HIV-Related Ocular Microangiopathic Syndrome and Cognitive Functioning

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Summary: Ocular microangiopathic syndrome is found frequently in patients with AIDS or severe HIV infection. Symptoms of this microvascular syndrome can include cotton–wool spots, hemorrhages, and Roth's spots. The clinical and functional significance of HIV-related ocular microangiopathic syndrome has not been clarified as yet. The objective of this study was to evaluate a possible association between HIV-related ocular microangiopathic syndrome and cognitive functioning. Thirty-seven patients infected with HIV (24 with AIDS) underwent ophthalmological and neuropsychological examination. HIV-related ocular microangiopathic syndrome was measured by counting the number of cotton–wool spots in both eyes. Neuropsychological examination included five standardized tests, with the first three primarily measuring function of short-term memory; these tests were as follows: the Auditory–Verbal Learning Test, the Benton Test, the Stroop Colour Word Test, the Trail-Making Part B test, and the Vocabulary for Measuring Premorbid Intelligence test. HIV-related ocular microangiopathic syndrome was found in 15 patients with AIDS (62.5%), and in one patient, staged Walter Reed 5. In 10 patients, one eye was affected (mean count of cotton–wool spots 1.5). In six patients, both eyes were affected (mean count of cotton–wool spots 7.0). Univariate correlations between the number of cotton–wool spots in both eyes and test scores were as follows: Auditory–Verbal Learning Test: 0.56 ($p < 0.001$); Benton Test: 0.51 ($p < 0.001$); Stroop Colour and Word: 0.50 ($p < 0.001$); Trail-Making Part B: 0.15 (not significant); Vocabulary for Measuring Premorbid Intelligence: −0.05 (not significant). Multiple correlation between the test scores and the number of cotton–wool spots was 0.70 ($p < 0.001$). There were a few statistically insignificant correlations between the neuropsychological test scores and the absolute $CD4^+$ lymphocyte count, or the Walter Reed classification. These findings suggest a close association between HIV-related ocular microangiopathic syndrome and a decrease in cognitive functioning—especially alteration of short-term memory—in patients with AIDS. Our results also suggest that microvascular abnormalities in patients with AIDS or HIV disease might contribute not only to the development of cotton–wool spots, but also to functional cerebral impairment. **Key Words:** HIV-related ocular microangiopathic syndrome—Retinal microvasculopathy—Neuropsychology—Cognitive impairment, Short-term memory—AIDS dementia complex.

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Ocular microangiopathic syndrome is found frequently in patients with AIDS or severe HIV disease. This microvascular syndrome was first reported as a manifestation of AIDS in 1982 (1). The appearance of cotton–wool spots is the most common sign of this syndrome's onset. With a frequency of 40–70%, these fluffy, white retinal lesions are the most frequent ocular finding in patients with AIDS (2–4). Other clinical retinal microvascular lesions include hemorrhages and Roth's spots. Fluorescein angiography shows microaneurysms, telangiectasis, focal areas of nonperfusion with capillary dropout, and focal leakage. These abnormalities occur frequently around cotton–wool spots (5).

The clinical and functional significance of HIV-related retinal microangiopathy has not been studied sufficiently. In one study, no association was found between HIV-related retinal microangiopathy and any symptoms studied (6). In another study, an association between the presence of cotton–wool spots and higher serum levels of fibrinogen was reported (7). Retinal microangiopathy is not restricted to HIV infection. Similar retinal microvascular abnormalities occur with diabetes mellitus, vasculitis, malignant hypertension, systemic lupus erythematosus (SLE), severe anemia, Nantucket fever, malaria, multiple myeloma, and leukemia (4,8–10). Cotton–wool spots are especially accurate as indicators of the severity of systemic vascular disease in diabetes mellitus, hypertension, and collagen vascular disease (11).

Symptomatic microvascular cerebral involvement in patients with ocular microangiopathy has been described for collagen–vascular diseases such as SLE (12,13). This coincidence has led to the proposal of a similar pathogenetic mechanism of ocular and cerebral microangiopathy in SLE. In diabetes mellitus, an association between microvascular disease and peripheral neuropathy has been reported (14), and cerebral microvascular involvement has been discussed (15).

