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RETINAL VESSEL CALIBER AMONG PEOPLE WITH AIDS: RELATIONSHIPS WITH VISUAL FUNCTION

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Abstract

Objective—To evaluate relationships between retinal vessel caliber and tests of visual function among people with AIDS.

Design—Longitudinal, observational, cohort study.

Methods—We evaluated data for participants without ocular opportunistic infections at initial examination (baseline) in the Longitudinal Studies of the Ocular Complications of AIDS (1998–2008). Visual function was evaluated with best corrected visual acuity, Goldmann

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Study design: (PSK, AAF, MLVN, GNH).

Data collection: (SG, LDH, RPD and the SOCA Research Group).

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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.

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perimetry, automated perimetry (Humphrey Field Analyzer), and contrast sensitivity (CS) testing. Semi-automated grading of fundus photographs (1 eye/participant) determined central retinal artery equivalent (CRAE), central retinal vein equivalent (CRVE), and arteriole:venule ratio (AVR) at baseline. Multiple linear regression models, using forward selection, sought independent relationships between indices and visual function variables.

Results—Included were 1250 participants. Smaller AVR was associated with reduced visual field by Goldmann perimetry ($p=0.003$) and worse mean deviation ($p=0.02$) on automated perimetry and possibly with worse pattern standard deviation (PSD) on automated perimetry ($p=0.06$). There was a weak association between smaller AVR and worse CS ($p=0.07$). Relationships were independent of antiretroviral therapy and level of immunodeficiency (CD4+ T-lymphocyte count, HIV RNA blood level). On longitudinal analysis, retinal vascular indices at baseline did not predict changes in visual function.

Conclusions—Variation in retinal vascular indices are associated with abnormal visual function in people with AIDS, manifested by visual field loss and possibly by reduced CS. Relationships are consistent with the hypothesis that HIV-related retinal vasculopathy is a contributing factor to vision dysfunction among HIV-infected individuals. Longitudinal studies are needed to determine whether changes in indices predict change in visual function.

We have shown that variations in retinal vessel caliber among people with AIDS are related to level of immunodeficiency (as manifested by CD4+ T-lymphocyte count) and use of highly active antiretroviral drug therapy (HAART).¹ Variations in vessel caliber are associated with increased mortality risk, which we attributed to the likelihood that morphologic changes of retinal arterioles and venules reflect life-threatening changes in cerebral and coronary vessels.

Reduced contrast sensitivity (CS) is also related to mortality among people with AIDS.² Retinal microvasculopathy, which has been a common AIDS-related finding at autopsy,³ is thought to be a contributor to vision abnormalities among people with AIDS, including changes in visual field (VF), reduced CS, and altered color vision.⁴⁻⁶ Such a relationship with retinal vascular disease is thought to be the basis for the association between CS and death, supported by the fact that abnormal CS is also related to systemic diseases characterized by microvascular disease.² An association between variations in retinal vessel caliber and visual function has not been shown directly, however.

In this study, we investigated relationships between vessel caliber indices and various measures of visual function (best corrected visual acuity [BCVA], visual field, and CS) among participants in the Longitudinal Study of the Ocular Complications of AIDS (LSOCA). Based on relationships seen in the setting of other diseases,⁷ we hypothesize that narrower arterioles and dilated venules will be markers of worse visual function.

METHODS

Patient Population

LSOCA is an NIH-sponsored, prospective, epidemiological study of people with AIDS, which began in September 1998. A description of its design and methods, and a summary of

data for participants at study enrollment (baseline) have been published previously.⁸ Data were collected from study participants every 6 months per protocol. The current study includes data collected through December 31, 2008 for participants without ocular opportunistic infections at baseline.

Data Collection

We collected baseline demographic, medical, and laboratory information as described in a companion article dealing with the same cohort.¹ AIDS-related information at baseline included time since AIDS diagnosis, lymphopenia as AIDS-defining illness, CD4+ T-lymphocyte count (baseline and nadir), CD8+ T-lymphocyte count, HIV RNA blood level (baseline and peak), history of HAART (on HAART at baseline; ever on HAART), and Karnofsky score. We collected data on the following visual function measures at baseline: BCVA, as per LSOCA protocol;⁸ CS; and various visual field variables, as described below. CS was determined using the method of Pelli-Robson^{9, 10} and analyzed using protocols described in a previous LSOCA publication.² Goldmann perimetry utilized a modified Diabetic Retinopathy Study protocol, in which a score is computed by summing the degrees of visual field along 12 meridians spaced 30 degrees apart, as described previously.⁸ Using this technique, the mean score for people with AIDS is approximately 700±100 degrees of visual field. Automated perimetry was performed using the Humphrey Field Analyzer Model 600 or 700 (Carl Zeiss Meditec, Dublin, CA) and the 24-2 full-threshold program, as described in a previous LSOCA publication.⁶ As recommended by the manufacturer, automated perimetry test results were excluded from analyses as being unreliable if fixation losses were 20% or false positive errors were 33% or false negative errors were 33%. We also identified those participants who had cataract on examination at baseline.

