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The relationship between AIDS retinal cotton wool spots and neuropsychological impairment in HIV-positive individuals in the pre-highly active antiretroviral therapy era

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Abstract

Purpose—To determine the relationship between AIDS retinal cotton wool spots (CWS) and neuropsychological impairment in HIV-positive individuals in the pre-HAART (highly active anti-retroviral therapy) era and the association between AIDS-related retinal CWS and neuropsychological impairment in HIV-positive patients not treated with HAART.

Methods—A case-control analysis of prospectively acquired data in HIV-infected individuals who underwent prospective and longitudinal evaluations of retinal findings as well as neuropsychological testing was performed. Individuals underwent prospective retinal ophthalmic examinations with fundus photography of any retinal lesions. They also underwent periodic neuropsychological testing. The occurrence of retinal CWS was analyzed in relationship to neuropsychological impairment.

Results—Thirty individuals with CWS were compared to 60 matched control AIDS patients. There was no association between either global clinical neuropsychological impairment or impairment in any of the five major domains tested and retinal CWS. There was an association between beta-2 microglobulin and CWS as well as an association between low CD4 T-cell count and the presence of retinal CWS.

Conclusions—We found no association between retinovascular disease and neurocognitive impairment in this case-control study. Retinal CWS in HIV disease are related to higher serum beta-2 microglobulin levels and lower CD4 T-cell counts, suggesting that these lesions are related to HIV disease progression but may be caused by a pathological process independent of CNS disease.

Keywords

AIDS retinopathy; cotton wool spots; dementia; neuropsychology; vision loss

Introduction

Retinopathy is common in HIV-infected individuals and is generally classified as either non-infectious (so-called AIDS-associated retinopathy or HIV-related microvascular disease) or infectious.¹ Cytomegalovirus (CMV) and rarely other herpes viruses are the most common infectious causes of retinal destruction in AIDS patients. Psychophysical studies of visual function have detected declines in color vision and contrast sensitivity in HIV-infected patients without infectious retinitis.^{2,3} In addition, the number of myelinated axons in the optic nerve is decreased in such patients at autopsy.⁴ This is possibly due to the cumulative destruction of retinal ganglion cells by multiple infarctions, which are manifest clinically as cotton wool spots (CWS). The pathogenesis of the retinal microinfarctions in HIV-positive individuals is unknown. Theories include viral infection of vascular endothelium, immune complex deposition, and cytokine damage.^{5,6} Ultrastructural studies of the retina in AIDS patients in areas adjacent to the CWS have shown vasculopathy.

Cerebral blood flow studies are sometimes abnormal in HIV-infected individuals, including those who have not yet progressed to AIDS.^{7,8} Cerebral blood flow changes are dynamic markers of a number of illnesses that involve the central nervous system or its vasculature.^{9–11} Although HIV infection does not result in a primary infectious CNS vasculitis, perturbations of the structural and functional integrity of the cerebrovascular system may be linked to decreased cerebral blood flow in HIV infection.^{12,13} While HIV has not been proven to infect the CNS endothelium, umbilical vein endothelial cells have diminished capacity for the secretion of mitogen-induced IL-2 when cultured in media containing HIV.¹⁴ Morphologic abnormalities in endothelial cells are associated with HIV infection whether or not endothelial cells are infected.^{12,13,15,16} Microvascular changes are most conspicuous in subcortical regions, but are present in the cortex as well.¹⁶ Microvascular-mediated neuronal injury may arise from failure of the blood-brain barrier with local immune complex deposition; release of cytotoxic molecules (monokines or proteolytic enzymes)¹⁰ or thrombosis and infarction may result from occlusion of microvasculature.¹⁶ Thus, in addition to the retinal vasculature, the cerebral vasculature may be altered in HIV-positive patients.

Both non-infectious AIDS retinopathy^{17–19} and neurocognitive dysfunction are most common in advanced stages of HIV infection,^{20,21} as are MRI indicators of cerebral atrophy.²² Thus, we hypothesized that both retinal and cerebral vasculature may be affected by the same or related pathogenetic processes in patients with advanced HIV infection. In addition, there may be other nonvascular causes of CNS damage or dysfunction, which may also effect the retina. Geier et al.^{23–26} found a correlation between AIDS retinopathy and lower neuropsychological test scores. They also reported an association between cerebral perfusion defects and CWS. Therefore, we attempted to confirm an association between non-infectious AIDS-related retinopathy and CNS disturbance as evidenced by neuropsychological impairment. We hypothesized that non-invasive measures of retinal microcirculatory disturbances (i.e., CWS) might serve as an indirect measure of micro-circulatory damage in the brain. Retinal examination might be a rapid and inexpensive method of identifying increased risk of neurological involvement of HIV.

Methods and materials

The study group consisted of 143 consecutive patients, who were enrolled in both the UCSD AIDS Ocular Research Unit Longitudinal Study Protocol and the HIV Neurobehavioral Research Center (HNRC) at the University of California-San Diego (UCSD). These patients were derived from a cohort of 184 patients, who had both prospective ophthalmologic and HNRC examinations. Forty-one patients who developed CMV retinitis were excluded. Participants were between 18 and 49 years of age and agreed to periodic fundus examination.

