Brain HMPAO-SPECT and ocular microangiopathic syndrome in HIV-1-infected patients

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Objective: The pathogenesis of neurologic and neuropsychologic dysfunction in HIV-1 infection is unclear. The purpose of the study was to determine an association between cerebral perfusion and HIV-1-related ocular microangiopathic syndrome.

Methods: We studied 28 HIV-1-infected patients, seven of whom presented with asymptomatic HIV infection, nine with lymphadenopathy syndrome or AIDS-related complex, and 12 with AIDS. Cerebral perfusion was semi-quantitatively measured by single photon emission computed tomography of the brain using technetium-99 hexamethyl-propylenamine oxime (HMPAO-SPECT). The conjunctival manifestation of HIV-1-related microangiopathic syndrome was measured by a rating scale determining blood-flow sludging and by counting retinal cotton-wool spots. CD4 count, neopterin, β_2-microglobulin (β_2M), haemoglobin, and age were determined as putative confounding variables.

Results: Mean conjunctival sludge in patients with normal HMPAO-SPECT findings was 1.3 ± 0.5 (mean ± s.e.m.); no cotton-wool spots were present. In patients with slightly impaired HMPAO-SPECT, it was 2.1 ± 0.6 and mean cotton-wool spot count was 1.1 ± 0.4. In patients with severely impaired HMPAO-SPECT, mean conjunctival sludge was 4.5 ± 0.3 and mean cotton-wool spot count was 4.9 ± 1.1 HMPAO-SPECT findings were closely associated with conjunctival sludge ($r = 0.72$; $P < 0.001$) and number of cotton-wool spots ($r = 0.78$; $P < 0.001$), whereas only a slight association with staging of HIV disease was found ($P = 0.052$). Analysis of covariance controlling for CD4 count, neopterin, β_2M, age, and haemoglobin demonstrated a significant difference between the three HMPAO-SPECT groups for both the number of cotton-wool spots ($P < 0.001$) and the conjunctival sludge rating ($P < 0.001$).

Conclusion: There was a close association between severity of HIV-1-related ocular microangiopathic syndrome and severity of cerebral hypoperfusion. Microvascular alterations might contribute to the pathogenesis of neurological and neuropsychological symptoms in patients with HIV-1 disease. Furthermore, the conjunctival sludge rating and the number of cotton-wool spots might be appropriate indicators for severity of microvascular changes of the central nervous system.

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Introduction

Involvement of the nervous system is a dreaded manifestation of HIV-1 infection [1–4]. Neurologic or neuropsychologic symptoms are found in at least 40–60% of patients with AIDS or HIV-1 disease [5–9]. However, results on the association between measurements of cognitive function and parameters of immunosystemic damage, such as CD4 count or β_2-microglobulin (β_2M), are inconsistent, and the pathogenesis of neurologic and neuropsychologic symptoms remains unclear [10–15].

Clinical studies show a higher risk for cerebral infarction or transient neurologic deficits in patients with AIDS [16,17]. In more than 90% of all patients with AIDS, post-mortem studies demonstrate abnormalities of the nervous system, and alterations of small cerebral vessels have been shown [18–21].

Single photon emission computed tomography (SPECT) of the brain using technetium-99m hexamethyl-propylenamine oxime (HMPAO) is a useful method for imaging regional cerebral blood-flow and has become especially interesting in the investigation of dementia [22,23]. HMPAO-SPECT studies in patients with symptomatic HIV-1 infection or AIDS suggested cerebral perfusion abnormalities [13,24–28].

HIV-1-related ocular microangiopathic syndrome was first described by Holland *et al.* [29] in 1982, and represents the most frequent ocular finding in patients with HIV-1 disease, including conjunctival and retinal microvascular abnormalities [29–33]. The conjunctival manifestation is present in approximately 75% of AIDS or AIDS-related complex patients, including a sludge phenomenon within small conjunctival vessels [30,32]. The typical retinal manifestation are cotton-wool spots visible on ophthalmoscopy found in 40–70% of patients with AIDS [29,31,33–35].

The purpose of this study was to evaluate the association of alterations of HMPAO-SPECT findings with parameters of immunosystemic damage and HIV-1-related ocular microangiopathic syndrome. Our specific hypothesis was that there is a close association between HIV-1-related ocular microangiopathic syndrome, especially abnormal blood-flow sludging in conjunctival vessels, and HMPAO-SPECT findings.

Materials and methods

Subjects

Twenty-eight male outpatients with confirmed HIV-1 infection were studied prospectively. Of these, 25 were homo-bisexual, one reported intravenous drug use and heterosexual transmission was reported by two. The mean age was 40.6 years (s.d.; 10.8 years; range, 24–75 years). According to our study protocol patients with the following conditions were excluded: diabetes mellitus, rheumatic disease, systemic lupus erythematosus, malignant hypertension, leukemia, opportunistic infections of the eye or the brain at the time of the study. Informed consent (both written and verbal) was obtained from all patients.