The following vessel caliber indices were determined in a semi-automated manner by certified graders at the University of Wisconsin Fundus Photograph Reading Center (IVAN software, Department of Ophthalmology and Visual Science, University of Wisconsin, Madison, WI) using a standardized protocol: central retinal artery equivalent (CRAE), central retinal vein equivalent (CRVE), and arteriole:venule ratio (AVR). An explanation of these indices, and procedures for their determination are described in the companion article dealing with this cohort.¹

Definitions

For purposes of this study, HAART was defined as the concurrent use of three or more antiretroviral drugs. Abnormal CS was defined as logCS<1.5, which corresponds to the lower 2.5 percentile for a normal control population described by Myers and associates.¹¹ With regard to automated VF testing, abnormal mean deviation (MD) was defined as < -2.63dB. Abnormal VF pattern standard deviation (PSD) was defined as >2.57dB. The rationale for use of these thresholds is discussed in previous LSOCA publications.^{5, 6}

Data Analysis and Statistical Techniques

Unless otherwise noted, the unit of analysis was the eye, and one eye per study participant was evaluated. Wong and associates have demonstrated a strong correlation between the eyes of an individual, for both CRAE and CRVE, and concluded that measurements from

one eye accurately reflect a person's systemic vascular status.¹² If vessel caliber indices could be determined for both eyes, the eye with better photographic quality was selected as the study eye. Values for each vessel caliber index were grouped by quartiles and modeled ordinally. With regard to CRAE and CRVE, the first quartile contained narrower arterioles and venules, respectively, while the fourth quartile contained wider arterioles and venules. With regard to AVR, the first quartile included relatively narrower arterioles vs. venules, while the fourth quartile included relatively wider arterioles vs. venules.

Demographic, medical, and laboratory factors that were statistically related to vessel caliber indices in the companion study of this cohort¹ were chosen as covariates in the adjusted models for each index in the cross-sectional portion of the study. The following baseline covariates were used in all adjusted models for the longitudinal portion of the study: current use of HAART, CD4+ T-lymphocyte count, HIV RNA blood level, age, black race, mean corpuscular volume, hematocrit, and time since diagnosis of AIDS. Vessel caliber indices were used as predictors in (1) cross-sectional analyses using linear regression of visual function variables at baseline; and (2) longitudinal analyses using Cox regression of incident events in visual function variables during follow-up.

Because diabetes mellitus can cause vascular disease similar to that seen in people with AIDS,³ we performed subgroup analyses, looking for significant ($p < 0.01$) interactions between diabetes mellitus and relationships that involve vessel caliber. Similar subgroup analyses were performed to look for significant ($p < 0.01$) interactions with hypertension. Because vessel caliber indices have been related to glaucomatous optic disc changes,^{13, 14} subgroup analyses were also performed to look for significant ($p < 0.01$) interactions with diagnoses of glaucoma or elevated intraocular pressure (> 21 mmHg) at baseline for those comparisons that involved visual field variables. Similar subgroup analyses were performed to look for significant ($p < 0.01$) interactions between cataract and relationships that involve vessel caliber.

P-values were two-sided and were not adjusted for multiple comparisons. Statistical analyses were performed using SAS (SAS/STAT User's Guide, Version 9.2, 2010; SAS Institute, Cary, North Carolina, USA) and Stata (Stata Statistical Software: Release 11, 2009; StataCorp LP, College Station, Texas, USA) statistical packages.

RESULTS

As of December 31, 2008, 2,221 individuals had enrolled in LSOCA, 1,712 of whom had no ocular opportunistic infections. The demographic, medical, laboratory, and ophthalmic examination data for this subpopulation are described in a previous publication.² Among these 1,712 eligible participants, 1250 eyes had vessel caliber measurements at baseline. There was a normal distribution of the vessel caliber indices.¹

Table 1 shows the relationships between vessel caliber indices and measures of vision function at baseline. There were significant relationships between smaller AVR and the following visual field measures: fewer total degrees of visual field on Goldmann perimetry ($p = 0.003$); as well as worse MD ($p = 0.02$) and worse PSD ($p = 0.06$) on automated perimetry.