Cerebral involvement is one of the most fearsome manifestations of HIV infection, and it is well-documented by neurologic and psychiatric studies. Neurologic and neuropsychologic symptoms are found in at least 40–60% of patients with AIDS (16–22), and postmortem studies show abnormalities of the nervous system in >90% of all patients with AIDS (23,24). Many patients with AIDS develop the so-called AIDS dementia complex (25). Notable decrease in cognitive functioning has been found in verbal and visual–spatial short-term memory problems, timed tasks, naming problems and complex sequential problem solving (26,27).

To our knowledge, no study has been performed to evaluate the association between retinal microangiopathy and functional cerebral damage in patients with AIDS. The specific objective of this study was to measure the possible association of retinal microangiopathy syndrome with a decrease in cognitive functioning. Our hypothesis was that there is an association between HIV-related ocular microangiopathic syndrome and cognitive functioning.

METHODS

Subjects

Forty HIV-positive outpatients, who were shared among the university eye hospital, the psychiatric clinic and the policlinic of internal medicine of the University of Munich, were enrolled in this study. Patients with an opportunistic infection of the brain or eye, psychiatric disorders, lack of education, or any other disease known to cause microangiopathy were excluded. Only patients with confirmation of HIV-infection by Western-blot technique were included. Informed consent was obtained from all patients. A diagnosis of depression was made in one patient, and a diagnosis of cerebral opportunistic infection was made in two patients during or shortly after neuropsychiatric testing or ophthalmologic investigation. Therefore, 37 patients remained in the study. Distribution by sex was 34 men and 3 women; mean age was 39 years with a standard deviation (SD) of 8 (range from 26 to 58 years). The 34 male subjects were either homo- or bisexual, the three female subjects were i.v. drug abusers.

Blood Tests and Classification of HIV Infection

The test for HIV antibodies was performed with commercial kits (Boehringer, Ingelheim, Ltd.). All positive results were confirmed by Western-blot immunoelectrophoresis. Staging of HIV infection was made on the basis of Walter Reed (WR) classification. Absolute CD4$^+$ lymphocyte count was determined by two-color flow cytometry of whole-blood preparations (28). No patient suffered from diabetes mellitus, hypertension, multiple myeloma, rheumatic disease, vasculitis, malignant hypertension, or leukemia. No patient had an opportunistic infection of the brain or eye at the time of the study.

Ophthalmologic Examination

Visual acuity was determined by Snellen charts, and patients were refracted on an autorefractor if visual acuity was <1.0. Following slit-lamp examination, fundus examination was performed by indirect ophthalmoscopy after dilatation of the pupils. A Nikon 14-dpt lens was applied for posterior pole and peripheral retinal examination. The outer retinal periphery was examined using a Nikon 20-dpt lens, and, if necessary, examination was extended with a Volk 78-dpt lens at the slit lamp. Criteria for the diagnosis of ocular microangiopathic syndrome were (a) cot-

ton–wool spots, (b) hemorrhages, or (c) Roth spots. Patients were classified into three groups as follows: Group I, "no microangiopathic changes;" Group II, "one eye shows at least one of the described criteria;" and Group III, "both eyes show at least one of the described criteria." As an indicator for the severity of the ocular microangiopathic syndrome, the number of cotton–wool spots was counted for each eye and additively combined to an index "number of cotton–wool spots."

Neuropsychological Examination

Neuropsychological examination, which lasted 45–60 min, included five standardized and validated tests as listed:

1. *Auditory–Verbal Learning Test* (AVLT). This was a list of 15 substantives, measuring short-term memory (29). For this study, only the recall after the third repetition was used.
2. *Trail-Making Part B*. This test measured motor speed, concentration and visual orientation (30).
3. *Benton Test*. This was used to evaluate visual–motor reproduction and short-term memory. Graphic signs of increased complexibility shall be reproduced mentally after 5 s of contemplation (31).
4. *Stroop Colour Word Interference Test*. This test was employed to measure short-term memory and cognitive functions of learning and naming (32).
5. *Vocabulary for Measuring Premorbid Intelligence*. This test measured long-term memory, education, and intelligence (33).

The validity of all tests for patients with AIDS or HIV infection is confirmed (16,34).

In addition to the seropositive group of patients, a group of 100 HIV-negative subjects underwent the same neuropsychological test battery. If the result of a HIV-positive subject showed a reduction of more than one standard deviation (SD) compared to the mean of controls, function was classified as "slightly-impaired." If the difference was more than two SDs, it was considered "markedly-impaired." Aside from the five tests, a total neuropsychological score was calculated as the sum of "slightly" (=1 point) and "markedly" (=2 points) reduced tests. If the score was 0–2 points, cognitive functioning was classified as "normal;" a score of 3–5 was classified as "slightly impaired;" if the sum was >6, cognitive functioning was classified as "markedly impaired" (16).

