-up Mean change [†] (95% CI) [†] P [†]
Vertical cup-to-disc ratio	0.39 (0.31, 0.46)	n/a	0.40 (0.33, 0.49)	0.004 (0.0001, 0.009) 0.04	n/a
Intraocular pressure, mmHG	13 (11, 16)	n/a	14 (12, 16)	-0.01 (-0.50, 0.46) 0.93	n/a
Mean deviation score on Humphrey visual field 24-2, dB	-1.87 (-3.76, -0.75)	-1.48 (-2.83, -0.21)	-0.92 (-2.55, 0.23)	0.93 (0.46, 1.39) <0.001	0.28 (-0.16, 0.74) 0.21
Pattern standard deviation score on Humphrey visual field 24-2, dB	2.13 (1.70, 3.16)	1.91 (1.60, 2.63)	1.84 (1.49, 2.62)	-0.29 (-0.54, -0.04) 0.02	-0.05 (-0.32, 0.22) 0.71

* 25th and 75th quartiles.

[†] Mean change, 95% confidence intervals, and P values obtained from simple linear regression models utilizing robust variance from generalized estimating equations.

Table 3

Prevalence at enrollment and 5-year incidence of optic nerve head and visual function characteristics in HIV positive eyes without CMV retinitis.

Characteristic	Prevalent at enrollment			Incident at 5-year follow-up		
	No. of events/ no. at risk	(%)	[95% CI]	No. of events/ no. at risk	(%)	[95% CI]
Optic nerve head						
Vertical cup-to-disc ratio 0.6	12/244	(4.9%)	[2.6%, 8.4%]	1/231	(0.4%)	[0.01%, 2.4%]
Pallor	4/246	(1.6%)	[0.4%, 4.1%]	2/242	(0.8%)	[0.1%, 2.9%]
Hemorrhage	0/246	(0.0%)	[0.0%, 1.5%]*	1/246	(0.4%)	[0.01%, 2.2%]
Notching	0/246	(0.0%)	[0.0%, 1.5%]*	0/246	(0.0%)	[0.0%, 1.5%]*
Papillary swelling	16/246	(6.5%)	[3.8%, 10.3%]	10/230	(4.3%)	[2.1%, 7.8%]
Visual function						
Visual acuity worse than 20/40	5/246	(2.0%)	[0.7%, 4.7%]	4/237	(1.7%)	[0.5%, 4.3%]
Ever had cataract surgery	1/246	(0.4%)	[0.01%, 2.2%]	0/243	(0.0%)	[0.0%, 1.5%]*
Ever had myopia	16/246	(6.5%)	[3.8%, 10.3%]	2/224	(0.9%)	[0.1%, 3.2%]

* One-sided 97.5% confidence interval.

Note: The denominators for prevalent and incident proportions exclude observations for which data were missing.