There was also a weak association between smaller AVR and worse CS ($p=0.07$). There was a weak association between smaller AVR and worse BCVA ($p=0.06$) on crude comparison, but the relationship was not significant on adjusted comparison.

Table 2 shows the relationships between vessel caliber indices at baseline and changes in vision function during follow-up. None of the vessel caliber indices at baseline were predictors of change in BCVA, CS, or visual field variables.

Only 103 (8.2%) of 1250 participants were diabetic. Subgroup analyses for those with and without diabetes mellitus showed significant interactions only for adjusted data from Goldmann perimetry. Specifically, non-diabetics changed 1.5 degrees per quartile of CRAE ($p=0.50$), while diabetics changed 23.6 degrees per quartile ($p=0.004$; interaction $p=0.007$). Non-diabetics changed -3.0 degrees per quartile of CRVE ($p=0.17$), while diabetics changed 20.3 degrees per quartile of CRVE ($p=0.02$; interaction $p=0.003$). (Neither CRAE nor CRVE had been related to Goldmann perimetry results in the primary analyses for the total cohort.) Diabetes mellitus had no significant effect on relationships between vessel caliber indices and any other factors demonstrated for the total cohort (data not shown). Hypertension (present in 249 [19.9%] of the 1250 participants) had no significant effects on relationships between vessel caliber indices and any factors shown for the total population (data not shown). A total of 30 (2.4%) of 1250 study eyes had either a diagnosis of glaucoma ($n=10$) or intraocular pressure >21 mmHg ($n=20$) at baseline. Only 15 of the 30 participants had reliable automated perimetry test results. Subgroup analyses for those with vs. those without glaucoma/elevated intraocular pressure showed significant interaction ($p=0.004$) only for the relationship between CRVE and PSD; specifically, there was no relationship between CRVE and PSD among participants without glaucoma/elevated intraocular pressure, while there was a positive relationship between CRVE and PSD, among participants with glaucoma/elevated intraocular (data not shown). There were no interactions between glaucoma/elevated intraocular pressure and visual field variables in any comparisons involving either CRAE or AVR.

A total of 56 (5.4%) of 1250 study eyes had cataracts at baseline. Subgroup analyses for those with and without cataracts showed no significant interaction for any of the relationships between vessel caliber indices and measures of vision function studied for the total cohort (data not shown).

DISCUSSION

HIV-infected individuals can have vision dysfunction, despite normal-appearing fundi; findings include abnormalities of VF, CS, and color vision.⁴⁻⁶ These abnormalities are believed to be mediated by HIV-related neuroretinal disorder, characterized by damage to ganglion cells.¹⁵ The cause of neuroretinal disorder remains unknown, but one hypothesis has been that it is the result of damage from retinal microvasculopathy,⁵ which is similar ultrastructurally to diabetic retinopathy.^{3, 16} Variations in vessel caliber indices predict the occurrence and progression of diabetic retinopathy,^{17, 18} which has also been associated with vision dysfunction.^{19, 20} Relationships between vessel caliber indices and measures of vision

function in this study could not be attributed to the presence of diabetes mellitus in some study participants, however.

Our study provides a direct link between retinal vascular disease and vision dysfunction; we found that smaller AVR was independently related to multiple measures of visual field at baseline, including fewer degrees of field on Goldmann perimetry, worse mean deviation, and possibly worse PSD on automated perimetry. Relationships between the retinal vasculature and visual field variables have been evaluated in several population-based studies of people with primary open-angle glaucoma (POAG). Although the BDES²¹ and Rotterdam²² studies did not find associations, the BMES¹³ and Singapore Malay Eye Study¹⁴ found relationships between small retinal arteriolar caliber and POAG (defined by visual field loss and optic disc cupping). The relationship supports the “vascular theory” of optic nerve damage, in which blood vessels are adversely affected by inflammation, arteriosclerosis, or thrombosis, leading to vascular dysregulation and poor blood flow to the optic nerve, ultimately resulting in damage to axons, manifesting as optic disc cupping and visual field loss.²³ We found no evidence, however, that the relationship between vessel caliber indices and visual field changes in our study was mediated through glaucomatous optic nerve damage. Instead, we hypothesize a direct effect of vascular disease on the retinal ganglion cell layer with changes in the retinal nerve fiber layer, as a cause for the visual field changes in people with AIDS. In the Singapore Malay Eye Study, narrower arterioles and narrower venules were related to thinner retinal nerve fiber layers in people without glaucoma;²⁴ the relationship may reflect vascular dysregulation and ischemic damage to the neuroretina.

