HIV-Related Ocular Microangiopathic Syndrome and Color Contrast Sensitivity

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Purpose. Color vision deficits in patients with acquired immunodeficiency syndrome (AIDS) or human immunodeficiency virus (HIV) disease were reported, and a retinal pathogenic mechanism was proposed. The purpose of this study was to evaluate the association of color vision deficits with HIV-related retinal microangiopathy.

Methods. A computer graphics system was used to measure protan, deutan, and tritan color contrast sensitivity (CCS) thresholds in 60 HIV-infected patients. Retinal microangiopathy was measured by counting the number of cotton-wool spots, and conjunctival blood-flow sludging was determined. Additional predictors were CD4+ count, age, time on aerosolized pentamidine, time on zidovudine, and Walter Reed staging. The relative influence of each predictor was calculated by stepwise multiple regression analysis (inclusion criterion; incremental P value = < 0.05) using data for the right eyes (RE). The results were validated by using data for the left eyes (LE) and both eyes (BE).

Results. The only included predictors in multiple regression analyses for the RE were number of cotton-wool spots (tritan: R = .70; deutan: R = .46; and protan: R = .58; $P < .0001$ for all axes) and age (tritan: increment of R [R_i] = .05, $P = .002$; deutan: $R_i = .10$, $P = .004$; and protan: $R_i = .05$, $P = .002$). The predictors time on zidovudine ($R_i = .05$, $P = .002$) and Walter Reed staging ($R_i = .03$, $P = .01$) were additionally included in multiple regression analysis for tritan LE. The results for deutan LE were comparable to those for the RE. In the analysis for protan LE, the only included predictor was number of cotton-wool spots. In the analyses for BE, no further predictors were included. The predictors Walter Reed staging and CD4+ count showed a significant association with all three criteria in univariate analysis. Additionally, tritan CCS was significantly associated with conjunctival blood-flow sludging.

Conclusion. CCS deficits in patients with HIV disease are primarily associated with the number of cotton-wool spots. Results of this study are in accordance with the hypothesis that CCS deficits are in a relevant part caused by neuroretinal damage secondary to HIV-related microangiopathy. Invest Ophthalmol Vis Sci. 1994;35:3011–3021.

Ocular microangiopathic syndrome is a frequent finding in patients with acquired immunodeficiency syndrome (AIDS) or with human immunodeficiency virus (HIV) disease. Cotton-wool spots were first described in patients with AIDS by Holland et al in 1982,[1] and cotton-wool spots are the most common manifestation of HIV-related ocular microangiopathic syndrome.[2–4] Other microvascular abnormalities in patients with HIV infection include hemorrhages, Roth's spots, and blood-flow sludging in conjunctival vessels.[5–7] Fundus fluorescein angiography shows microaneurysms, telangiectasis, focal areas of nonperfusion with capillary drop-out, or focal leakage in patients with AIDS or HIV disease.[8,9]

Ocular microvascular changes are not restricted to HIV infection. Similar retinal abnormalities occur in patients with diabetes mellitus, hypertension, systemic lupus erythematosus, severe anemia, malaria, Nan-

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tucket fever, multiple myeloma, and in immunosuppressed patients after bone marrow transplantation.[10–14] Color vision deficits are a known complication of diabetic retinopathy[15] and other retinal diseases.[16]

Recently, deficits in color vision were reported in patients with AIDS[17,18] or symptomatic HIV infection.[18] The pathogenesis of these color vision deficits has not been elucidated as yet. Factors that might contribute to the pathogenesis of deficits in color vision include HIV-related microangiopathic syndrome, infection of the retina with HIV,[19] subclinical opportunistic infections,[20] glutathione deficiency,[21] methyltransferase inhibition,[22] toxic effects of HIV proteins,[23] and adverse drug effects.[24] The purpose of this study was to evaluate the association of color contrast sensitivity (CCS) with indicators of HIV-related microangiopathy,[25] use of zidovudine, use of aerosolized pentamidine, CD4+ lymphocyte count, and Walter Reed staging. Our specific hypothesis was that CCS deficits in patients infected with HIV are primarily associated with HIV-related retinal microvascular abnormalities.

MATERIAL AND METHODS

Subjects

Sixty outpatients with HIV infection were prospectively studied. All patients were homosexual or bisexual men diagnosed with HIV-1 infection. According to our study protocol, patients with the following conditions were excluded: visual acuity below 0.8 with best correction; visual complaints; hereditary deut-/prot-/tritanomalia; hereditary deut-/prot-/tritanopia; diabetes mellitus; rheumatic disease; systemic lupus erythematosus; use of dideoxyinosine or dideoxycytidine; abuse of illegal drugs; psychiatric disorders; lack of education; malignant hypertension; leukemia; AIDS dementia complex; opportunistic infections of the eye or the brain at the time of the study. The only administered prophylaxis for *Pneumocystis carinii* pneumonia was aerosolized pentamidine in our patients. Informed consent was obtained from all patients, and the tenets of the Declaration of Helsinki were followed. Ophthalmic examinations included examination at the slit-lamp biomicroscope and indirect ophthalmoscopy, and all patients were refracted on an autorefractor. Mean age was 38.7 years (±1.19 SEM), with a range from 25 to 63 years. Absolute CD4+ lymphocyte count was determined by two-color flow cytometry of whole blood preparations (FACScan, Beckton Dickinson, Heidelberg, Germany). Staging of HIV disease was done according to the Walter Reed (WR) classification.[26] Six patients were staged Walter Reed 1 (asymptomatic, CD4+ count > 400 cells/μl); three patients Walter Reed 2 (LAS, CD4+ count > 400 cells/μl); four patients Walter Reed 3 (no delayed hypersensitivity, CD4+ count ≤ 400 cells/μl); eight Walter Reed 4 (delayed hypersensitivity, CD4+ count ≤ 400 cells/μl); 11 Walter Reed 5 (thrush); and 28 Walter Reed 6 (opportunistic infection).