Seven patients presented with asymptomatic HIV infection, nine were staged lymphadenopathy-associated syndrome/AIDS-related complex (LAS/ARC), and 12 presented with AIDS. Absolute CD4 lymphocyte count was determined by two-color flow cytometry of whole-blood preparations (FACScan, Becton Dickinson, Inc., Heidelberg, Germany) [36]. Serum neopterin (Henning, Inc., Berlin, Germany) and serum β_2M (Pharmacia, Inc., Uppsala, Sweden) were measured by radioimmunoassay. Haemoglobin was measured using the cyanohaemiglobin method.

HMPAO-SPECT

SPECT was performed using a rotating double head gamma camera (Siemens Rota II; high resolution collimator) after intravenous injection of 370–550 MBq 99m-Tc-HMPAO. The system was connected to a MicroDelta/Vax 11/730 computer system. Data were collected from 60 projections (360° rotation) in a 64×64 matrix, and images were reconstructed by filtered back-projection. Transverse, sagittal, and coronal slices (slice thickness: 6.0 mm) were processed. SPECT findings were semi-quantitatively evaluated using the region of interest technique. Six right-over-left gray matter ratios of corresponding regions were calculated in selected transverse slices. A difference in ratios of more than 2 s.d. of a control population was considered pathologic. Results were classified into three groups as follows: 0, normal findings; I, one or two areas of decreased activity in two or more consecutive slices; II, three or more areas of decreased activity.

Measuring ocular microangiopathic syndrome

Ophthalmic examinations were performed blinded to the HMPAO-SPECT results including examination at the slit-lamp and indirect ophthalmoscopy. Conjunctival microangiopathy was determined by one of the authors (S.A.G) for each eye using a standardized rating scale: value 0 (no sludge); value 1 (sludge just visible); value 2 (sludge clearly visible, but low); value 3 (moderate sludge); value 4 (strong sludge); value 5 (extreme sludge). Rating scales with five to six categories show a high reliability and feasibility [37,38]. A biomicroscope with a magnification factor 32 was used in all patients, and a conjunctival blood-flow sludging score was calculated as the mean value of the rating for the right and the left eye.

Fundus examination was performed by indirect ophthalmoscopy after dilation of the pupils. A 14-dioptre

(dpt) lens was used for posterior pole and peripheral retina examination. The outer retinal periphery was additionally examined using a 20-dpt lens, and, if necessary, examination was extended with a 78-dpt lens at the slit-lamp. The number of cotton-wool spots was counted for each eye and combined into one score as indicator of severity of retinal microvasculopathy.

Statistical analysis

Statistical analysis was carried out on a personal computer system with use of SPSS/PC+V4.0 (SPSS, Inc., Chicago, Illinois, USA). Analysis of variance was calculated for the different parameters with HMPAO-SPECT findings as independent variable. Addressing our specific hypothesis of an association between HMPAO-SPECT findings and ocular microangioapathic syndrome, analysis of covariance was calculated for the dependent variables, conjunctival sludge and number of cotton-wool spots including the other parameters as covariates. Furthermore, a matrix of intercorrelations was calculated using the Spearman rank-order correlation coefficient with the intention of looking for near regular patterns, and numerical *P* values for a two-tailed approach are reported [39].

Results

HMPAO-SPECT findings were normal in seven patients, 11 presented with HMPAO-SPECT value I, and 10 with HMPAO-SPECT value II (Table 1). Association of HMPAO-SPECT findings with the staging of HIV-1 disease was almost statistically significant (likelihood ratio $\chi^2 = 9.37$; $P = 0.052$), whereas a close association of HMPAO-SPECT findings with conjunctival microvasculopathy was found ($\chi^2 = 20$; $P < 0.001$).

Mean conjunctival sludge rating in patients with HMPAO-SPECT value 0 was 1.29±0.52 (mean± s.e.m.), no cotton-wool spots were present, and mean CD4 count was 245.29±73 (Table 2). In patients with HMPAO-SPECT value I, this rating was 2.09±0.56, mean count of cotton-wool spots was 1.09±0.44, and mean CD4 count was 233.36±60.86. In the 10 patients with hypoperfusion in three or more regions (HMPAO-SPECT value II) mean conjunctival sludge (4.50±0.31) and mean count of cotton-wool spots (4.90±1.07) were even higher, but mean CD4 count was even lower (11.20±49.30).

Table 1. HMPAO-SPECT results and its association with HIV-1 disease stage (n = 28; $\chi^2 = 9.37$; $P = 0.052$) and conjunctival microangiopathy ($\chi^2 = 20$; $P < 0.001$): cross-tabulation.