Statistical Analysis

The severity of the microangiopathic syndrome was operationalized by the clinically visible number of cotton–wool spots in both eyes. Neuropsychological assessment was made by the five tests described. The primary question was "is there an association between the number of cotton–wool spots and cognitive functioning, measured by the five test scores?" A multiple significance level of 0.05 was accepted. We used the Bonferroni adjustment to determine the critical p value for each correlation coefficient ($p = 0.05/5 = 0.01$) (35–37). The degree of association between the number of cotton–wool spots and the test scores was determined by correlation analysis using the Pearson product–moment correlation coefficient (38,39). In addition, a multiple correlation analysis was calculated.

Depending on scale quality, in the next step of statistical analysis, correlations between the grouping variable for microangiopathy, number of cotton–wool spots, WR classification, $CD4^+$ lymphocyte count, and the neuropsychiatric tests were calculated using Pearson or Goodman–Kruskal correlation coefficients. One-way analysis of variance was also performed. Numerical p values are reported for these calculations and the results were interpreted with the intention of looking for "near regular patterns" (40). Statistical analysis was carried out on an IBM/PS2 with use of an SPSS/PC + V2.0 (41).

RESULTS

The mean $CD4^+$ lymphocyte count was 182/μl (SEM: ± 31) with a range from 2 to 658 cells/μl. As expected, it was closely related to the WR classification. Three patients were classified WR 1, 2, or 3 each. Seven patients were classified WR 4, three WR 5, and 24 WR 6.

Ocular microangiopathic syndrome was found in 15 of the 24 patients (62.5%) with AIDS (WR 6), and in one patient classified WR 5 (Table 1). All patients with retinal microangiopathic syndrome showed cotton–wool spots, and four showed hemorrhages additionally. No Roth's spots were seen. No patient preclassified as WR 4 or lower showed any signs of a retinal microangiopathic syndrome. The Goodman–Kruskal correlation between the number of cotton–wool spots and the WR classification was 0.84 ($p < 0.001$). There was a close association between the number of eyes affected and the $CD4^+$ lymphocyte count (Table 2). Visual acuity was ≥0.8 with best correction in all patients. There was no association between visual acuity and retinal microangiopathy.

TABLE 1. *Ocular microangiopathic syndrome and Walter Reed classification*

Walter Reed classification	Ocular microangiopathy			$CD4^+$ lymphocyte count (per μl)[b]
	Monocular[a]	Biocular[a]	Total	
<=4 (n = 10)	0	0	0	376 ± 88 (91–621)
5 (n = 3)	1	0	1	223 ± 72 (78–307)
6 (n = 24)	9	6	15	80 ± 18 (2–364)

[a] Coclassification: number of patients.
[b] Values are mean ± SEM (range).

TABLE 2. *Results of the ophthalmoscopic examination: number of patients with ocular microangiopathic syndrome, mean number of cotton–wool spots, and absolute CD4⁺ lymphocyte count*

Microangiopathy eyes affected	No. of patients	Cotton–wool spots (mean)[a]	CD4⁺ lymphocyte count (per μl)[a,b]
I No eye affected	21	0	240 ± 45
II One eye affected	10	1.5 ± 0.3	100 ± 31
III Both eyes affected	6	7.0 ± 2.7	27 ± 9

[a] Values are mean ± SEM.
[b] $p = 0.01$ (analysis of variance).

In the neuropsychological tests, 17 patients showed reduced cognitive functioning according to our scoring system compared with the control group. Mean scores of the neuropsychological (according to the WR classification) tests are presented in Table 3. With progression of HIV disease, there was a trend toward dysfunction in all tests except the Trail-Making Part B test, but this trend was not significant using one-way analysis of variance. None of the tests showed a significant correlation with the WR classification or CD4⁺ lymphocyte count, but there was a similar pattern with all tests except for the Trail-Making Part B: negative correlation with WR classification and positive correlation with the CD4⁺ lymphocyte count (Table 4, the Vocabulary for Measuring Premorbid Intelligence test was inversely scaled).