Measuring Ocular Microangiopathic Syndrome

Fundus examination was performed by indirect ophthalmoscopy after dilatation of the pupils. A Nikon 14 diopter (D) lens was used for posterior pole and peripheral retina examination. The outer retinal periphery was additionally examined using a Nikon 20 D lens, and, if necessary, examination was extended with a Volk 78 D lens at the slit lamp. The number of cotton-

TABLE 1. Basic Descriptive Statistics for the Criteria and the Predictors Measuring HIV-Related Ocular Microvascular Abnormalities

Variable	*Mean*	*SEM*	*Range*
Tritan contrast sensitivity			
RE	6.81	0.39	2.1–24.0
LE	6.75	0.38	2.3–14.4
BE	6.78	0.25	2.1–24.0
Protan contrast sensitivity			
RE	4.54	0.16	1.8–9.9
LE	4.41	0.17	1.5–8.0
BE	4.47	0.12	1.5–9.9
Deutan contrast sensitivity			
RE	4.94	0.17	2.0–9.3
LE	4.89	0.17	2.1–8.0
BE	4.91	0.12	2.0–9.3
Age-corrected tritan contrast sensitivity*			
RE	1.58	0.39	−2.8–18.4
LE	1.53	0.38	−2.6–9.16
BE	1.55	0.25	−2.8–18.4
Age-corrected protan contrast sensitivity*			
RE	0.58	0.16	−2.1–5.5
LE	0.46	0.17	−2.4–3.8
BE	0.52	0.12	−2.4–5.5
Cotton wool spots (number)			
RE	1.27	0.32	0–11
LE	1.32	0.35	0–12
BE	1.29	0.23	0–12
Conjunctival sludging score			
RE	1.98	0.16	0–5
LE	1.97	0.21	0–5
BE	1.98	0.15	0–5

RE = right eye, n = 60; LE = left eye, n = 60; BE = both eyes, n = 120.

* Age-corrected values (deviation to the age-corrected norm value) were calculated according to the two equations published by Arden et al.[27]: age-corrected tritan vision = tritan vision − (4.38 + 0.022 * age); age-corrected protan vision = protan vision − (2.99 + 0.0247 * age).

TABLE 2. Matrix of Intercorrelations: Pearson Correlations for the Criteria and the Predictors

	Color Contrast Thresholds				*Walter Reed Conjunctival*				
Variable	*Tritan*	*Deutan*	*Protan*	*CD4+ Count*	*Staging*	*Sludging*	*Age*	*Time on Zidovudine*	*Time on Pentamidine*
Cotton wool spots									
RE	0.70*	0.46*	0.58*	−0.35†	0.26‡	0.51*	0.10	0.27‡	0.34†
LE	0.65*	0.34†	0.31‡	−0.37§	0.20	0.47*	0.10	0.22	0.26‡
BE	0.67*	0.40*	0.44*	−0.36*	0.23†	0.50*	0.09	0.24†	0.30§
Time on pentamidine									
RE	0.13	−0.01	0.09	−0.29‡	0.34†	0.18	−0.04	0.51*	
LE	0.27‡	0.11	0.08	−0.29‡	0.34†	0.17	−0.04	0.51*	
BE	0.19‡	0.05	0.09	−0.29§	0.34*	0.18	−0.04	0.51*	
Time on zidovudine									
RE	0.19	0.21	0.28‡	−0.17	0.31‡	0.03	0.09		
LE	0.43§	0.21	0.29‡	−0.17	0.31‡	0.09	0.09		
BE	0.30§	0.21†	0.29†	−0.17	0.31§	0.06	0.09		
Age									
RE	0.35†	0.37†	0.31‡	−0.26‡	0.14	0.06			
LE	0.36†	0.28‡	0.16	−0.26‡	0.14	0.02			
BE	0.35*	0.32§	0.22‡	−0.26†	0.14	0.04			
Conjunctival blood flow sludging									
RE	0.40†	0.24	0.29‡	−0.66*	0.63*				
LE	0.40†	0.17	0.19	−0.68*	0.61*				
BE	0.40*	0.21‡	0.24†	−0.67*	0.62*				
Walter Reed staging									
RE	0.34†	0.25‡	0.29‡	−0.74*					
LE	0.43§	0.23	0.13	−0.74*					
BE	0.38*	0.24†	0.21‡	−0.74*					
CD4+ count									
RE	−0.29‡	−0.20	−0.31‡						
LE	−0.46§	−0.24	−0.23						
BE	−0.36*	−0.22‡	−0.27†						
Protan vision									
RE	0.74*	0.84*							
LE	0.47*	0.73*							
BE	0.61*	0.79*							
Deutan vision									
Re	0.69*								
LE	0.54*								
Be	0.62*								

RE = right eye, $n = 60$; LE = left eye, $n = 60$; BE = both eyes, $n = 120$.
* $P < 0.0001$; † $P < 0.01$; ‡ $P < 0.05$; § $P < 0.001$.

wool spots was counted for each eye as an indicator of retinal microvasculopathy.