HMPAO-SPECT	HIV-1 disease stage			Conjunctival microangiopathy* rating		
	Asymp.	LAS/ARC	AIDS	0 or 1	2 or 3	4 or 5
Value 0	2	3	2	4	3	0
Value I	5	3	3	5	2	4
Value II	0	3	7	0	1	9
Cumulative	7	9	12	9	6	13

*Conjunctival microangiopathy: patients are divided into three groups according to their conjunctival blood-flow sludging score: value 0 or 1; value 2 or 3; value 4 or 5. Asymp., asymptomatic; LAS, lymphadenopathy-associated syndrome; ARC, AIDS-related complex.

Using analysis of variance, significant differences between the three HMPAO-SPECT groups were found for the conjunctival sludge rating ($P < 0.001$), and the number of cotton-wool spots ($P < 0.001$). A trend of a CD4 count decrease is seen, but not significant ($P = 0.24$). In addition, no significant differences were found for haemoglobin, neopterin, and β_2M. Age as putative confounding variable was not associated with HMPAO-SPECT findings.

The main effect of HMPAO-SPECT remained significant using analysis of covariance for both conjunctival sludge ($P < 0.001$) and number of cotton-wool spots ($P < 0.001$) with covariates as follows: CD4 count, neopterin, β_2M haemoglobin and age.

Table 2. HMPAO-SPECT results, manifestations of HIV-1-related microangiopathic syndrome, parameters of immunosystemic damage, and covariates.

Variable (mean value±s.e.m.)	HMPAO-SPECT Value 0 (n = 7)	Value I (n = 11)	Value II (n = 10)	ANOVA *P*
Conjunctival sludge	1.29±0.52	2.09±0.56	4.50±0.31	0.0003
Cotton-wool spots	0.0	1.09±0.44	4.90±1.07	0.0002
CD4 count (×10⁶/l)	245.29±73	233.36±60.86	111.20±49.30	0.24
Neopterin (nmol/l)	25.87±2.28	30.96±4.18	30.28±4.11	0.67
β_2-microglobulin (mg/l)	4.00±0.29	4.50±0.46	3.80±0.27	0.37
Haemoglobin (g/dl)	12.17±0.59	13.98±0.64	12.42±0.62	0.11
Age (years)	45.57±5.55	38.82±3	39.00±2.61	0.38

HMPAO-SPECT findings: value 0, no area of hypoperfusion; value I, one or two areas of hypoperfusion; Value II, three or more areas of hypoperfusion. ANOVA, analysis of variance.

Table 3. Correlations between the variables (n = 28).

	HMPAO-SPECT	Age	Haemoglobin	β_2-microglobulin	Neopterin	CD4 count	Cotton-wool spots
Conjunctival sludge	0.72 ($P<0.001$)	–0.12 ($P>0.05$)	–0.42 ($P=0.034$)	0.18 ($P>0.05$)	0.31 ($P>0.05$)	–0.75 ($P<0.001$)	0.86 ($P<0.001$)
Cotton-wool spots	0.78 ($P<0.001$)	–0.7 ($P>0.05$)	–0.29 ($P>0.05$)	0.18 ($P>0.05$)	0.11 ($P>0.05$)	–0.66 ($P<0.001$)	
CD4+ count ($\times 10^6$/l)	–0.38 ($P=0.049$)	0.01 ($P>0.05$)	0.57 ($P=0.003$)	–0.16 ($P>0.05$)	–0.28 ($P>0.05$)		
Neopterin (nmol/l)	0.12 ($P>0.05$)	0.02 ($P>0.05$)	–0.20 ($P>0.05$)	0.45 ($P=0.017$)			
β_2-microglobulin (mg/l)	–0.14 ($P>0.05$)	0.29 ($P>0.05$	–0.09 ($P>0.05$)				
Haemoglobin (mg/dl)	–0.09 ($P>0.05$)	–0.16 ($P>0.05$)					
Age (years)	–0.18 ($P>0.05$)						

Intercorrelations of the different variables are summarized in Table 3. There was a close Spearman correlation between conjunctival sludge and number of cotton-wool spots ($r = 0.86$; $P<0.001$), as well as between CD4 count and conjunctival sludge ($r = -0.75$; $P<0.001$), or CD4 count and number of cotton-wool spots ($r = -0.66$; $P<0.001$). Correlation of HMPAO-SPECT results with conjunctival sludge was $r = 0.72$ ($P<0.001$), and correlation of HMPAO-SPECT results with the number of cotton-wool spots was $r = 0.78$ ($P<0.001$). Spearman correlation between HMPAO-SPECT results and CD4 count was –0.38 ($P = 0.049$).