In the companion article describing our cohort,¹ we discussed potential reasons that vascular changes occur in people with AIDS. They include premature aging, which may also accelerate the potential effects of other factors, such as smoking and hypertension. In addition, AIDS-specific factors were also related to vessel caliber indices, including use of HAART and low CD4+ T-lymphocyte count. These relationships may reflect a pro-atherogenic effect of HAART on the vasculature and a heightened state of inflammation that has been associated with chronic HIV infection. People with AIDS are also more likely to have hematologic abnormalities that may result in hypoxia, as described in detail in the companion article.¹

On longitudinal analysis, vessel caliber indices were not predictors of change in any of the variables related to visual field. Future longitudinal studies will evaluate vessel caliber indices as time-dependent measures, which may be more sensitive for identifying such risk.

Other vision functions (BCVA, CS) can vary independently of one another and from visual field measures.^{5, 6} Baseline vessel caliber indices were not strongly associated with either BCVA or CS in the cross-sectional analysis or in the longitudinal portion of the study. This observation does not, however, rule out the possibility of a vascular basis for observed dysfunction of visual acuity or CS; these measures may be related to vascular disease at the capillary level, which is seen ultrastructurally, but would not be reflected in vessel caliber indices.

There are several limitations to this study. Causation cannot be shown with cross-sectional analyses. Lipids might influence the retinal vasculature, but we did not have serum lipid values at baseline for all participants. With regard to vessel caliber indices, values used in this study are not true measures of vessel caliber; they are based on the observable blood column, but do not take into account the immeasurable plasma cuff at the periphery of the vessel lumen. The normal systolic and diastolic cardiac cycle will alter retinal vessel caliber, but fluctuations are small and random, and not felt to be capable of causing major miscalculations.⁷ The limitations of AVR as a measure of retinal vessel caliber, and alternatives for future studies, were discussed in detail in the companion article.¹

In conclusion, our study has shown that people with AIDS have variations in the retinal vasculature that are related to abnormalities of vision function, manifested by variations in measures of visual field. These relationships cannot be explained by other ophthalmic disorders, including glaucoma, cataract, or clinically apparent retinal lesions. The ability to visualize retinal vessels directly provides investigators with a potential tool to study the role of vascular disease in neuroretinal disorder, thought to be responsible for HIV-related vision dysfunction. Such knowledge might lead to early risk factor intervention. Additional longitudinal studies are warranted to determine which of the vessel caliber indices will be most useful clinically for the study of people with AIDS, and whether changes in vascular caliber indices over time will be predictors of adverse visual events.

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Biography

Partho S. Kalyani, M.D. undertook this project during research and clinical uveitis fellowships at the Jules Stein Eye Institute, David Geffen School of Medicine at UCLA (2009-2011). He has been involved in a variety of research projects dealing with HIV-related eye disease, and has a clinical interest in AIDS-related CMV retinitis in the developing world. Dr. Kalyani is currently a vitreoretinal fellow at the University of Michigan in Ann Arbor.

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TABLE 1

RELATIONSHIPS BETWEEN RETINAL VESSEL CALIBER INDICES AND MEASURES OF VISUAL FUNCTION AT BASELINE FOR 1250 STUDY PARTICIPANTS WITHOUT OCULAR OPPORTUNISTIC INFECTIONS IN THE LONGITUDINAL STUDY OF OCULAR COMPLICATIONS OF AIDS

	Quartile				Comparisons			
	1	2	3	4	Crude		Adjusted ^a	
					β^b	P	β^b	P
Visual function (median)								
Visual acuity (standardized letters)								
CRAE	90	90	90	89	0.1	0.76	0.3	0.39
CRVE	90	90	90	89	-0.1	0.64	0.2	0.60
AVR	89	90	90	90	0.6	0.06	0.5	0.13
Contrast sensitivity (log CS units)								
CRAE	1.63	1.64	1.64	1.63	0.000	0.89	0.004	0.38
CRVE	1.63	1.64	1.64	1.61	-0.006	0.18	-0.003	0.57
AVR	1.61	1.62	1.66	1.63	0.008	0.08	0.008	0.07
Goldmann Visual field (degrees)								
CRAE	738	748	746	740	1.3	0.52	3.4	0.10
CRVE	746	746	745	732	-2.3	0.25	-0.7	0.74
AVR	736	740	743	748	6.0	0.003	6.0	0.003
Humphrey Visual Field ^c								
Mean deviation (dB)								
CRAE	-1.88	-1.62	-1.78	-2.21	-0.07	0.49	0.16	0.10
CRVE	-2.06	-1.22	-1.82	-2.30	-0.22	0.02	-0.02	0.82
AVR	-2.07	-1.72	-1.76	-1.94	0.19	0.04	0.22	0.02
Pattern standard deviation (dB)								
CRAE	2.19	2.04	2.02	2.10	-0.03	0.62	-0.09	0.15
CRVE	2.16	1.97	2.13	2.10	0.06	0.29	0.00	0.94
AVR	2.22	2.00	2.12	2.09	-0.11	0.06	-0.11	0.06