Conjunctival microvasculopathy was determined by one of us (SAG) for each eye by means of a standardized rating scale as described earlier:[25] value 0 (no sludge); value 1 (sludge just visible); value 2 (sludge clear visible, but low); value 3 (moderate sludge); value 4 (strong sludge); value 5 (extreme sludge). A biomicroscope with a magnification factor 32 was used in all patients.

Measuring Color Contrast Sensitivity

The computer graphics system described by Arden et al[27] was used. Colors were displayed on a monitor with a 90-Hz refresh rate and with a 760 to 980 pixel resolution (noninterlaced). The dot pitch was 0.31 mm. The monitor requires a graphic engine and a 100-MHz card based on the Hitachi ACRTC chip set with single pixel scrolling, pan, and zoom facilities, and foreground–background display with alternate screens was used with a Brooktree 24-bit palette. We used a personal computer with an 80286 CPU with an 80287 mathematical coprocessor with software written in C. The stimuli composed of letters were 8.1 cm high and were displayed for 200 msec/sec in the center of a large uniform field. We performed heterochromatic flicker photometry to measure the relative luminance of the blue:green and red:green guns before the mea-

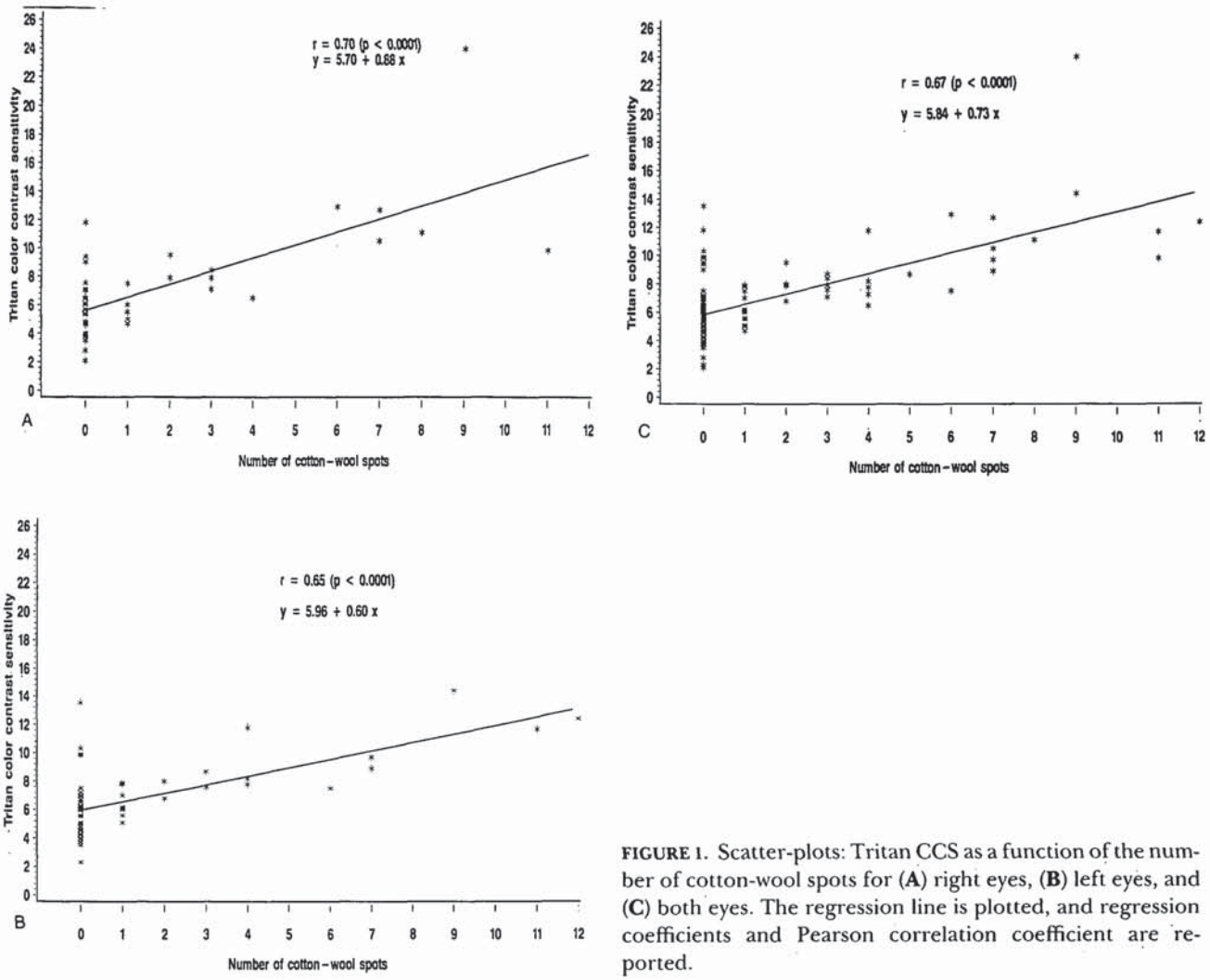

FIGURE 1. Scatter-plots: Tritan CCS as a function of the number of cotton-wool spots for (**A**) right eyes, (**B**) left eyes, and (**C**) both eyes. The regression line is plotted, and regression coefficients and Pearson correlation coefficient are reported.