The dates of entry into the study for controls and CWS patients was between 1986 and 1994. Based on their history, most were presumed to have been infected with HIV through sexual exposure. Exclusions included concurrent intravenous drug abuse or prior intravenous drug abuse more than 10 times, neurologic conditions unrelated to HIV, and/or other neuromedical conditions that might independently influence neurocognitive performance or lead to finding neurologic or ophthalmologic structural abnormalities unrelated to HIV (e.g., head injury with loss of consciousness for over 30 minutes, epilepsy, diabetes, or hypertension). The inclusion and exclusion criteria for the parent HNRC protocol are described fully elsewhere.²¹ Patients were requested to return to the study center semi-annually (if CD4 <200 cells per microliter) or annually for a panel of medical, neurological, and neuropsychologic testing and brain MRI examination. In addition, medical and immunologic data, including CD4 and CD8 cell counts, were assessed at each visit by methods described elsewhere.²¹

Ophthalmologic examination included determination of visual acuity using the ETDRS chart²⁷ and dilated funduscopy examination utilizing indirect ophthalmoscopy. All data were collected prospectively on a form designed for this purpose. Retinal CWS or hemorrhages were counted, diagrammed, and documented by fundus photography. The details of the examination techniques and photography have been previously reported.^{19,28}

Neuropsychologic (NP) testing utilized a battery of tests that have been previously described in detail.²¹ The NP tests assessed the following cognitive domains: verbal, abstraction, perceptual/motor, attention/processing speed, learning, memory, motor, and sensory. Also considered was the composite or global rating, which is based on blinded ratings of all demographically corrected test data from the eight cognitive domains by a clinical neuropsychologist unaware of ocular findings or clinical status, using a method that was described and validated previously.^{29–31} All of the domains as well as the global judgment were scored on a nine-point scale with 1 representing excellent neuropsychological function and 9 being severely impaired. A score of 5 indicated definite mild impairment. For this study, all those scoring 5 or greater on the global rating were classified as neuropsychologically impaired. Previous research has indicated that such ratings are reliable, sensitive, and specific indicators of brain disease.²⁹

Case-Control Selection

Of the 143 subjects with ophthalmologic visits as well as medical and neuropsychologic evaluations over varying periods of time, 30 had at least one ophthalmologic visit at which CWS were found. The remaining 113 individuals did not show any CWS. Individuals with CMV retinitis were excluded. Based on the requirements of the two prospective research protocols, ophthalmologic visits took place at intervals of every 3–6 months and neuropsychologic evaluations were scheduled yearly. Therefore, the following approach was adopted. For the 30 persons who had a CWS diagnosis at any point in their ophthalmologic record (the CWS group), we selected a medical and neuropsychologic HNRC visit closest in time to the first CWS determination, and no more than one year apart. Controls (subjects who did not have a CWS determination throughout their ophthalmologic record) were matched two-to-one to patients with CWS based on the CD4 count at the visit closest to the ophthalmologic visit and no more than a year apart. Because CWS are strongly associated with a low CD4 count, controls were selected to have their CD4 count within 25% of the CD4 count of their CWS case.^{18,32,33}

All ophthalmologic data, neuropsychological data, and imaging data were initially collected on Macintosh personal computers using either Foxbase (Fox Software, Perysberg, OH, USA) or Fourth Dimension (ACI Incorporated, Cupertino, CA, USA) software. Subsequently, flat files were transferred to a SUN sparc workstation (Sun Microsystems, Mountainview, CA, USA) for analysis using S-plus (Statistical Sciences Inc., Seattle, WA, USA).

Data Management and Statistical Analysis

Once the controls were selected, matching the cases at a 2/1 ratio, all eight NP domains as well as the global rating were dichotomized into impaired and unimpaired, and a test of proportions was used to compare the CWS group and the control group. Patients were matched for sex (they were all male) and the ages of the two groups were similar. We also used a t-test to compare the CWS group and the scales Global, Sensory and Perceptual/Motor, as well as several individual NP tests including the WAIS-R Digit Symbol Test, Grooved Pegboard Test, and Tactual Performance Test. The investigations were performed according to the guidelines of the 'Declaration of Helsinki'.

Results

A total of 139 men and 4 women had 455 ophthalmologic examinations and 1026 medical and 622 neuropsychologic evaluations. Their CD4 counts during a visit closest to the first ophthalmologic exam had a median of 222, a mean of 331, and SD of 234. Median age was 35 years; median education was 15 years. Of the 143 subjects, 30 (21%) had CWS during their observation period. Sixty matched controls were chosen who had no CWS. The median duration of the ophthalmologic follow-up was 5.6 months, and the mean was 10.8 months (SD: 14 months). In the entire group of 143 participants, retinal CWS were associated with a lower CD4 T-cell count ($p = 0.01$, Student's t-test) and serum beta-2 microglobulin (square-root transformed to symmetrize the distribution) ($p = 0.0016$, Student's t-test) (Table 1).