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AVR=arteriole:venule ratio

CRAE=central retinal arteriolar equivalent

CRVE=central retinal venular equivalent

^aAnalyses involving CRAE were adjusted for age, race, hematocrit, time since diagnosis of AIDS, HAART (ever used), and CD4+ T-lymphocyte count; analyses involving CRVE were adjusted for age, race, mean corpuscular volume, history of smoking, time since diagnosis of AIDS, and HAART (ever used and current use); analyses involving AVR were adjusted for age, race, mean corpuscular volume, hematocrit, time since diagnosis of AIDS, and current use of HAART.

^bRegression coefficient defined as change in outcome per increase in one quartile of vascular measurement.

^cExcluded were 382 (31%) of 1250 eyes because of unreliable automated perimetry results. The number of eyes with reliable results for both mean deviation and pattern standard deviation by increasing quartile of CRAE were 222, 223, 204 and 219, respectively; by increasing quartile of CRVE were 211, 213, 222, and 222, respectively; and by increasing quartile of AVR were 217, 203, 214 and 234, respectively.

RETINAL VESSEL CALIBER INDICES AT BASELINE AS PREDICTORS OF VISUAL EVENTS DURING FOLLOW-UP FOR 1250 PARTICIPANTS WITHOUT OCULAR OPPORTUNISTIC INFECTION IN THE LONGITUDINAL STUDY OF OCULAR COMPLICATIONS OF AIDS.

TABLE 2

Visual Event	Crude			Adjusted ^a		
	RR ^b /quartile	95% CI	P	RR ^b /quartile	95% CI	P
Visual acuity worse than 20/40 ^c						
CRAE	0.95	0.72-1.25	0.70	1.04	0.77-1.40	0.81
CRVE	0.93	0.70-1.22	0.93	0.99	0.73-1.35	0.97
AVR	0.92	0.70-1.21	0.56	0.94	0.71-1.26	0.70
Visual acuity 20/200 or worse ^d						
CRAE	0.89	0.51-1.57	0.69	1.00	0.56-1.76	0.99
CRVE	0.84	0.48-1.49	0.55	0.92	0.51-1.66	0.79
AVR	0.90	0.52-1.57	0.71	0.84	0.49-1.54	0.63
Contrast sensitivity <1.5 log units ^e						
CRAE	1.04	0.91-1.20	0.53	1.03	0.89-1.19	0.71
CRVE	1.12	0.97-1.28	0.12	1.03	0.89-1.20	0.68
AVR	0.94	0.82-1.07	0.33	0.99	0.86-1.14	0.91
Mean deviation <-2.63 dB ^f						
CRAE	0.94	0.80-1.12	0.50	0.98	0.81-1.18	0.80
CRVE	1.09	0.91-1.29	0.35	1.08	0.89-1.31	0.43
AVR	0.89	0.76-1.05	0.17	0.91	0.76-1.08	0.28
Pattern standard deviation >2.57 dB ^g						
CRAE	1.04	0.89-1.21	0.65	1.07	0.90-1.28	0.44
CRVE	1.08	0.92-1.26	0.36	1.03	0.87-1.22	0.75
AVR	0.95	0.82-1.11	0.54	0.98	0.83-1.15	0.77

AVR=arteriole:venule ratio

CRAE=central retinal arteriolar equivalent

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CRVE=central retinal venular equivalent

^a Adjusted for following variables at baseline: current use of HAART, CD4+ T-lymphocyte count, HIV RNA blood level, age, black race, mean corpuscular volume, hematoctrit, and time since diagnosis of AIDS.

^b Relative risk estimated from Cox regression

^c 42 events/1114 eyes without event at baseline; median follow-up, 5.1 years; rate, 0.7 /100 person-years (PY).

^d 10 events/1130 eyes without event at baseline; median follow-up, 5.4 years; rate, 0.2 /100 PY.

^e 168 events/1016 eyes without event at baseline; median follow-up, 4.6 years; rate, 3.6 /100 PY.

^f 111 events/479 eyes without event at baseline; median follow-up, 4.9 years; rate, 4.7/100 PY.

^g 131 events/501 eyes without event at baseline; median follow-up, 4.0 years; rate, 6.5/100 PY.