surement of color contrast thresholds. Color contrast thresholds were determined along protan–deutan and tritan color confusion axes (orthogonal to each other in Commission Internationale d'Eclairage color space). We used a modified binary search scheme, and subjects were asked to determine if a slightly noticeable difference between background and stimulus was detected. This search scheme started with a letter superthreshold for most subjects (in this study, value 12). If the stimulus was detected, the signal presented became the new upper bound and half the contrast became the lower bound (value 6). If the stimulus value was not detected, value 12 became the lower bound and value 24 the upper bound. The next stimulus was midway between values 12 and 24, and so on. Thresholds were measured to within 0.3, which is the limit for the precision of the analogue to digital converter system.[28]

Statistical Analysis

To account for the problem of correlation between fellow eyes, we decided to analyze the data for the right eye addressing our specific hypothesis (primary issue).[29,30] Additionally, we validated our results by calculating stepwise multiple regression analysis for the left eye and for both eyes. Intercorrelations were calculated using the Pearson product–moment correlation coefficient. Furthermore, we calculated correlation coefficients using age-corrected values for tritan and protan CCS, obtained according to the equation published by Arden et al.[26] Stepwise multiple regression analysis was used to extract a parsimonious combination of predictors.[31] Criteria were tritan, protan, and deutan CCS. Predictors in each multiple regression analysis were the following variables: absolute CD4+ lymphocyte count μl; age in years; number of cotton-wool spots; conjunctival blood-flow sludging score; time on aerosolized pentamidine in months; time on zidovudine in months; and Walter Reed staging. Inclusion criterion (primary issue—right eye; validation—left eye, both eyes) for a predictor variable in one of the three stepwise multiple regression analyses was a P-value < 0.05 for the increment of the multiple correlation coefficient. Statistical analysis was carried