Discussion

Our results demonstrate a close correlation between impairment of regional brain perfusion and severity of two different manifestations of HIV-1-related ocular microangiopathic syndrome, and both associations are only slightly confounded by the CD4 count. In addition, neither association is confounded by serum neopterin levels, serum β_2M levels, haemoglobin levels, or age.

Conjunctival sludge and cotton-wool spots are the most frequent manifestations of HIV-1-related ocular microangiopathic syndrome [29–34]. Conjunctival vascular abnormalities similar to patients with HIV-1 infection have been described in sickle cell disease [40], chronic myelogenous leukemia [41,42], and many other diseases [43,44]. However, conjunctival sludge is occasionally a non-specific finding in patients without vascular disease. Therefore, we have grouped the conjunctival sludge value 1 together with value 0. According to this classification, clinically significant conjunctival sludge (values 2 to 5) was found in 68% of our patients, a finding comparable to reports by Teich [30] or Engstrom *et al.* [32]. Cotton-wool spots are fluffy yellowish-white retinal lesions caused by focal retinal ischemia [45,46]. Fundus fluorecein angiography in AIDS patients shows microaneurysms frequently occurring around cotton-wool spots [47]. Recently, microaneurysms were also demonstrated in ophthalmoloscopically normal patients with LAS or ARC [48]. Histopathologic studies of small retinal vessels reveal swollen endothelial cells, duplication of the basal lamina, loss of pericytes and endothelial cells, immune complex deposits, and vasoconstriction [33,47,49,50]. These changes are typically adjacent to cotton-wool spots, suggesting that cotton-wool spots are caused by vaso-occlusion or vasoconstriction [33,50].

An association of ocular perfusion abnormalities with cerebral perfusion abnormalities is not restricted to HIV-1 disease. Symptomatic microvascular cerebral involvement in patients with ocular microangiopathy is well documented for autoimmune diseases such as systemic lupus erythematosus [51,52] and infectious diseases such as malaria [53]. An association between microvascular disease and peripheral neuropathy has been reported in diabetes mellitus [54] and cerebral microvascular involvement is discussed [55].

HMPAO-SPECT studies by other authors demonstrate perfusion abnormalities in HIV-1-infected patients [24–27], but no significant association of HMPAO-SPECT findings with the CD4 count was reported by Rosci *et al.* [13]. This finding is partly in accordance with our own results showing a significant trend using correlation analysis, but no significant difference between the three HMPAO-SPECT groups. Furthermore, the pattern of associations found in our study is comparable to studies suggesting only a minor association of neuropsychologic deficits with parameters of immunosystemic damage [15,35]. The pathogenesis of HIV-1-related microvascular abnormalities in AIDS patients remains unknown. Blood-flow sludging might contribute to the pathogenesis of alterations of vessel structure. For example, the delivery of oxygen at the capillary level is compromised if sludge in vessels increases [44], and local hypoxia might stimulate the formation of microaneurysms similar to patients with diabetes [56,57]. In addition, reduced retinal perfusion pressure in combination with retinal blood-flow sludging in patients with AIDS was observed [58,59]. Increased levels of the highly potent vasoconstrictor endothelin-1 were reported in patients with retinal ocular microangiopathic changes

[60,61], suggesting that endothelin-1-related vasoconstriction might play a role in the pathogenesis of HIV-related microangiopathic syndrome. Studies demonstrating an infection of endothelin cells suggest a direct role of HIV-1 in the pathogenesis of vascular changes [62–65].

Recently, we demonstrated a close association between the number of cotton-wool spots and cognitive impairment as well as neuroretinal dysfunction [35,66]. These findings are consistent with the hypothesis that HIV-1-related microvascular alterations contribute to the pathogenesis of neuropsychological dysfunction and abnormal HMPAO-SPECT findings. The relevance of this hypothesis is emphasized by the finding that the number of cotton-wool spots correlates primarily with impairment of short-term memory, a function thought to be closely associated with cerebral perfusion. It should be noted that there has been renewed interest in vascular dementia in aged patients [67,68]. However, HIV-1-related microangiopathic syndrome should be considered as only one factor in the pathogenesis of functional cerebral impairment in patients with HIV-1 disease [62–64,69–71]. Furthermore, the obvious analogy of HIV-1-related microangiopathic syndrome with microvascular alterations in autoimmune diseases needs further consideration, and the study of HIV-1-related microangiopathic syndrome might help to clarify the relevance of autoimmune processes in the pathogenesis of AIDS [72,73].

In conclusion, the present study suggests that neurologic and neuropsychological deficits in patients with HIV-1 disease are caused partly by HIV-1-related microangiopathic syndrome. In this context, the determinations of cotton-wool spots or the conjunctival blood-flow sludge rating might be used as indicators of cerebral perfusion abnormalities. Further studies are necessary to investigate the pathogenesis of microvascular lesions of the central and peripheral nervous system in patients with HIV infection, and therapeutic implications should be considered.

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