The associations between the number of cotton–wool spots and the five neuropsychological tests are reported in Table 4. The correlations with the following tests are statistically significant according to our primary question (critical p value = 0.01): AVLT ($r = 0.56$, $p < 0.001$); Benton Test ($r = 0.51$, $p < 0.001$); and Stroop Colour Word Interference Test ($r = 0.50$, $p < 0.001$). These three tests measure primarily the function of short-term memory. No clinically or statistically significant correlation is found for the Trail-Making Part B test ($r = 0.15$) or the Vocabulary for Measuring Premorbid Intelligence ($r = 0.05$). These two tests do not primarily measure the function of short-term memory.

Correlation coefficients between the number of affected eyes and the five test scores show a similar pattern of associations. There is a significant association between the grouping variable of ocular microangiopathic syndrome and the three tests measuring function of short-term memory. The multiple correlation between the number of cotton–wool spots and the five test scores was 0.70 ($p < 0.001$).

DISCUSSION

HIV-related ocular microangiopathic syndrome is found frequently in patients with AIDS or AIDS-related complex (7,42–44). The most common manifestation is the appearance of cotton–wool spots, which are distributed typically near the optic disc and along the major retinal vessels. These white, feather-edged lesions usually are less than one-quarter the size of the optic-nerve disc diameter in size. Cotton–wool spots almost never cause impaired vision, but, in rare instances, a macular ischemia with loss of vision can develop. Individual spots spontaneously fade away, but new spots can develop. Cotton–wool spots have been examined with regard to their prognostic implications, with the focus mainly on cytomegalovirus infection and *Pneumocystis carinii* infection of the chorioidea and retina (45). Conjecture that cotton–wool spots in patients with AIDS are a sign of chorioretinal *Pneumocystis* infection has not been proven, and there is still no evidence that the risk for cytomegalovirus retinitis increases when cotton–wool spots are present (2,46,47). As in this study, other investiga-

TABLE 3. *Neuropsychological test scores and absolute CD4⁺ lymphocyte count (mean values) according to the Walter Reed classification*

Variable	Walter Reed classification				Total (SEM) ($n = 37$)	Numerical p value
	<= 3 ($n = 3$)	4 ($n = 7$)	5 ($n = 3$)	6 ($n = 24$)		
CD4⁺ count (per μl)	433	343	223	80	172 (30.8)	<0.0001
AVLT	11.0	10.2	10.0	9.2	9.6 (0.4)	0.62
Trail-Making	59.7	63.6	56.0	63.5	62.6 (1.3)	0.44
Benton	−0.3	−1.4	−2.3	−1.7	−1.6 (0.3)	0.50
Colour Word	51.3	48.9	53.3	45.9	47.7 (1.2)	0.19
Vocabulary	99	109	111	112	110 (2.3)	0.51

AVLT, Auditory–Verbal Learning Test.

TABLE 4. *Correlations between the severity of ocular microangiopathic syndrome (OMS), neuropsychologic test scores, and parameters of immunosuppression*

Test Function[a]	AVLT STM	Trail-Making Mot	Benton STM	Colour Word STM, colour	Vocabulary LTM, education
Cotton–wool spots (number)[b]	−0.56*	0.15	−0.51*	−0.50*	−0.05
Mon-/Biocular OMS	−0.52[c]	0.28[c]	−0.47[c]	−0.41[d]	0.19
Walter Reed classification	−0.22	0.11	−0.21	−0.25	0.12
Absolute CD4$^+$ lymphocyte count (per μl)	0.27	0.01	0.22	0.11	−0.08

AVLT, Auditory–Verbal Learning Test; STM, short-term memory; LTM, long-term memory; Mot, motor skills.

[a] Cognitive function primarily measured.

[b] Primary question: correlations denotated with * are significant on the multiple significance level ($p < 0.001$).

[c] $p < 0.001$.

[d] $p = 0.006$.

[e] $p = 0.04$.

tors have shown that cotton–wool spots develop only in the more severe stages of HIV infection (4,6,7). There is limited evidence that cotton–wool spots indicate a poor prognosis quoad vitam, because they are related to an increasing incidence of opportunistic infection and increased mortality (7, 48,49). This association can be caused primarily by the progression of HIV disease, classified or measured by the WR classification or decrease of absolute CD4$^+$ lymphocyte count, respectively. One group has reported a possible relationship between proteinuria and retinal microangiopathy in patients with AIDS-related complex (2). The presence of HIV antigen in paravascular retinal tissue near cotton–wool spots could be demonstrated (50).