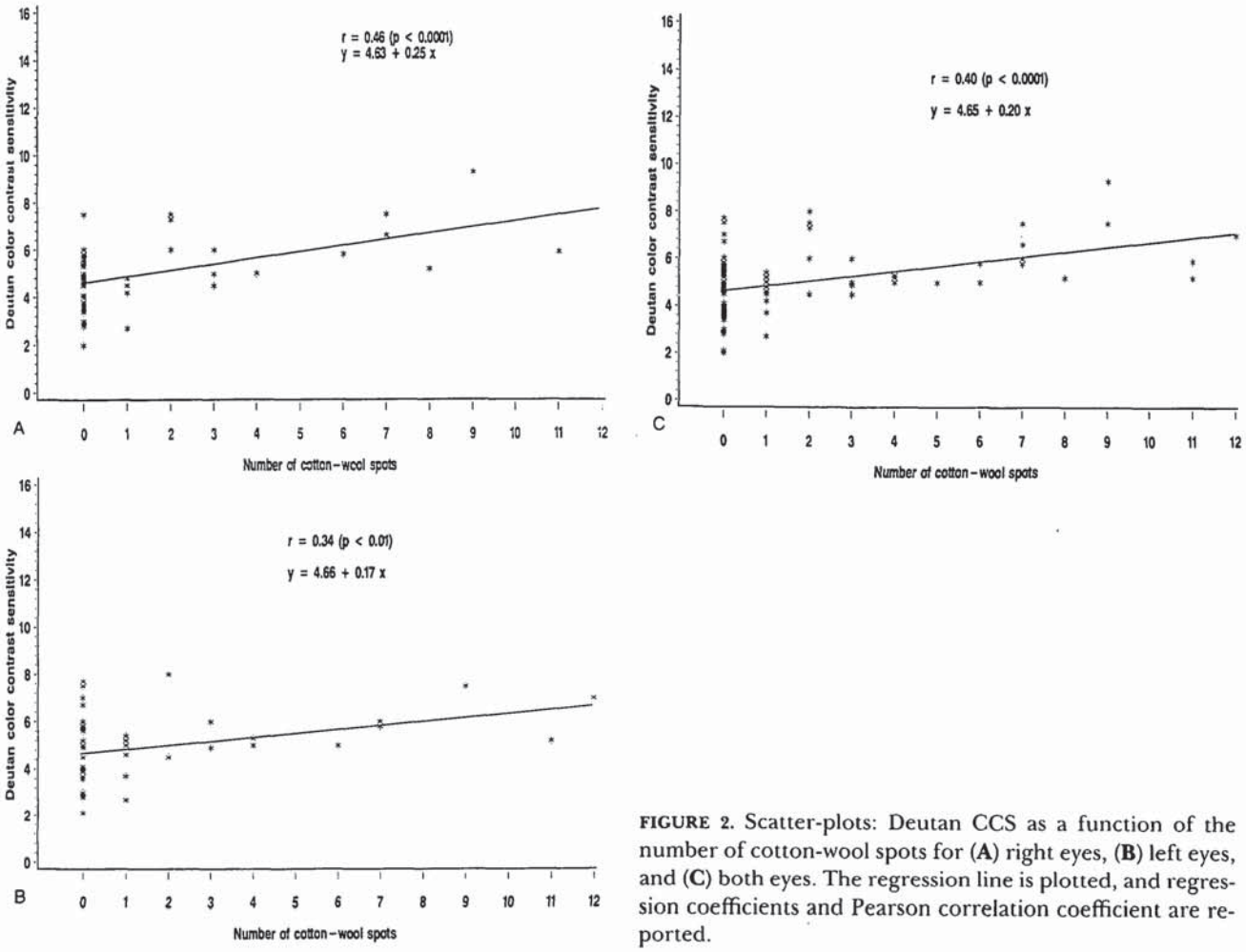

FIGURE 2. Scatter-plots: Deutan CCS as a function of the number of cotton-wool spots for (**A**) right eyes, (**B**) left eyes, and (**C**) both eyes. The regression line is plotted, and regression coefficients and Pearson correlation coefficient are reported.

out on a personal computer with use of SAS (SAS Inc., Carey, NC).

RESULTS

Basic descriptive statistics for the criteria and the predictors measuring HIV-related ocular microvascular abnormalities are summarized in Table 1. Mean absolute CD4+ lymphocyte count (± SEM) was 213 ± 28.91 cells per μl, mean age was 38.7 ± 1.19 years, mean time on zidovudine was 8.97 ± 1.27 months, and mean time on aerosolized pentamidine was 5.49 ± 0.96 months.

Table 2 shows the correlations of the predictors with the three criteria (RE, LE, and BE), and results of univariate regression analysis of the criteria with the predictor number of cotton-wool spots are reported in Figures 1 to 3. Table 3 shows the correlation for age-corrected CCS with the predictors. The predictor number of cotton-wool spots shows the highest correlations with all three criteria in univariate analysis for RE, LE, and BE. Time on aerosolized pentamidine shows the lowest associations with our criteria.

Table 4 summarizes the results of stepwise multiple regression analyses. Stepwise multiple regression analysis for the criterion tritan CCS (right eye, primary issue) included the predictor number of cotton-wool spots in the first step (R = .70, $P < 0.0001$). In the second step, the predictor age was added. The increment of the multiple regression coefficient was .05 ($P < 0.01$). Partial correlations of .67 for number of cotton-wool spots and .28 for age indicate that both variables explain independent parts of variance of the criterion tritan CCS. No further predictor was included. Stepwise multiple regression for the criterion deutan (RE) included the predictor number of cotton-wool spots in the first step (R = .46, $P < 0.0001$). In the second step, age was added. The increment of the multiple regression coefficient was .10 ($P < 0.01$). Partial correlations for both variables indicate that the predictors number of cotton-wool spots and age explain independent amounts of variance of the criterion deutan CCS. No further predictor was included. Stepwise multiple regression for the criterion protan (RE) included the predictor number of cotton-wool spots in the first step (R = .58, $P < 0.0001$) and age in the second step. The increment of the multiple regression coefficient in the second step was .05 ($P < 0.05$).