We next compared the neuropsychologic performance of cases and controls on multiple tests, including the WAIS-R Digit Symbol Test, Grooved Pegboard Test, and Tactual Performance Test. These tests of sensory and motor functioning have been shown to test factors that deteriorate with advancing stages of HIV infections.^{34,35} We, therefore, hypothesized that these tests might be related to the presence of retinal CWS (Table 2). No significant difference was found between the CWS and control groups on any of these measures.

In addition, we compared the proportion of subjects with CWS in two groups: one group showed a clear longitudinal worsening (8 subjects) on the Neuropsychologic Global Rating and one group remained stable or showed clear improvements (15 subjects). In the worsening group, 50% of the individuals had a CWS diagnosis (4/8). In the improving/steady group, 53% had a CWS diagnosis (8/15). Thus, the prevalence of CWS did not differ in patients experiencing deteriorating or improving cognitive functioning.

Discussion

We found no association between retinal CWS and neurocognitive impairment in 90 HIV-infected individuals, of whom 30 had CWS and 60 were controls matched on CD4 count.³ We chose to analyze retinal CWS because they can be clearly discerned by indirect ophthalmoscopy. Analysis of more subtle lesions, such as vascular changes and microaneurysms, would require that fluorescein angiography be performed on each examination. Geier and co-workers reported that ocular HIV-related retinal microvasculopathy was associated with cerebral blood flow abnormalities as determined by SPECT scanning.²³ In that study of 25 patients, the number of retinal CWS was positively associated with abnormalities in cerebral perfusion patterns. We did not find an association between retinal CWS and neuropsychological function. It is possible that SPECT scanning results do not predict or correlate with neuropsychological function; it is also important to note that the Geier study was a small one. In another study of 37 HIV patients by Geier's group,²⁴ a correlation between CWS and a small battery of neuropsychological function tests was found. Unfortunately, the CD4 cell count was not controlled for in that study and would be a likely confounding variable.

Our study is the largest study undertaken to date to investigate the association between CNS abnormalities and retinal changes in AIDS patients. There is not even a trend suggesting a difference in neuropsychological function between the patients with and without CWS. Care was taken to avoid confounding associations with stage of HIV disease as both retinal CWS and neurocognitive changes as well as CNS neuroimaging changes are associated with advanced stages of HIV. This study was performed in the pre-HAART era and is therefore unlikely to be confounded by highly effective antiretroviral therapy. We acknowledge, however, that the case-control design did have some weaknesses. For example, it was not possible to examine all patients every three months for retinal CWS. Similarly, the time interval between the finding of a retinal CWS and the neuropsychological examination could have been up to a year. It is for this reason that we classified patients as either ever having or not ever having retinal CWS. The associations between CWS and declining CD4 cell count (t test p-value = 0.01) and increasing serum beta-2 microglobulin (t test p-value = 0.0016) suggest that retinal microinfarctions are related to HIV disease progression and immunosuppression. Serum beta-2 microglobulin is known to be an important indicator of immune activation in HIV patients³⁶ and its association with retinal CWS, independent of the CD4 T-cell count, further suggests an immunological pathogenesis to these lesions. We did not match CWS and non-CWS patients for this variable. However, our negative findings regarding neurocognitive functioning support the concept that microvascular disease in the retina, as manifest by CWS, is an independent pathological process underlying neuropsychological impairment in patients with AIDS from the pathologic processes underlying CNS disease.

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Table 1

	<i>Controls (n = 60)</i>		<i>CWS group (n = 30)</i>		<i>p-value</i>
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	
Global clinical rating*	4.13	1.54	4.04	1.53	0.80
Sensory domain*	2.52	1.50	3.17	1.97	0.14
Perceptual/motor* domain	3.00	1.77	2.48	0.99	0.19
WAIS-R Digit Smbol (T-score)	50.56	12.56	48.48	9.33	0.50
Grooved Pegboard Test (non-dominant hand) (T-score)	44.89	12.09	44.04	8.08	0.76
Tactual Performance Test (T-score)	55.40	16.51	51.87	14.02	0.39
Square root B2 microglobulin	1.30	0.37	1.56	0.33	0.012

Neuropsychological testing performed using a scale of 1 (excellent function) to 9 (severely impaired). See text.

Table 2

	<i>CWS group (% impaired)</i>	<i>Control group (% impaired)</i>	<i>OR</i>	<i>95% CI</i>	<i>p-value</i>
Global	0.44	0.41	1.071	(0.441, 2.596)	0.41
Verbal	0.24	0.15	1.725	(0.572, 5.200)	0.26
Abstraction	0.08	0.19	0.318	(0.066, 1.540)	0.80
Perceptual/motor	0.12	0.19	0.685	(0.198, 2.366)	0.66
Attention/ processing speed	0.40	0.30	1.556	(0.623, 3.886)	0.29
Learning	0.16	0.40	0.3	(0.101, 0.893)	0.97
Memory	0.12	0.22	0.556	(0.164, 1.882)	0.76
Motor	0.40	0.36	1.152	(0.468, 2.831)	0.47
Sensory	0.30	0.14	2.786	(0.947, 8.193)	0.11