The pathogenetic etiology underlying HIV-related retinal microangiopathic changes may be multiple. Cotton–wool spots are the result of ischemic microinfarcts in the superficial layer of the retina.They are regarded as localized accumulations of axoplasmic debris in the nerve-fiber layer, resulting from obstruction of axoplasmic flow. Ischemia is the most common cause of this obstruction, but any other factor that causes focal interruption of axonal flow will give rise to similar accumulations appearing clinically as cotton–wool spots (51,52). Ultrastructural studies of small retinal vessels reveal swollen endothelial cells, duplication of the basal lamina, vasoconstriction, loss of pericytes, and immune complex deposits. These changes are more common adjacent to cotton–wool spots (2). Studies demonstrating an infection of retinal endothelial cells suggest a direct role of HIV in the pathogenesis of the retinal microangiopathy syndrome (50,53).

The association between the severity of the retinal microangiopathy and cognitive dysfunction shown in this study was statistically and clinically significant. This was correct even with consideration of the multiple significance level. The importance of this association is underlined by three features, as follows: (a) Only the three tests that measure primarily function of short-term memory and speed of information processing correlate significantly with ocular microangiopathic syndrome. (b) There are only slight and statistically insignificant correlations among the three tests that measure short-term memory and the WR classification or the CD4$^+$ count. The correlations of the other two tests are minor. (c) The patterns of association with ocular microangiopathic syndrome and severity of HIV disease are the same for the three tests measuring short-term memory (Table 4).

Therefore, the multiple correlation of 0.70 between the number of cotton–wool spots and the neuropsychological tests may explain a substantial portion (50%) of variance of decreased cognitive functioning in patients with HIV infection. This portion of variance is only slightly confounded by the WR classification and CD4$^+$ lymphocyte count. Furthermore, the common variance is due largely to the dysfunction in different forms of short-term memory, such as verbal (AVLT), visual–spatial (Benton Test), and visual (Stroop Colour Word Interference Test) short-term memory. Another unexpected finding is the much closer association between the neuropsychological tests and ocular microangiopathic syndrome if compared to the association between the neuropsychological tests and the parameters of HIV disease progression.

Analysis of correlations does not allow statements of causality. Yet the described associations

suggest that microvascular changes or hematologic and hemorheologic factors contribute not only to the microvascular retinal changes, but also contribute substantially to a decrease in cognitive functioning in patients with AIDS. Retinal and cerebral vessels have the same embryogenetic origin. There is a widespread (but unproven) belief based on clinical experience that short-term memory is closely related to cerebral blood flow. Thus, our findings are not unexpected. In another study based on a different sample of HIV infected patients, we were able to demonstrate a close association ($r = 0.71$, $p < 0.0001$) of ocular microangiopathic syndrome, measured by the number of cotton–wool spots, with cerebral blood flow measured by hexamethyl–propyleneamine oxime single-photon emission computed tomography (HMPAO–SPECT) of the brain (54). Similar to the results presented in this study, the correlations of HMPAO–SPECT and of number of cotton–wool spots with absolute $CD4^+$ lymphocyte count were lower than the correlation between the two vascular parameters HMPAO–SPECT and cotton–wool spots. Moreover, similar results were reported for the association of cotton–wool spots with damage to the neuroretina measured by color-contrast sensitivity (55). Recently, Dugel et al. (56) were able to observe a low retinal vascular perfusion pressure intraoperatively in 19 patients with AIDS undergoing vitreoretinal surgery.

The question of therapeutic consequences arises. However, evidence presented in this study is still limited. The influence of blood viscosity should be considered (7). In patients on dialysis, presumably anemia-dependent cognitive impairment could be improved by erythropoetin (57). Possibly, similar effects can be expected in patients with AIDS. The study by Freeman et al. (6) was able to show a trend toward decreased hematocrit levels in HIV patients with cotton–wool spots.

Our results hint at the importance of microangiopathic changes in patients with HIV disease. They suggest the hypothesis that microvascular changes, in combination with hematologic and hemorheologic changes in patients with HIV disease or AIDS, contribute not only to the development of cotton–wool spots, but also to the development of functional cerebral damage. Further studies are necessary to study retinal and cerebral function in combination with ocular microangiopathic syndrome and alterations of ocular and cerebral blood flow.

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