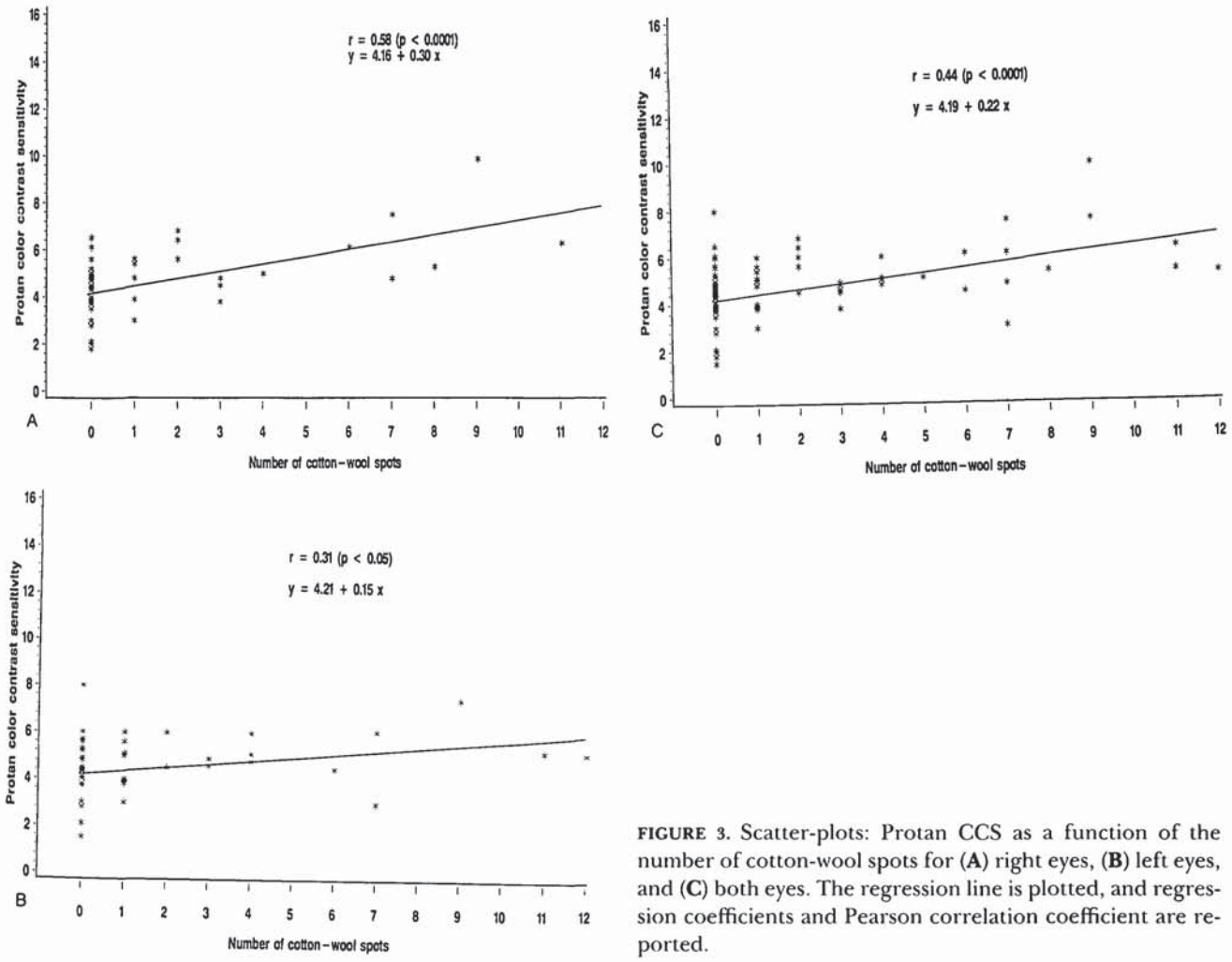

FIGURE 3. Scatter-plots: Protan CCS as a function of the number of cotton-wool spots for (**A**) right eyes, (**B**) left eyes, and (**C**) both eyes. The regression line is plotted, and regression coefficients and Pearson correlation coefficient are reported.

Again, partial correlations indicate that both variables explain independent parts of variance of the criterion protan CCS. No further predictors were included.

Results of calculations for the left eye and for both eyes were comparable for the predictor number of cotton-wool spots. The predictor age was included in all stepwise regression analyses except the one with protan LE as criterion (Table 5). Time on zidovudine was only included in two stepwise regression analyses: tritan LE and protan BE. Walter Reed classification was included in the stepwise regression analysis for tritan LE and tritan BE. Stepwise regression with age-corrected tritan and protan CCS as criteria did not differ except for age, which was not included in stepwise regression analysis for protan RE, LE, and BE (Table 4). In summary, the only included predictor in all stepwise regression analyses was number of cotton-wool spots.

DISCUSSION

Our results demonstrate that the number of cotton-wool spots is the most important predictor for impairment of CCS in patients with HIV disease. Cotton-wool spots are the main feature of HIV-related ocular microangiopathic syndrome. Cotton-wool spots are the clinical sign of localized accumulations of axoplasmic debris following obstruction to orthograde and retrograde axoplasmic flow.[10,32] This damage to the retinal nerve fiber layer is usually caused by retinal ischemia, but other factors that cause focal interruption of axoplasmic flow might cause a similar clinical appearance. Histopathologic studies of small retinal vessels in patients with AIDS reveal swollen endothelial cells, duplication of the basal lamina, vasoconstriction, vasodilation, loss of pericytes, and immune complex deposits. These changes are more common adjacent to cotton-wool spots.[2,8]

According to retinal fluorescein angiographic and histopathologic studies, there is evidence that cotton-wool spots in patients with AIDS are caused by microvascular abnormalities and retinal ischemia.[2,8,33] Studies demonstrating an infection of retinal endothelial cells suggest a direct role of HIV in the pathogenesis of vascular alterations,[19,20] but other authors demonstrated no pathologically significant HIV infection of

TABLE 3. Correlations of Age-Corrected Tritan and Protan Contrast Sensitivity With the Predictors (Pearson Correlations)

Variable	*Cotton Wool Spots*	*CD4+ Count*	*Walter Reed Conjunctival*		*Age*	*Time on Zidovudine*	*Time on Pentamidine*
			Staging	*Sludging*			
Tritan							
RE	0.71*	−0.28†	0.27†	0.41‡	0.28†	0.19	0.10
LE	0.66*	−0.45‡	0.43‡	0.41‡	0.29†	0.44‡	0.28†
BE	0.68*	−0.35*	0.38*	0.41*	0.28§	0.30‡	0.20†
Protan							
RE	0.58*	−0.28†	0.33§	0.29†	0.12	0.27†	0.13
LE	0.30†	−0.19	0.11	0.19	−0.05	0.28†	0.09
BE	0.43*	−0.23§	0.20†	0.23†	0.04	0.27§	0.10

* $P < 0.0001$; † $P < 0.05$; ‡ $P < 0.001$; § $P < 0.01$.

TABLE 4. Results of Stepwise Regression Analysis*

Color Axis	*Step*	*Predictor Included*	*Multiple Correlation*	*P Value*	*Partial Correlation*	*Regression Coefficient*
Right eye						
Tritan	1	Cotton wool spots	0.70	<0.0001†	0.67	0.89
	2	Age constant	0.75	0.0017†	0.28	0.09
						2.22
Deutan	1	Cotton wool spots	0.46	<0.0001	0.46	0.23
	2	Age constant	0.56	0.004	0.31	0.05
						2.90
Protan	1	Cotton wool spots	0.58	<0.0001†	0.58	0.29
	2	Age constant	0.63	0.02‡	0.24	0.03
						2.88
Left eye						
Tritan	1	Cotton wool spots	0.65	<0.0001†	0.65	0.57
	2	Age	0.72	0.001†	0.31	0.08
	3	Time on zidovudine	0.77	0.002†	0.28	
	4	Walter Reed classification	0.80	0.01†	0.21	
		constant				2.78
Deutan	1	Cotton wool spots	0.34	<0.008	0.34	0.16
	2	Age	0.42	0.003	0.26	0.04
						3.24
Protan	1	Cotton wool spots	0.31	<0.0001†	0.31	0.12
		constant				3.99
Both eyes						
Tritan	1	Cotton wool spots	0.67	<0.0001†	0.67	0.65
	2	Age	0.73	<0.0001†	0.29	0.08
	3	Walter Reed classification	0.76	0.002†	0.19	0.34
		constant				1.19
Deutan	1	Cotton wool spots	0.40	<0.0001	0.40	0.19
	2	Age constant	0.49	0.0003	0.29	0.04
						3.05
Protan	1	Cotton wool spots	0.44	<0.0001†	0.44	0.29
	2	Time on zidovudine	0.48	0.02†	0.18	0.02
	3	Age constant	0.50	0.04‡	0.16	0.02
						3.14

* Inclusion criterion: improvement $P < 0.05$.
† Variables that remained in the equation when age-corrected criteria were used.
‡ Variables that did not remain in the equation when age-corrected criteria were used.

TABLE 5. Overview: Predictors Included in Stepwise Multiple Regression Analyses With Tritan, Deutan, and Protan Color Contrast Thresholds as Criteria

	RE			*LE*			*BE*		
Predictor	*Tritan*	*Deutan*	*Protan*	*Tritan*	*Deutan*	*Protan*	*Tritan*	*Deutan*	*Protan*
Cotton wool spots (number)	+	+	+	+	+	+	+	+	+
Age (years)	+	+	+	+	+	−	+	+	+
Time on zidovudine (months)	−	−	−	+	−	−	−	−	+
Walter Reed staging	−	−	−	+	−	−	+	−	−

retinal vascular endothelium.[34–36] Dugel et al[37] were able to observe a low retinal vascular perfusion pressure intraoperatively in 19 patients with AIDS undergoing vitreoretinal surgery, a finding that is in accordance with our own experience in patients with AIDS undergoing vitreoretinal surgery.[38]

Recently, a close association between HIV-related retinal microangiopathic changes and deficits in short-term memory was demonstrated.[39] Moreover, a highly significant correlation was reported between HIV-related retinal microvasculopathy and cerebral hypoperfusion measured by HMPAO single photo emission computed tomography.[40] Both studies suggest a relevant role of HIV-related microangiopathic syndrome in the pathogenesis of neurologic dysfunction. This is underlined by the relatively high incidence of unexpected ischemic attacks and cerebral infarctions in patients with HIV disease,[41,42] and the role of the highly vasoconstrictive peptide endothelin-1 is discussed in the pathogenesis of cerebral and ocular vascular alterations in patients with HIV disease.[43] However, no association of ocular microangiopathic syndrome with any visual symptom or any measurement of visual function was demonstrated until now.[3,6,44]

Recently, we were able to demonstrate a prominent tritan defect in patients with symptomatic HIV infection and even more impaired in patients with AIDS.[18] Quantitatively, tritan CCS was about four times more impaired than deutan or protan CCS. In view of the fact the number of tritan cones is about four times lower than the number of deutan or protan cones–receptive fields, and in view of Köllner's rule[45] stating that tritan deficits are related to retinal damage, we concluded that color vision deficits in patients with symptomatic HIV infection or AIDS are caused by neuroretinal damage. Additionally, we introduced the hypothesis that HIV-related microangiopathic syndrome is the major cause for this neuroretinal damage.[18]

The present study was designed to evaluate this hypothesis, and our results demonstrate that the influence of all other tested predictor variables—age excluded—is low compared to our predictor measuring retinal microangiopathic syndrome. Therefore, the results of this study provide evidence for our hypothesis that HIV-related microvascular changes are the major cause of neuroretinal damage measured by CCS tests. This is especially relevant because multiple regression analysis shows that for all criteria, the number of cotton-wool spots is the most important predictor, even compared to the two parameters indicating severity of HIV disease—Walter Reed staging and absolute CD4+ lymphocyte count. However, this finding does not imply that Walter Reed staging and absolute CD4+ lymphocyte count are not associated with CCS deficits. Univariate analysis clearly demonstrates that both predictors are associated with CCS deficits.

An individual cotton-wool spot in patients with AIDS is a transient phenomenon.[46] In a study consisting of 14 patients, the average time to disappearance of an individual cotton-wool spot was estimated to be 6.9 weeks.[47] Thus, some patients with normal fundal appearance might have had cotton-wool spots earlier in their course of AIDS, and some patients might have had more cotton-wool spots earlier than the time of measurement of CCS. Because of the transient nature of an individual cotton-wool spot and because of the remaining defect on the neuroretina,[10] the number of cotton-wool spots counted at a given time represents the lowest number of cotton-wool spots in this patient and should be considered a lower border for an estimate of the neuroretinal damage that has occurred. Therefore, our results concerning an association between CCS impairment and the number of cotton-wool spots is an estimate of a lower border for this association.

The finding that age-corrected tritan CCS remains associated with age requires a short comment. An analysis of the proportion of variances attributable to age reveals that nearly exactly the amount of variance attributable to age itself according to Arden et al[27] [r^2(tritan, age) = $.22^2$ = .0484; thus, 4.8 percent of variance is related to age] was excluded by using age-corrected color vision in our analysis: r(tritan RE,

age)^2 = r(age-corrected tritan RE, age)^2 = .0441. Consequently, in our patients the amount of variance attributable to age itself is 4.4% of 12.3% common variance between tritan and age. This finding suggests that age might be confounded with HIV disease progression, a finding that is consistent with the literature.[48,49]

Recently, a relevant loss of optic nerve axons in patients with AIDS was reported,[50] and the relation of this nerve fiber loss to our findings needs to be discussed. Experimental studies have shown that most nerve fiber layers passing through a cotton-wool spot area are irreversibly damaged, and axon degeneration follows the accumulations of axoplasmic debris.[32] Therefore, the reported loss of retinal ganglion cell axons in the optic nerve should be expected to be secondary to focal ischemic damage on the retinal ganglion nerve fiber layer. The damage to the ganglion cell axons on the retinal level leads to antegrade degeneration of axons and affects the axonal population in the optic nerve.[10] In our opinion, there is considerable evidence for the hypothesis that degeneration of the axonal population in the optic nerve in patients with AIDS is secondary to ischemic retinal alterations of the nerve fiber layer. The relevance of this pathogenic speculation is underlined by the finding that loss of retinal nerve fiber layer correlates with the impairment of tritan vision in patients with glaucoma.[51]

The analogy of HIV-related microangiopathic syndrome with retinal microvascular damage seen in patients with diabetes mellitus needs to be discussed. Color vision deficits were demonstrated for patients with diabetic retinopathy,[15] and different studies demonstrated that tritan vision is more impaired than deutan or protan vision.[52,53] Moreover, the correlations of diabetic retinopathy severity with color vision impairment were r = .46 using the Farnsworth-Munsell 100-hue test[54] and r = .59 using a blue cone spectral sensitivity test.[53] These results are similar to our findings. Recently, Greenstein et al[55] demonstrated that loss of S cone (blue cone) system activity occurs at a postreceptoral level in patients with early diabetic retinopathy. The analogy with diabetic retinopathy provides additional evidence for the hypothesis that HIV-related retinal microvasculopathy is a relevant cause of color vision deficits in patients with HIV disease. In contrast, Hardy et al[56] reported impaired color discrimination in a group of patients with type 1 diabetes without retinopathy, and they suggest that this early loss of color discrimination in patients with diabetes might be of metabolic origin.

In our study, we controlled for other potential factors that might contribute to the pathogenesis of deficits in color vision, such as treatment with zidovudine or treatment with aerosolized pentamidine. Recently, two cases of a temporary shift of tritan CCS were reported for patients starting zidovudine treatment.[24] It was suggested that the dideoxynucleoside zidovudine might be associated with retinal dysfunction. Our data show that there is a low association between time of treatment with zidovudine and the three criteria significant for tritan LE and BE, deutan BE, and protan RE, LE, and BE. However, time of treatment with zidovudine was not included in any of our multiple regression analyses for the right eye, and it was included in only one multiple regression analysis for the left eye (criterion: tritan), or both eyes (criterion: protan), respectively. Thus, our data cannot rule out a minor toxic effect of long-term zidovudine use on neuroretinal functioning. However, this toxic effect might not be of relevant magnitude if compared to other factors, and it might be confounded by other factors.

Analysis of correlations as well as multiple regression analysis cannot prove a causal relationship, but multiple regression analysis is appropriate in an attempt to falsify our specific hypothesis: We were not able to falsify our specific hypothesis that color vision deficits are primarily associated with HIV-related retinal microangiopathic syndrome. Therefore, and because of the above reported analogies, we conclude that there is reliable evidence for our hypothesis that HIV-related retinal microangiopathic syndrome is a major pathogenic factor in the etiology of color vision deficits in patients with HIV disease.

However, this study is not able to rule out additional mechanisms in the pathogenesis of color vision deficits, such as direct infection of neural and retinal cells with HIV[19,20,57] or other viruses,[35,58] metabolic alterations,[21,22] or toxic effects of HIV proteins.[23] We assume that some of those mechanisms might additionally contribute to the pathogenesis of neuroretinal damage in patients with HIV disease. Nevertheless, our analyses suggest that at least about 40 to 50 percent of the variation of tritan CCS can be explained by retinal microvascular alterations in patients infected with HIV.

In conclusion, our results are an important suggestion of the importance of HIV-related microangiopathic syndrome in patients with HIV disease or AIDS. Taking other studies into account, this study provides evidence for the hypothesis that color vision deficits in patients with HIV disease are caused by HIV-related retinal microvascular changes. HIV-related microangiopathic syndrome appears to be an important factor in the pathogenesis of HIV-related neurologic and neuroophthalmic dysfunction.

Key Words

color vision, acquired immunodeficiency syndrome (AIDS), human immunodeficiency virus (HIV), retinal microangiopathy, microcirculation, HIV-1 related microangiopathic

syndrome, color contrast sensitivity, CD4+ lymphocyte count

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